CLINICAL PRESENTATION AND ECHOCARDIOGRAPHIC DIAGNOSIS OF RARE AND SUBTLE CONGENITAL CARDIOVASCULAR ANOMALIES IN THE ADULT.

JAMES KER

MBChB, MMED, MSc, MRCP, FRCP, PhD, FESC, FACC

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PROMOTER:

Professor Doctor WFP van Heerden

Head Department of Oral Pathology and Oral Biology

Faculty of Health Sciences

University of Pretoria

CO-PROMOTER:

Professor Doctor G Tintinger

Head Department of Internal Medicine

Faculty of Health Sciences

University of Pretoria

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DECLARATION

I, the undersigned, declare that the work contained in this presentation of publications is my own original work, as set forth in the statements which precede the published articles, and has not previously in its entirety or in part been submitted at any university for a degree.

JAMES KER

I certify that on the 1`st day of February 2019 James Ker signed this declaration in my presence.

COMMISIONER OF OATHS

DEDICATION

I dedicate this thesis to my father, Professor James Alastair Ker and my mother Catharina van der Merwe. Thank you.

Also to all who crossed my path—the deceased, the dying, the sick and the living. Thank you for teaching me.

ACKNOWLEDGEMENTS

Professor W.F.P van Heerden

Professor G Tintinger

Teachers who became friends.

Professor C.W.I Pistorius

For inspiring conversations when I needed them.

INTRODUCTION

The author graduated in medicine (MBChB) *cum laude* from the University of Pretoria in 1996. He completed his Internship at the Pretoria Academic Hospital in 1997. During this year he became interested in the subject of Internal Medicine and subsequently was appointed as a registrar in the Department of Internal Medicine of the University of Pretoria in 1998. His years as a registrar stimulated a keen interest in the cardiovascular manifestations of systemic diseases and specifically how this affects the electrocardiogram (ECG). He graduated as an internist (physician) MMED *cum laude* in 2001. The author then spent a year working in the intensive care unit of the Pretoria Heart Hospital, caring for a wide variety of patients in critical condition due to various cardiovascular diseases. In 2003 he joined the Department of Physiology of the University of Pretoria as a senior lecturer with the purpose of working on his PhD which was awarded in 2006 with the title: “Cardiac memory T wave frequency as an electrocardiographic surrogate for structural myocardial alteration in the hearts of Dorper sheep”. Additional academic qualifications subsequently obtained, include MRCP (Member of the Royal College of Physicians of Edinburgh and London). He was elected Fellow of the European Society of Cardiology (FESC) in 2005 and Fellow of the American College of Cardiology (FACC) in 2008. In 2012 he received a Fellowship from the Royal College of Physicians of Edinburgh. In 2015 he completed and was awarded an MSc in Internal Medicine from the University of Edinburgh.

Since 2001 to the present the author practices clinical cardiology on a daily basis and currently has eight thousand and eight hundred patient files available for peer review. Since 2013 he is also an extraordinary professor of Internal Medicine at the University of Pretoria. He is the author of sixty six publications and currently has a C2 rating from the National Research Foundation of South Africa. He served as the associate editor of the Cardiovascular Journal of Africa under the late professor Andries Brink between 2008 and 2012.

For the purpose of this thesis, thirty six publications are presented, dealing with the clinical presentation and echocardiographic diagnosis of rare and subtle congenital cardiovascular anomalies in the adult. This research topic evolved over the span of two decades, as echocardiography evolved as an excellent non-invasive tool to detect subtle structural congenital cardiovascular anomalies, explaining a wide variety of clinical syndromes and electrocardiographic abnormalities in the adult.

SUMMARY

This presentation consists of thirty six selected publications that have appeared in international peer reviewed journals over the last thirteen years (2004 – 2017). The presentation consists of five sections, namely:

i) Apico-basal muscle bundles

ii) Papillary muscle anomalies.

iii) Left ventricular hypertrabeculation.

iv) Congenital anomalies of the left atrium and interatrial septum.

v) Diverse group of anomalies.

i) Apico-basal muscle bundles

Seven publications are presented. Six peer reviewed publications and one peer reviewed chapter in a textbook. These seven publications demonstrate the echocardiographic appearance of these muscle bundles, how they may echocardiographically mimic hypertrophic cardiomyopathy and moreover how they may be the cause of ST-segment elevation on the electrocardiogram (ECG). In addition, the physiology of how they may be the cause of right bundle branch block is also demonstrated. The author`s work and publications on this entity culminated in the invitation in 2014 by senior Lancet editor Dr. Richard Turner to write an editorial for this esteemed journal.

ii) Papillary muscle anomalies

Eight publications are presented.

These eight publications demonstrate the appearance of isolated hypertrophy of a papillary muscle, an inverted (mirror) papillary muscle, accessory papillary muscles, a bifid papillary muscle and how these mentioned anomalies may alter the normal electrocardiogram.

iii) Left ventricular hypertrabeculation

Four publications are presented in this section.

The first publication in 2006 describes the entity of left ventricular hypertrabeculation/non-compaction as a cause of recurrent cerebral emboli at a time when this entity was quite new to most clinicians.

iv) Congenital anomalies of the left atrium and interatrial septum

Seven publications are presented in this section.

Among these, cor triatriatum sinister is noted as an unusual cause for refractory atrial fibrillation. This article then led to an invitation by Prof Andrew.J Coats, the then editor of the International Journal of Cardiology, to write an editorial for the journal on cor triatriatum sinister.

v) Diverse group of anomalies

Ten publications are presented in this section.

i) It is described how a congenital diaphragmatic hernia may lead to left atrial compression and be the subsequent cause of postprandial syncope.

ii) The peculiar appearance of a left ventricular false tendon between the two left ventricular papillary muscles is described.

iii) It is described how congenital hepatic cysts may be the cause of a cardiac arrhythmia.

iv) It is described how mitral valvular strands (the “serpentine” valve) may lead to cerebral embolism.

v) It is described how hypothyroidism may be the cause of cardiac late potentials and thus be a risk factor for sudden cardiac death.

vi) The importance of lipoprotein(a) levels in congenital bicuspid aortic valve anomalies are shown.

vii) A rare congenital anomaly of the inferior vena cava is presented.

viii) It is described how congenital aortic diverticulae may be the cause of cerebral emboli.

ix) Two articles demonstrate how the immunogenetic marker, HLA-B27, may cause electrocardiographic anomalies.

LIST OF PUBLISHED SUBMISSIONS

SECTION 1:

STUDIES ON APICO-BASAL MUSCLE BUNDLES

1. **Ker J.** (2009). “False Tendon Induced Subaortic Hypertrophy—A New Variant of Hypertrophic Cardiomyopathy”. Peter H. Bruno and Matthew T. Giordano, editors. *Cardiomyopathies*. *Causes, Effects and Treatments*. New York. Nova Science Publishers. Page 27 **56-65**
2. **Ker J.** Subaortic tendon induced ST-segment elevation---a new echo-electrocardiographic phenomenon? Cardiovascular Ultrasound 2009; 7(1):13.**66-68**
3. **Ker J.** The subaortic tendon as a mimic of hypertrophic cardiomyopathy. Cardiovascular Ultrasound 2009; 7(1): 31. **69-71**
4. **Ker J.** Structural causes of right bundle branch block---time for a closer look? Open Cardiovascular Medicine Journal 2010; 4(1): 105-109. **72-76**
5. **Ker J.** Subaortic (Type 6) muscular band---innocent bystander or pathologic structure? Clinical Medicine Insights Cardiology 2010; 4(1): 69-71. **77-79**
6. **Ker J.** Hemochromatosis and the heart---heavier than iron? International Journal of Cardiology 2014; 170(3): e70-71. **80-82**
7. **Ker J.** A new phenotypic marker of hypertrophic cardiomyopathy. Lancet 2014; 384(9956): 1731. **83**

SECTION 2:

PAPILLARY MUSCLE ANOMALIES

SECTION 3:

LEFT VENTRICULAR HYPERTRABECULATION

16. **Ker J, van der Merwe C.** Isolated left ventricular non-compaction as a cause of thrombo-embolic stroke: a case report and review. Cardiovascular Journal of South Africa 2006; 17(3): 146-147. **117-118**
17. **Ker J, du Toit-Prinsloo L, van Heerden WFP, Saayman G.** Post-mortem echocardiography—a worthwhile concept? Clinical Medicine Insights: Cardiology 2010; 4(1): 59-61. **119-121**
18. **Ker J, du Toit-Prinsloo L, van Heerden WFP, Saayman G.** Sudden infant death syndrome and left ventricular hypertrabeculation—hidden arrhythmogenic entity? Clinical Medicine Insights: Cardiology 2010; 4(1): 85-87. **122-124**
19. **Ker J, du Toit-Prinsloo L, van Heerden WFP, Saayman G.** Subendocardial fibrosis in left ventricular hypertrabeculation—cause or consequence? Clinical Medicine Insights: Cardiology 2011; 5(1): 13-16. **125-128**

SECTION 4:

CONGENITAL ANOMALIES OF THE LEFT ATRIUM AND INTERATRIAL SEPTUM

SECTION 5:

DIVERSE GROUP OF ANOMALIES

36. Ker J. HLA-B27 and an electrocardiographic peculiarity. Journal of Clinical and Experimental Cardiology 2011(1); 2: 8. **177-180**

SECTION 1

APICO-BASAL MUSCLE BUNDLES

Declaration

Seven publications are included. I am the sole author of all seven publications.

Abstract

The expansion of knowledge on the presence, appearance and clinical significance of apico-basal muscle bundles evolved over the span of five years.

The first observation and description of apico-basal muscle bundles in the literature was that by the author in 2009, which clearly demonstrated muscular, intraventricular bundles extending between the left ventricular apex and the basal part of the interventricular septum. These should not be confused with left ventricular false tendons, a well-described entity, that differs from apico-basal bundles. Apico-basal muscle bundles always extend between the left ventricular apex and the basal part of the interventricular septum and constitute a unique and novel observation.

The first publication, "**False Tendon Induced Subaortic Hypertrophy—A New Variant of Hypertrophic Cardiomyopathy**", submitted in this section was a retrospective analysis of three thousand adult echocardiograms. This study was published as a chapter in a textbook on cardiomyopathy in 2009. The aforementioned echocardiograms were performed between 2004 and 2008. During this period the term

apico-basal muscle bundle did not yet exist and the reader will note that the name given to these apico-basal structures differs in the different publications, until the final editorial in the Lancet when the term “apico-basal muscle bundle” was finally coined. In this first publication, a total of six echocardiograms of patients with apico-basal muscle bundles were presented and described. Furthermore, a novel observation of a striking, localised, left ventricular hypertrophic response at the site of the septal implantation was also demonstrated. This was also a novel observation and the importance of this will emerge in the ensuing discussion.

With the second publication, “**The U wave and papillary muscle variants: revisiting an old association**”, it was clearly shown how such an apico-basal muscle bundle may be the cause of ST-segment elevation on the electrocardiogram. This finding added a further novel cause for ST-segment elevation unrelated to myocardial infarction to the current literature. Of note, the term subaortic tendon was used, as the term apico-basal muscle bundle did not yet exist at that time.

The clinical impact this publication had in the field is demonstrated by the following:

Philip et al.[1] included the clinical information from this publication in their review and study of left ventricular false tendons in the paediatric population.

Gilbert and Ionescu[2] referred to this publication in their description on how such an entity may constitute an important caveat leading to unnecessary re-exploration after elective aortic valve replacement. The impact of this study in the field of caveats in the post-operative cardiac patient is evident. Another important impact of this second

publication is that a new and unique cause for ST-segment elevation on the electrocardiogram was added to the literature.

Furthermore, this paper had a clear impact on the study of **Pisiak et al.**[3] of the echocardiographic characteristics of left ventricular false tendons in the Polish population and was cited by **Sanchez et al.**[4] in their work on the association of false tendons with heart disease and innocent murmurs in children.

Lange et al.[5] did a very interesting study with an important conclusion. They studied the effects of such muscle bundles in the hearts of patients with left bundle branch block. They found that these muscle bundles significantly reduced the QRS duration in patients with left bundle branch block which then posed a relevant research question—will this have a positive impact on mortality in these patients? My study clearly influenced their work [5]. A description of the sounds made by such muscle bundles in the hearts of the young by **Hussain et al.**[6] is clear evidence this publication had on their study.

The third publication, "**The subaortic tendon as a mimic of hypertrophic cardiomyopathy**", raised the issue of how the entity of apico-basal muscle bundles may mimic hypertrophic cardiomyopathy. The impact of this publication is evident by the following: The publication influenced the work of **Sanosyan et al.**[7] on their assessment of asymmetrical hypertrophy of the left ventricle and how the caveat of apico-basal muscle bundles may present in such a scenario.

The publication was useful for the work of **Altug and Danisman**[8] in their discussion of how such bundles may alter the echocardiogram of the fetal heart and was cited by **Silbiger**[9] in a comprehensive overview of the presentation of left ventricular false tendons.

Zinovyeva et al.[10] who called for a unified approach to the detection and classification of these structures in order to study any possible effects they may have on left ventricular function.

Wolf et al.[11] referred to this publication in a veterinary journal of how these structures may lead to focal thickening of the left ventricle of the feline heart. The importance of this citation is twofold. First, if the reader refers to the first and fifth publication, it can be seen that the concept of “implantation hypertrophy”—a striking, localised site of left ventricular hypertrophy at the site of septal implantation of apico-basal muscle bundles was seen in such human patients. Secondly, this has been observed in the feline heart, which implies that a feline model may be a valid model to study the molecular mechanisms of such an observation of “implantation hypertrophy.”

The fourth publication, “**Structural causes of right bundle branch block---time for a closer look?**” was a prospective, observational study, which enrolled eight hundred and eighty patients and it was shown how apico-basal muscle bundles may be the cause of right bundle branch block in these patients. This proof of concept study identified a third type of right bundle branch block which was discussed in the article. The importance of this publication becomes clear when one refers to the citation by **Lange et al.**[5]

Although they cited the second publication this article is of major relevance to their work. **Lange et al.**[5] studied the effect of apico-basal muscle bundles on QRS-duration and intraventricular conduction in patients with left bundle branch block. My study looked at this phenomenon from another angle—in patients with normal left ventricles and apico-basal muscle bundles in the left ventricle, the increased velocity of intraventricular conduction presents as a right buncle branch block.

The fifth publication, "**Subaortic (Type 6) muscular band---innocent bystander or pathologic structure?**" was another descriptive study of apico-basal muscle bundles. In this publication, a retrospective analysis of four thousand and nine hundred adult echocardiograms, the novel concept of localized left ventricular hypertrophy at the site of septal implantation of these apico-basal muscle bundles was clearly illustrated in all three hundred and seventy six patients with apico-basal muscle bundles. This paper was also cited by **Gilbert and Ionescu**[2] in their publication warning about the important caveat these structures may pose to the cardiac surgeon.

The sixth publication, "**Hemochromatosis and the heart---heavier than iron?**" was a case series of eighty five patients with apico-basal muscle bundles which found that 81% of these patients were heterozygous for one of the three mutations associated with hemochromatosis. A research question that originated from this publication was what the exact nature of this association may turn out to be in future.

The seventh publication, "**A new phenotypic marker of hypertrophic cardiomyopathy**" was an editorial in the Lancet. Dr Richard Turner, then a senior editor at the Lancet, asked me to put into perspective the concept of apico-basal muscle bundles—the term used to describe this entity for the first time by Gruner et al.[i] In their publication in the European Heart Journal, the authors demonstrated that this entity may be added to the pool of non-hypertrophic stigmata of hypertrophic cardiomyopathy.

In summary, my work on apico-basal muscle bundles clarified important echocardiographic caveats when these structures are visualized on the echocardiogram. Stimulating research questions flowing from these publications include the following: Will we see long-term mortality benefits in patients with left bundle branch block, and what, if any, will be the long-term consequences of right bundle branch block? Will we see any detrimental effects of "implantation hypertrophy" over the long-term? What is the exact physiological explanation of the strong association with the mutations associated with hemochromatosis?

Finally, apico-basal muscle bundles was added to the pool of non-hypertrophic, echocardiographic stigmata of hypertrophic cardiomyopathy.

SECTION 2

PAPILLARY MUSCLE ANOMALIES

Declaration

Eight publications are included. I am the sole author of all these publications, except one. In the one publication where I am not the sole author, I presented the clinical case, made the diagnosis and wrote the article.

Abstract

Congenital papillary muscle anomalies are a fascinating and relatively common group of disorders. Since publishing the first observation on how papillary muscle anomalies may cause electrocardiographic abnormalities, I strongly suspected that this group of anomalies may be the cause of sudden death in a subgroup of people who experience sudden cardiac death. Subsequent work by other authors compounded this suspicion.

The eighth publication, "**Solitary papillary muscle hypertrophy: A new echo-electrocardiographic syndrome?**" presented a case of isolated papillary muscle hypertrophy and the unique constellation of electrocardiographic abnormalities was described.

The importance of this publication becomes evident by the following.

Cresti et al.[12] referred to this article in their publication which discusses the finding that isolated hypertrophy of a papillary muscle may cause an electrocardiographic pattern of

left ventricular hypertrophy in the absence of hypertrophy of the left ventricular walls. They concluded that an electrocardiographic pattern of left ventricular hypertrophy in the presence of normal left ventricular wall thickness should raise the clinician`s suspicion for the presence of an early or variant form of hypertrophic cardiomyopathy and that the measurement of the papillary muscle heads should be mandatory in such patients. This fact is unknown to most clinicians.

The work **by Uhm et al.**[13] is of great importance as their published analysis of 190 patients who presented with sudden cardiac arrest strongly suggests that isolated papillary muscle hypertrophy is a risk factor for sudden cardiac arrest. The eighth publication had a clear impact on their study.

Sung et al.[14] referred to this publication in their report and discussion of how solitary papillary muscle hypertrophy represents a unique type of hypertrophic cardiomyopathy that may lead to a dynamic pressure gradient during systole in the mid-cavity of the left ventricle.

My publication had an impact on the discussion by **Ferreira et al.**[15] on isolated papillary muscle hypertrophy which describes the spectrum of clinical presentations of hypertrophic cardiomyopathy.

Talbot et al.[16] referred to the publication in their description of the first published case report of hemifacial microsomia in a domestic kitten. The importance of this citation lies in the observation that this kitten also had isolated hypertrophy of the anterolateral papillary muscle. This is interesting if one refers back to the citation by **Wolf et al.**[11] in the previous section on apico-basal muscle bundles—the concept of “implantation

hypertrophy" was also seen in cats with left ventricular false tendons. This implies that a feline model to study these hypertrophic as well as papillary muscle variants may be a valid research model.

Attisani et al.[17] cited this publication in their discussion on T wave inversion in young subjects and **Patil et al.**[18] referred to this paper in their publication on the clinical presentation of papillary muscle hypertrophy in a septuagenarian. The importance of this citation is that the isolated papillary muscle variant of hypertrophic cardiomyopathy may also present to the clinician at an advanced age.

Lombardi et al.[19] in their publication on how to investigate atypical ECG changes in the examination of athletes cited my paper which contributed to the risk assessment for sudden death in athletes.

Perez et al.[20] in their publication, discussed the U wave of the ECG. The importance of my publication is evident by the fact that a novel cause for a prominent U wave was added to the literature.

The ninth publication, "**The U wave and papillary muscle variants: revisiting an old association**" demonstrated how an accessory papillary muscle may be the cause of a prominent U wave on the electrocardiogram. The significance of this publication is highlighted by the fact that **Uhm et al.**[13] referred to this article in their study of causes of sudden cardiac death. They found that accessory papillary muscles may be the cause of sudden death. Note that **Uhm et al.**[13] also referred to the eighth publication in their analysis of the role of papillary muscle anomalies in sudden cardiac death.

The tenth publication, "**The accessory papillary muscle with inferior J-waves—peculiarity or hidden danger?**" described the presence of J waves on the electrocardiogram in a patient with an accessory papillary muscle. The notability of this publication is that it was the first observation published in the literature that J waves may be present on the electrocardiogram in patients with accessory papillary muscles. The significance of J waves as a strong risk factor for sudden cardiac death in the community was demonstrated by the publication by Tikkanen et al [ii] **.** Note that my article was published in 2009, the same year that Tikkanen et al [ii] proved that J waves on the electrocardiogram is a risk factor for sudden cardiac death.

Moreover the impact of the tenth publication becomes more evident by the following**:** **Uhm et al.**[13] also referred to this work in their publication on the risk factors for sudden cardiac death. It is noteworthy that **Uhm et al.**[13] cited the eighth, ninth and tenth articles in their publication. Accessory papillary muscles (both with and without accompanying J waves on the electrocardiogram) are associated with sudden cardiac death according **to Uhm et al.**[13]

The publication had an important impact on **Nakagawa et al.**[21] who demonstrated that J waves may also be associated with false tendons in the left ventricle.

The eleventh publication, "**The "mirror" papillary muscle**" described how a papillary muscle may be inverted and lead to the appearance of a "mirror" papillary muscle. The importance of this publication is reflected in the work by **Misra et al.**[22] describing such anomalies.

The twelfth publication, "**Bigeminy and the bifid papillary muscle**" outlined how a papillary muscle may have a bifid appearance and in addition this article also described a ventricular dysrhythmia due to such a papillary muscle anomaly. The importance of this article is further highlighted by the citation by **Sung et al.[14] .** In this publication, **Sung et al.[14]** described how accessory papillary muscles (as well as hypertrophied papillary muscles) may cause symptomatic, dynamic mid-wall obstruction in the left ventricle. The ventricular dysrhythmia described in this twelfth publication correlates with the risk for sudden cardiac death due to the presence of accessory papillary muscles as described in the paper by **Uhm et al.[13]** who cited three of my publications.

The thirteenth publication, "**Right ventricular variants and pulmonary embolism—association or coincidence?**" described a large, aberrant papillary muscle complex in the apical part of the lateral wall of the right ventricle and importantly it was shown how this aberrant muscular complex was the source of thrombi with resultant pulmonary emboli. The importance of this paper is further demonstrated by the fact that **Loukas et al.[23]** referred to this publication in their review article on the double-chambered right ventricle [23].

The fourteenth publication, "**The double U wave—should the electrocardiogram be interpreted echocardiographically?**" was a retrospective analysis of four thousand seven hundred and twenty nine echocardiograms which proved that accessory papillary muscles may be the cause of a prominent U wave on the electrocardiogram and was cited by **Ong et al.[24]**

The fifteenth publication, "**Electrocardiographic intricacies clarified by echocardiography-should the electrocardiogram be interpreted echocardiographically?**" was a review article which summarized the electrocardiographic manifestations of apico-basal muscle bundles and papillary muscle anomalies and the research question asked was: Should the electrocardiogram be interpreted in association with echocardiographic findings?

In summary, my work on papillary muscle anomalies led to the realization that such anomalies may not only cause electrocardiographic anomalies, but may also lead to symptomatic, dynamic mid-ventricular obstruction in the left ventricle. A new concept arose from this work, namely that such anomalies may be the source of thrombi in the right ventricle with resultant pulmonary emboli. Furthermore, these anomalies are strongly linked to an increased risk for sudden cardiac death. I hope that one day the evaluation of risk for sudden death in the athlete (and other populations) will include the systematic evaluation of the papillary muscles of both the right and left ventricles.

SECTION 3

LEFT VENTRICULAR HYPERTRABECULATION

Declaration

Four publications are included in this section. I am the first author of all four publications. I am the sole author of the first publication. The other three publications were all my original research ideas and I wrote the articles.

Abstract

Left ventricular hypertrabeculation/non-compaction is characterized by a persistence of the embryonic pattern of a highly trabeculated myocardium in the left ventricle. This can occur in a sporadic or familial pattern and may be caused by a variety of mutations in genes coding for mitochondrial, cytoskeletal, Z-line or sarcomeric proteins. Unknown before the observation by Jenni in 1999, isolated left ventricular non-compaction is currently classified as a primary cardiomyopathy with heart failure, arrhythmias and thromboembolism as the main complications. Left ventricular hypertrabeculation, which has unique diagnostic criteria, may be viewed as a less severe form of left ventricular non-compaction.

The sixteenth publication, "**Isolated left ventricular non-compaction as a cause of thrombo-embolic stroke: a case report and review**" described a case of isolated left

ventricular non-compaction as a cause of recurrent, cerebral thromboembolism in a young woman. This was published two years before the condition was listed as a primary cardiomyopathy and clinical descriptions of this condition were rare. The clinical impact and significance of this publication is demonstrated by the following:

Sahin et al.[25] referred to the publication in their description of left ventricular non-compaction as an unusual cause of cardioembolic stroke in 2008—at a time when the entity was fairly new and unknown to most clinicians. The paper was cited by **Fazio et al.**[26] in their novel description of supraventricular arrhythmias as a complication of left ventricular noncompaction.

Fazio et al.[27] also referred to my work in their publication which discussed the need for anticoagulant drugs in patients with left ventricular noncompaction—one of the first discussions on the need for anticoagulation in this condition.

The publication had an impact on the work of **Finsterer et al.**[28] who analysed the risk for stroke in patients with and without heart failure in the presence of left ventricular noncompaction and was cited by **Grizzard et al.**[29] in their book on cardiovascular MRI in practice.

The paper had a significant impact on the work of **Jaramillo et al.**[30] who referred to the publication in their work highlighting how ischemic stroke may be the first manifestation of left ventricular noncompaction. **Jimenez-Caballero et al.**[31] then focused on how left ventricular noncompaction may also be the cause of stroke in the juvenile and they also referred to my publication.

This paper has been cited by numerous other authors including, **Captur et al.**[32] in their discussion on unresolved issues and the entity of left ventricular hypertrabeculation/non-compaction, **Mayosi** [33] in his discussion of cardiomyopathies in Africa, **Baquero et al.**[34] in their publication which adds further evidence to the fact that this entity is a cause of stroke in the young, **Sliwa et al.**[35] in their publication on the epidemiology of cardiomyopathy in Africa and **Kulhari et el.**[36] who discussed the risk for stroke in left ventricular noncompaction.

My publication had an impact on the work **of Myasnikov et al.**[37] as reflected in their publication which discusses the secondary prevention of stroke in patients with left ventricular noncompaction.

The seventeenth publication, "**Post-mortem echocardiography—a worthwhile concept?**" was a proof of concept article. I wanted to know if post-mortem echocardiography of intact hearts may alter the standard method of dissection in cases of sudden, unexpected death in the young. The importance of this proof of concept article is reflected in the fact that this publication was cited by **Javan et al.**[38] in their book on the forensic assessment of cases of unexpected cardiac death.

The eightheenth publication, "**Sudden infant death syndrome and left ventricular hypertrabeculation-hidden arrhythmogenic entity?**" raised the research question of whether left ventricular hypertrabeculation may be the cause of death in a subgroup of patients with sudden infant death syndrome. The importance of this article is reflected

by the fact that **Yoshinaga et al.**[39] cited this publication and concept in their article on electrocardiographic screening of infants for risk of sudden death.

The nineteenth publication, "**Subendocardial fibrosis in left ventricular hypertrabeculation—cause or consequence?**" documented the presence of subendocardial fibrosis in a case of sudden infant death syndrome and left ventricular hypertrabeculation. This publication raised the research question of whether subendocardial fibrosis is strongly associated with left ventricular hypertrabeculation or whether it may be present only in those cases presenting with sudden death.

The importance of this publication is demonstrated by the following: **Blagova et al.**[40] referred to the paper in their discussion on diagnostic and therapeutic issues in left ventricular noncompaction.

Finsterer et al.[41] referred to the publication in their work which demonstrates how the intertrabecular recesses may disappear when left ventricular hypertrophy develops in a heart with left ventricular noncompaction. This is an important caveat which may mask the underlying cause of systolic dysfunction in a hypertrophic left ventricle.

Gerger et al.[42] referred to the paper in their publication with a very interesting and important observation—subendocardial fibrosis in cases of left ventricular hypertrabeculation. They concluded that subendocardial fibrosis in left ventricular hypertrabeculation deserves further research.

Stöllberger et al.[43] cited to my work in their review article on fetal ventricular hypertrabeculation/noncompaction. These authors also concluded that subendocardial

fibrosis merits further research in these patients. Furthermore, **Blagova et al.**[44] referred to my work in their publication—a case series and discussion of myocardial infarction as a complication of left ventricular hypertrabeculation/noncompaction due to thromboembolism of the coronary arteries and subendocardial ischemia of the noncompacted layer. **Stöllberger et al.**[45] referred to this paper when they presented a convincing argument on the presence of subendocardial fibrosis in the hearts of patients with left ventricular hypertrabeculation/noncompaction and **Finsterer et al.**[46] cited my work in their publication on the computed tomographic appearance of familial noncompaction. **Stöllberger and Finsterer**[47] referred to the work in their review of unsolved issues in left ventricular hypertrabeculation/noncompaction and **Finsterer et al.**[48] cited my publication in their review in *Nature* on left ventricular noncompaction.

In summary, my work on left ventricular hypertrabeculation/noncompaction contributed to the realization that this may be an important cause of stroke in the young.

My work on the concept of post-mortem echocardiography in order to alter the standard practice of cardiac dissection in cases of sudden infant death syndrome in whom left ventricular hypertrabeculation was suspected was accepted and cited in a textbook.

My work on the histological finding of subendocardial fibrosis in hearts with left ventricular hypertrabeculation was also recognised by other investigators and is widely cited. This contributed to the current research question of what the possible reasons and consequences of subendocardial fibrosis in these hearts may be. I predict that this will be widely researched and explained in the ensuing years.

SECTION 4

CONGENITAL ANOMALIES OF THE LEFT ATRIUM AND INTERATRIAL SEPTUM

Declaration

Seven publications are included in this section. I am the sole author of all these publications.

Abstract

Unusual congenital anomalies of the left atrium and interatrial septum are presented in this section. These anomalies are clinically important as they may present with refractory atrial fibrillation and/or cerebral thromboembolism.

The twentieth publication, "**The enigma of bulging to the left—a case report of an unusual atrial septal aneurysm**" described and discussed the echocardiographic presentation of an interatrial septal aneurysm. The discussion then focused on the peculiarity of why such an aneurysm would bulge into the left atrium where the intra-atrial pressure exceeds right atrial pressure. The importance of this publication is that it focuses attention on this peculiar phenomenon which still remains unexplained.

The twenty-first publication, "**Cor triatriatum sinister presenting with adult onset atrial fibrillation—another rare cause for a common clinical problem**" documented

and discussed cor triatriatum sinister as a cause of refractory atrial fibrillation. The clinical importance of this publication is evident by the following:

Siniorakis et al.[49] referred to this publication in their work on cor triatriatum sinister in atrial fibrillation and stroke. Cor triatriatum sinister in the adult is important as it may cause refractory atrial fibrillation and echocardiography should be carried out in these patients to evaluate the structure of the left atrium. The clinical importance of cor triatriatum sinister in the adult is further reinforced by the citations by **Strickland et al.**[50] and **Jha et al.**[51]

Following the publication by **Siniorakis et al.**[49] I was asked by Prof Andrew J Coats, then the editor of International Journal of Cardiology, to write an editorial for the *International Journal of Cardiology* on the concept of cor triatriatum sinister as a cause of refractory atrial fibrillation in the adult. This editorial, "**On the many possible futures of atrial fibrillation**" became the twenty-second publication.

The importance of the twenty-third publication, "**Congenital left atrial bands and cardioembolic events**" is that it reinforced the observation by **Ozer et al.**[52] that left atrial bands, which are anomalous muscular bands in the left atrium, may be the cause of cardioembolic events. The paper was also cited by **Crosca et al.**[53]

The importance of the twenty-fourth publication, "**Interatrial septal aneurysm with mitral valve prolapse in a patient with Marfan syndrome—a caveat of note**" lies in the important clinical caveat that if an interatrial septal aneurysm is present in a patient with mitral valve prolapse, the clinician may overestimate the echocardiographic diameter of the left atrium. This in turn may lead to an overestimation of the severity of mitral incompetence that usually accompanies mitral valve prolapse and result in unnecessary mitral valve replacement surgery.

The importance of the twenty-fifth publication, "**The interatrial septal aneurysm as a diagnostic aid in pulmonary embolism**" is that the bulging of an interatrial septal aneurysm into the left atrium may be the only echocardiographic manifestation of raised intrapulmonary pressures in a patient with dyspnea.

The twenty-sixth publication, "**Unilateral atrial fibrillation-how common is atrial divorce?**" described and discussed a novel concept—a case of atrial fibrillation where one atrium is fibrillating, while the other atrium is in sinus rhythm. Although this is not a congenital anomaly, it is important to include the paper in this thesis, as many congenital cardiovascular anomalies will ultimately lead to atrial fibrillation. A valid research question is what percentage of such patients may have unilateral atrial fibrillation. This article added a novel concept to the existing pool of literature on atrial fibrillation.

In summary, the publications presented in this section demonstrate the importance of a careful echocardiographic evaluation of the inner aspect of the left atrium in cases of unexplained cerebral thromboembolism in order to exclude left atrial bands as an underlying cause. Furthermore, the importance of evaluating the interatrial septum in order to exclude the presence of an interatrial septal aneurysm is emphasized in this section.

SECTION 5

DIVERSE GROUP OF ANOMALIES

Declaration

Ten publications are included in this section. I am the sole author in all these publications, except publication twenty seven. In this publication, I made the diagnosis and I am the first author.

Abstract

These ten submitted publications represent a diverse group of subtle and congenital cardiovascular anomalies that may be present in the adult.

The twenty-seventh publication, "**Diaphragmatic hernia mimicking an atrial mass: a two-dimensional echocardiographic pitfall and a cause of postprandial syncope**" documented a peculiar phenomenon. A hiatal hernia may compress the left atrium and cause post-prandial syncope and mimic a left atrial mass. The impact of this publication is evident by the fact that **Smelley and Lang**[54] referred to this paper in their work on masses impinging on the left atrium and also the fact that **Khouzam et al.**[55] referred to the publication in their review on the echocardiographic features of hiatal hernias. The paper also had an impact on the work of the following authors who subsequently observed this phenomenon: **Koskinas et al.**[56] , **Kocatürk et al.**[57] , **Maheshwari et al.**[58] and **Chang et al**[59] .

The publication had an impact on the work of **Dencker at al.**[60] on the use of echo contrast and was cited by **Goyal et al.**[61] and **Ono et al.**[62] in their discussion on how this condition may mimic cardiac disease. The impact of the twenty-seventh paper on subsequent work on this phenomenon is clear—congenital diaphragmatic pathology may lead to cardiac compression.

The twenty-eighth publication, "**The violin heart**" demonstrated the peculiar appearance of a left ventricular myocardial band, also known as a false tendon. This paper had an impact on the work of **Pisiak et al.**[3] and **Silbiger et al.**[9] as they referred to this publication in their description of left ventricular false tendons in the Polish population and a review of the characteristics of such tendons, respectively.

The twenty-ninth publication, "**The liver and right atrium—hepatic cyst as a cause of arrhythmia**" documented another unusual phenomenon, namely atrial arrhythmia due to right atrial compression by a hepatic cyst. This was a novel observation and the first published in the pool of available literature. The impact of this publication is evident by looking at the subsequent work and publications by the following authors: **Zheng et al.**[63] referred to this work in their book on simple hepatic cysts and polycystic liver disease and by **Zippi et al.**[64] and **Shi et al.**[65] in their work on the effects of hepatic cysts. **Panchal et al.**[66] later also documented a case of right atrial and right ventricular outflow tract compression caused by a hepatic cyst. The importance of this twenty-ninth

publication is that it focused attention on the important potential influence of structural liver lesions on cardiac function.

The thirtieth publication, "**The serpentine mitral valve and cerebral embolism**" is a description of how valvular strands attached to the mitral valve may be the source of cerebral emboli with resultant neurological sequelae. This publication was cited by **Alekhin et al.**[67] in their work on the clinical significance of these filiform structures (also known as Lambl`s excrescences) on the cusps of cardiac valves. The importance of the thirtieth publication is that it described a new and novel cause for stroke in humans. By extending the base of knowledge on causes of stroke in humans, this paper may improve the quality of medical care and prevention of stroke.

The thirty-first publication, "**Thyroxine and cardiac electrophysiology—a forgotten physiological duo?**" documented the presence of electrocardiographic ventricular late potentials with a resultant risk for ventricular arrhythmias and the disappearance of these late potentials when hypothyroidism was corrected with thyroxine. As hypothyroidism can also be a congenital condition with these resultant cardiac effects, this paper is included in this thesis. The impact of this publication is evident by the following: **Potempa et al.**[68] referred to the publication in their review on the effects of thyroid disorders on the heart and **Chatzitomaris et al.**[69] cited the paper in their description of the cardiovascular effects of myxedema.

The publication was cited by **Araque et al.**[70] in their work that demonstrated how the primary manifestation of Hashimoto's disease may be T-wave inversions on the electrocardiogram. The publication also had a clear impact on the laboratory work of **Wu et al.**[71] and was referred to by **Mozos et al.**[72] in their work on the signal-averaged electrocardiogram. **Wisniowska et al.**[73] referred to my publication in their work on drug-disease interactions. The importance of the thirty-first publication is thus that it describes a novel link between thyroid disease and resultant cardiovascular pathology, both of which may be congenital in origin. My publication has contributed to improving the quality of care in patients with thyroid disease and cardiac disease.

The thirty-second publication, "**Bicuspid aortic valve disease and lipoprotein(a)—a concept worth exploring?**" described a case series of patients with bicuspid aortic valves. It was found that lipoprotein(a) levels are a risk factor for calcification of the aortic valve cusps in these patients. This was a novel observation and the first published in the available literature. The impact of this publication is that it identified a new risk factor for premature calcification of the aortic valve cusps in these patients. This gives rise to a new scientific question—will the lowering of lipoprotein(a) levels in these patients improve their clinical outcome? **Wang et al.**[74] cited this work in their publication on the possible role of PCSK9 inhibitors in preventing aortic valve calcification in these patients. The impact of the thirty-second publication is thus that a novel risk factor for aortic valve calcification in patients with bicuspid aortic valves was identified and furthermore, this stimulated other researchers to explore the role of new

therapeutic agents to prevent this common and dreaded complication of calcification of bicuspid aortic valves[74] .

The thirty-third publication, "**Rare congenital anomaly of the inferior vena cava**" demonstrated a rare variant of an inferior vena cava anomaly. Such anomalies are known to be more common in patients with other congenital cardiovascular anomalies. However, this particular case is unusual in that it demonstrates a combined absence of the suprarenal as well as the infrarenal portions of the inferior vena cava—a rare variant with only eight previously described cases so far. The importance of the thirty-third publication lies in the fact that various congenital anomalies of the inferior vena cava are possible and in patients presenting with edema and other stigmata of cardiovascular disease, this is an important anatomical region to evaluate. The publication will thus contribute to the evaluation and care of patients with this condition.

The thirty-fourth publication, "**Aortic diverticulae and transient cerebral ischemic attacks—Another reason for aortic imaging in unexplained TIA?**" demonstrated the concept of aortic diverticulae. The importance of this publication is that it added yet another new aetiology to that of known causes for cerebral emboli. Stroke due to emboli from various cardiac sources constitutes a very important cause for this common human affliction across all age groups. As the bank of knowledge on this entity will surely grow in the years to come, more causes of cerebral emboli will be described in the literature and this publication will undoubtedly contribute to this pool of knowledge.

The thirty-fifth publication, “**HLA-B27 associated J-wave—a new variant of HLA-B27 associated cardiac disease?**” was a case series which demonstrated the high incidence of electrocardiographic abnormalities in patients with the immunogenetic marker, HLA-B27. The importance of this publication is that it alerts the clinician to this possibility in patients with unexplained electrocardiographic abnormalities.

The thirty-sixth publication, “**HLA-B27 and an electrocardiographic peculiarity**” was a case series that demonstrated how J-waves on the electrocardiogram may occur more frequently in patients with the immunogenetic marker HLA-B27. The importance of this publication is that it adds another variant of HLA-B27 associated cardiac disease to the existing literature.

CONCLUSION

The thirty six publications included in this thesis were selected in order to reflect the focus of my research over the past thirteen years, namely the clinical presentation and echocardiographic diagnosis of rare and subtle congenital cardiovascular anomalies in the adult. All of these manuscripts have been published in international, peer reviewed journals between 2004 and 2017.

For the purpose of this DSc thesis I needed to demonstrate the impact that these publications had on my field of study. In evidence of this, reference has been made to current international citations of my work. Such citations will likely increase in number over the ensuing years, so this discussion therefore reflects the current snapshot in time of our knowledge of these congenital cardiovascular anomalies and their complications.

My work contributed significantly to the clarification of apico-basal muscle bundles, how they differ from left ventricular false tendons, how they may cause electrocardiographic abnormalities and how they finally were added to the pool of non-hypertrophic stigmata of hypertrophic cardiomyopathy.

My work on papillary muscles and their variants and pathology contributed significantly to the field of study. I demonstrated the appearance of isolated papillary muscle hypertrophy as a variant of hypertrophic cardiomyopathy, I published a peculiar electrocardiographic pattern of abnormalities unique to this condition. I have published various congenital anomalies of the papillary muscles and it was subsequently shown how such anomalies may cause intraventricular pressure gradients. I then published on

ventricular dysrhythmia due to papillary muscle variants. Numerous authors subsequently published articles on the association of papillary muscle anomalies with an increased risk of sudden cardiac death. My work contributed to the indication of papillary muscle assessment when evaluating a patient for risk of sudden cardiac death.

My work on left ventricular hypertrabeculation led to one of the first reports that this may be a cause of stroke in the young at a time when this was a newly discovered and unknown entity. In my quest to link this with a risk for sudden cardiac death in infants, a new method of cardiac dissection in babies who succumbed to sudden infant death syndrome was developed—one based on a post-mortem echocardiogram of the excised heart. This led to this method being published in a textbook of forensic medicine and the novel concept of post-mortem echocardiography to guide subsequent dissection of the heart was published. Later work by me clearly demonstrated the presence of left ventricular hypertrabeculation in a subgroup of infants who died from sudden infant death syndrome. The peculiar phenomenon of subendocardial fibrosis was present in this subgroup. Later work by other authors confirmed the presence of subendocardial fibrosis in a subgroup of patients with left ventricular hypertrabeculation.There is currently a major focus of research on subendocardial fibrosis in left ventricular hypertrabeculation and my work played a significant role in focusing research on this yet unexplained phenomenon.

My work on congenital anomalies which affect the left atrium also had a significant impact on the literature. I have shown how an interatrial septal aneurysm may be utilized to diagnose pulmonary hypertension, I have raised some yet unanswered

questions on the physiology and it was shown that this is an important entity to understand and recognize, especially if associated with mitral valve prolapse, as this may lead to an erroneous impression of left atrial enlargement.

I have published an article and an invited editorial on cor triatriatum sinister and my work on this entity added a new and novel cause for refractory atrial fibrillation to the existing pool of literature on atrial fibrillation.

I have added yet another cause of cerebral emboli with resultant stroke in the young—the entity of congenital left atrial bands as a source of cerebral emboli.

My work on the cardiac sequelae of a congenital diaphragmatic hernia is widely cited and added a unique cause of syncope and specifically post-prandial syncope to the literature.

My work on congenital hepatic cysts leading to right atrial compression and arrhythmia is widely cited and added a new and novel cause for arrhythmia to the literature.

These two entities—diaphragmatic hernia and hepatic cysts—focused the attention on the diaphragmatic and subdiaphragmatic area when evaluating a patient with unexplained syncope and/or arrhythmia.

My work on mitral valvular strands added another cause of cerebral emboli and resultant stroke in the young to the literature. The value of a properly performed

echocardiogram in a case of unexplained stroke is proven beyond any doubt with this thesis.

My work on the electrocardiographic abnormalities in hypothyroidism—which is often a congenital affliction—added new and novel information to existing literature. This described a new risk factor for sudden cardiac death—cardiac late potentials due to hypothyroidism reversible with T4 therapy.

My work on bicuspid aortic valves identified a new and novel risk factor for calcification of the cusps of such valves—a common and dreaded complication. My publication subsequently stimulated other authors to explore therapeutic agents to prevent such calcification and a prominent publication on PCSK9 inhibitors subsequently appeared.

My work on congenital anomalies of the inferior vena cava added valuable information on this possibility and the clinical presentation of such patients.

My work on aortic diverticulae added another cause of cerebral emboli and stroke in the young to the growing pool of literature on causes of cerebral emboli.

Finally, the importance of knowledge of the immunogenetic marker HLA-B27 in patients with electrocardiographic abnormalities is highlighted by the addition of two publications as a result of my work on this entity.

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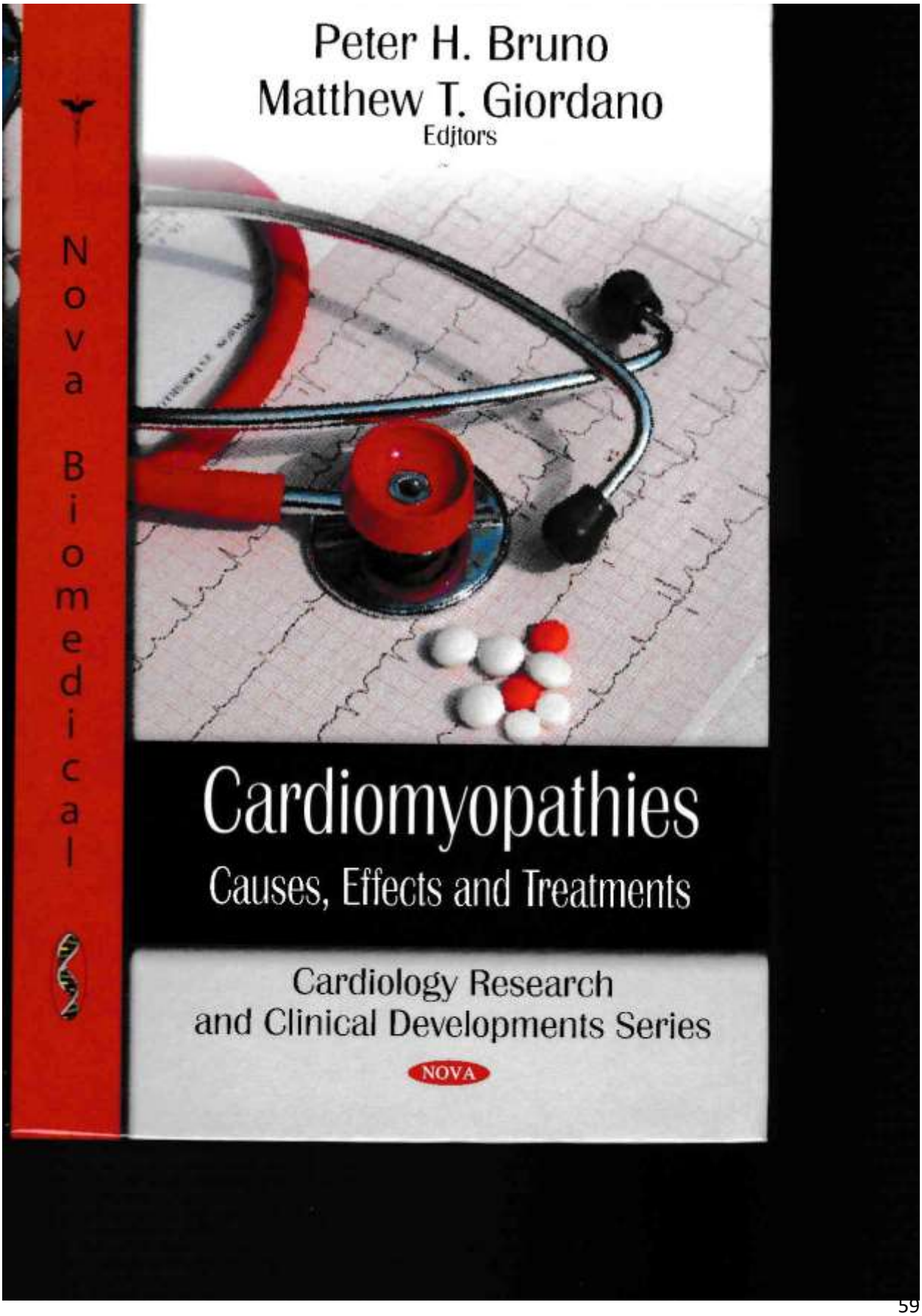
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CARDIOMYOPATHIES: CAUSES, EFFECTS AND TREATMENT

PETER H. BRUNO
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MATTHEW T. GIORDANO
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Short Communication B

False Tendon Induced Subaortic Hypertrophy—A New Variant of Hypertrophic Cardiomyopathy

James Ker*
University of Pretoria, South Africa

Abstract

Left ventricular false tendons are a common echocardiographic finding and consist of thin fibrous or fibromuscular structures traversing the left ventricular cavity. They have no connection to any valvular cusps and may be single or multiple. Histologic examination has shown that they can be composed of any combination of cardiac muscle, fibrous tissue, blood vessels and Purkinje cells.

At present the clinical significance of these false tendons is uncertain, with some studies showing a possible causal role for ventricular arrhythmias. These tendons have been divided into five categories, based on the site of implantation.

In this study a sixth category of left ventricular false tendon is identified, with implantation into the ventricular septum in a subaortic position. These subaortic false tendons are associated with localized subaortic hypertrophy and it is suggested that they play a causal role in the genesis of localized subaortic hypertrophy with a possible new variant of hypertrophic cardiomyopathy—false tendon induced subaortic hypertrophy.

Keywords: false tendons, hypertrophy, cardiomyopathy.

* Address for correspondence: Professor James Ker; MRCP, PhD, FESC, FACC; Department of Physiology; University of Pretoria; PO Box 24318; Gesina; Pretoria; South Africa; 0031; E-mail: jker@wol.co.za; Tel: +2712-3430078; Fax: +2712-3430079

Introduction

Left ventricular false tendons are thin, fibrous or fibromuscular structures that traverse the left ventricular cavity[1]. They may be single or multiple and have no connection to the valvular cusps.[1]

False tendons can be an isolated finding or can be associated with cardiac abnormalities.[2] These tendons are usually of no clinical significance but has been associated with rate-dependent ventricular arrhythmias and has also been shown to be a cause of musical murmurs when pulled taut by ventricular dilatation.[2]

Loukas et al[3] examined 200 formalin fixed, adult hearts and divided false tendons into five categories: In type I the false tendon is located between the posteromedial papillary muscle and the ventricular septum. In type II the false tendon is located between the two papillary muscles. In type III the false tendon is located between the anterolateral papillary muscle and the ventricular septum. In type IV the false tendon is located between the ventricular septum and the free wall. In type V the false tendons appear weblike and have three or more points of insertion.

After careful histological examination Abdulla et al[2] suggested that false tendons may be intracavitary radiations of the bundle of His and that their clinical significance may be more relevant than previously believed and merits further study.

Methods

This study was a retrospective analysis.A total of 3000 adult echocardiograms, performed between 2004 and 2008 for various clinical indications, were reviewed and analyzed for the presence of a left ventricular false tendon in the subaortic position.

Results

A total of 6 adult echocardiograms clearly demonstrated the presence of a false tendon located between the left ventricular lateral wall and the subaortic interventricular septum (see figure 1-6). In all 6 of these cases a striking local ventricular hypertrophic response was present at the site of septal implantation of the false tendon (see figure 1-6).

No systolic and/or diastolic dysfunction, valvular disease or pericardial disease were present in any of these patients. All 6 echocardiograms were from men, aged from 35 years to 64 years.

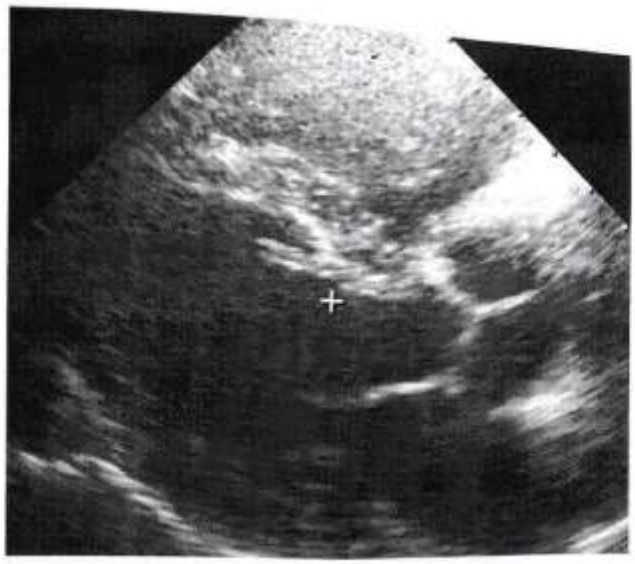

Figure 1. Parasternal long-axis view on a transthoracic echocardiogram of patient 1. Note the subaortic implantation of a false tendon, with a prominent localized hypertrophic response.

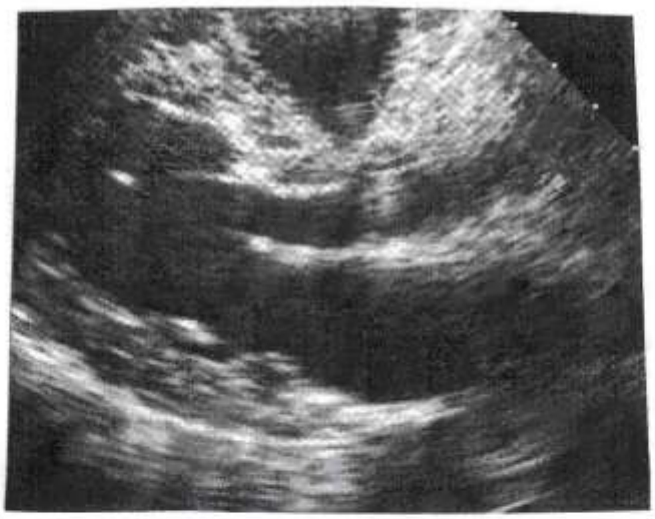

Figure 2. Parasternal long-axis view of a transthoracic echocardiogram of patient 2, demonstrating the same subaortic false tendon as in patient 1, also with a localized hypertrophic response.

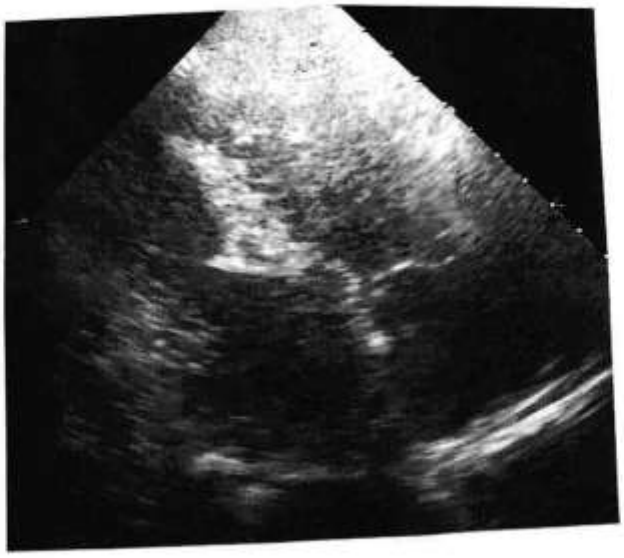

Figure 3. Parasternal long-axis view of patient 3. The presence of the same type of subaortic false tendon with localized hypertrophy is shown.

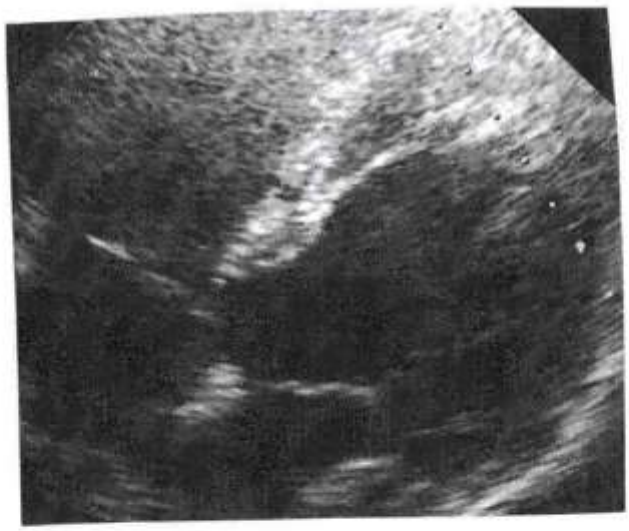

Figure 4. Apical two-chamber view of patient 4. The presence of a subaortic false tendon with a striking localized hypertrophic response is shown.

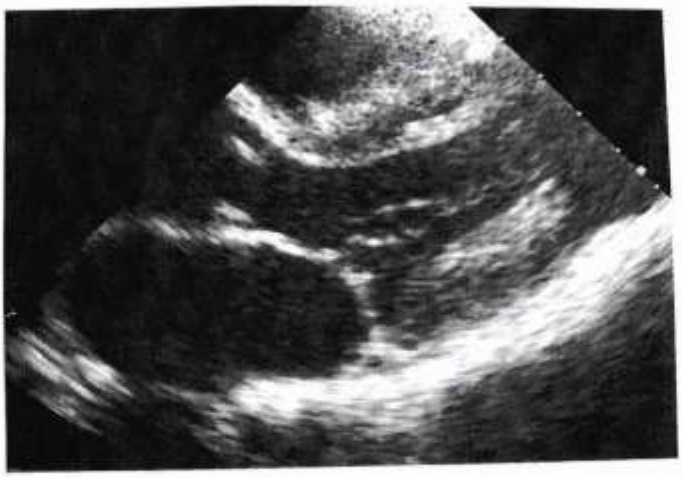

Figure 5. Apical two-chamber view of patient 5. The subaortic false tendon is clearly shown.

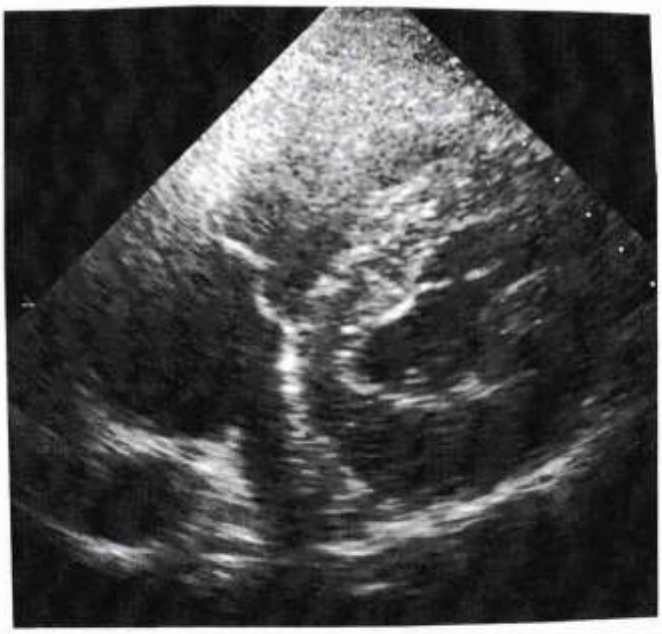

Figure 6. Parasternal short-axis view of patient 6. The localized hypertrophic response is clearly shown.

Discussion

A sixth type of left ventricular false tendon is identified—with the specific location between the subaortic portion of the interventricular septum and the left ventricular free wall. In each of the six cases presented, a striking localized ventricular hypertrophic response is present at the site of subaortic implantation of the false tendons.

Hypertrophic growth is the primary mechanism by which the heart reduces stress on the ventricular wall.[4] Mechanical stress on the ventricular wall elicits auto-and paracrine signaling by inducing the synthesis and secretion of growth factors, such as angiotensin II, insulin like growth factor 1 and endothelin 1 and furthermore, mechanical stretch is also capable of activating angiotensin II receptors directly, without the involvement of angiotensin II.[4,5]

The predominant feature of the hypertrophic cardiomyopathy phenotype is increased thickness of the left ventricular wall.[6] However, hypertrophic cardiomyopathy is both genotypically and phenotypically a highly heterogeneous disorder with more than 150 mutations, scattered throughout 10 genes, encoding various proteins of the cardiac sarcomere, as known genetic causes for the condition.[7,8,9] Phenotypically, there can be marked regional differences in ventricular wall thickness,[10] with the hypertrophic process affecting either the left and/or right ventricle,[7] being symmetrical or asymmetrical.[7] Septal hypertrophy is the most common phenotype, with midventricular and apical hypertrophy less common.[7] Even in patients with identical mutations striking inter-and intra-family variations have been noticed in the presence and severity of left ventricular hypertrophy.[11] So-called modifier genes may contribute to this phenotypic diversity and indeed the rs2106809 and rs6632677 polymorphisms of the angiotensin-converting enzyme 2 gene have been shown to increase the risk for expressing greater magnitude of ventricular hypertrophy in hypertrophic cardiomyopathy.[11]

Kobashi *et al [12]* noted that patients can present with isolated papillary muscle hypertrophy and suggested that this is a newly identified subtype of hypertrophic cardiomyopathy.

Harrigan *et al [6]* have shown on the other hand, that in patients with established hypertrophic cardiomyopathy, both the number and the mass index of the papillary muscles may be increased and that in these patients accessory papillary muscles can even contribute to ventricular outflow obstruction.

Adult-onset hypertrophic cardiomyopathy is a prevalent condition[13] and is caused by either inherited or new mutations in cardiac sarcomere protein genes, such as: cardiac beta-myosin heavy chain (MYH7), cardiac myosin-binding protein C (MYBPC3), cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), essential myosin light chain (MYL3), regulatory myosin light chain (MYL2), alpha-tropomyosin (TPM1), cardiac actin (ACTC) and titin (TTN). The age range at clinical diagnosis of hypertrophic cardiomyopathy is broad, however, clinical manifestation before the age of 14 years are atypical.[13]

In view of the above background of hypertrophic cardiomyopathy three issues are relevant to this study: First, it is possible that the local hypertrophic response is due to local mechanical stretch, induced by the false tendon attachment. Second, the involvement of the papillary muscles in hypertrophic cardiomyopathy has been clearly shown -an increase in

their mass index and number with accessory papillary muscles—has been documented. It is perhaps time to focus on false tendons in hypertrophic cardiomyopathy—will there be an increase in their mass index and number the same as for the papillary muscles? Thirdly, the striking local hypertrophic response at the site of septal implantation of these false tendons may be caused by the false tendon itself in a manner other than a local stretch induced response—a true false tendon-induced hypertrophic cardiomyopathy. Lastly, an important clinical question is whether these localized hypertrophic responses will remain static or will progress with generalized ventricular involvement over time?

A sixth type of ventricular false tendon is proposed—the subaortic false tendon, giving rise to false tendon-induced subaortic hypertrophy. Whether this is due to a local stretch response or a true hypertrophic cardiomyopathy will need to be determined by further studies, also performing genetic analyses for possible mutations in genes encoding proteins of the cardiac sarcomere.

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Case report

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Sub aortic tendon induced ST segment elevation – a new echo electrocardiographic phenomenon?

James Ker

Address: Department of Physiology, University of Pretoria, PO Box 24318, Gesina, Pretoria, 0031, South Africa

Email: James Ker - jker@wol.co.za

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Abstract

The causes for ST-segment elevation other than myocardial infarction are numerous.

The existence of left ventricular false tendons has been known for more than a century. Currently, the clinical entities associated with these left ventricular false tendons include innocent murmurs and premature ventricular contractions.

A case report is presented where such a false tendon, attached to the interventricular septum, is responsible for striking ST-segment elevation in the anterior precordial leads.

It is proposed that this is a newly observed entity – that of subaortic tendon-induced ST-segment elevation. This is proposed as a totally benign phenomenon with the clinical importance in that it should not be confused with other pathological processes, such as the Brugada syndrome.

Introduction

The first description of so called false tendons inside the left ventricle was published 115 years ago [1]. These structures are also described in the literature as: left ventricular moderator bands, anomalous cords, left ventricular bands and aberrant tendons [2]. Abdulla *et al* [3] examined these tendons histologically and suggested that they are intracavitary radiations of the bundle of His. Embryologically, these false tendons are thought to derive from the inner muscle layers of the primitive heart and in addition to Purkinje cells, they also contain myocardial fibers, blood vessels, connective tissue and fibrous tissue [2]. Anatomically, these tendons have been divided into longitudinal and transverse tendons – longitudinal tendons extending from the ventricular septum to the posteroapical wall and transverse tendons extending between the septum and the lateral wall [4]. These tendons have been shown to be a cause of functional ejection murmurs [2-5]. It has also been documented that they are associated with both uni-and multifocal premature ventricular contractions (PVC's) [4,6]. These PVC's are poorly controlled by antiarrhythmic drugs, but easily suppressed by exercise [4].

There are currently two hypotheses for the generation of these PVC's [4]: These tendons contain Purkinje fibers and it is known that the automaticity of Purkinje cells is increased by mechanical stretching [4,7]. It may be that mechanical stretching of the tendon can generate the PVC or alternatively, the mechanical stretch of the ventricular wall, where the tendon inserts, may trigger the PVC.

Case report

A case report is presented where it is postulated that a left ventricular false tendon, attaching to the interventricular septum in a subaortic location, is responsible for striking ST-segment elevation in the anterior precordial leads.

A 34-year old Caucasian male was referred for a cardiovascular examination, because of an abnormal electrocardiogram, demonstrating striking ST-segment elevation in

leads V1, 2 and 3 (Figure 1). The patient is totally asymptomatic. The ECG was done by his primary care physician for insurance purposes for an insurance policy he applied for. He is an athlete who competes in marathon running in his spare time.

The clinical examination was normal. No chest pain or any symptoms were present. Troponin T and creatine kinase levels were all normal. Other known causes for ST-segment elevation, such as hypothermia, trauma, hypercalcemia and hyperkalemia were all excluded. Echocardiography demonstrated a heart without any pathological findings.

The only peculiarity noted was the presence of a left ventricular false tendon, extending between the apical wall and the interventricular septum (see Additional file 1 and Additional file 2). Note the parasternal, long-axis view from a transthoracic echocardiographic image, demonstrating the false tendon, marked with + (See Additional file 1, Additional file 2 and Additional file 3.) The subaortic location of implantation is clearly shown. Also note the same false tendon from the parasternal short axis view, marked with + (see Additional file 4). Note the localized, hypertrophic response at the site of implantation (see Additional file 4, Additional file 5 and Additional file 6).

The patient was closely followed for a period of three years. During this period no symptoms or signs of any cardiovascular disease and specifically no rhythm disturbances was ever present. He remains totally asymptomatic to date.

Discussion

The differential diagnosis of ST-segment elevation is wide and diverse, and includes the following [8]: myocardial ischemia or infarction, Prinzmetal angina pattern, Takotsubo cardiomyopathy, ventricular aneurysm, pericarditis, normal variant ("early repolarization"), left ventricular hypertrophy, left bundle branch block, other causes of myocardial injury, such as myocarditis, trauma or tumor invading the left ventricle, hypothermia, after DC cardioversion, hyperkalemia, hypercalcemia, type 1C antiarrhythmic drugs, intracranial hemorrhage and the Brugada pattern.

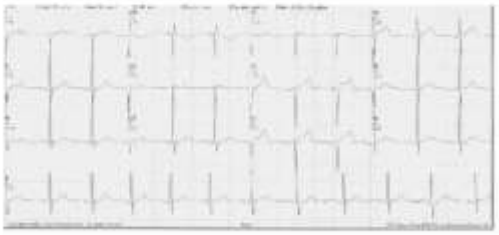

Figure 1
File format: JPEG. Title: 12-lead electrocardiogram. Description: This is the 12-lead electrocardiogram which clearly demonstrates the striking ST-segment elevation in leads V2 and V3.

Three aspects are important in the discussion of this case:

Firstly, Loukas et al [9] divided false tendons into five categories, according to the site of implantation. Ker [10] described a sixth type of false tendon where the specific location is between the subaortic portion of the interventricular septum and the left ventricular free wall. Six cases were described and in all of them a striking, localized ventricular, hypertrophic response was present at the site of subaortic implantation. This condition was named "false tendon-induced subaortic hypertrophy" and it was proposed as a new variant of hypertrophic cardiomyopathy [10]. This case clearly belong to this sixth group of false tendons with a clear subaortic implantation location.

Secondly, repolarization changes in leads V1–V3 can be associated with Brugada syndrome. This case does not fulfill the criteria for Brugada syndrome [11]: Three ECG patterns for Brugada syndrome have been identified but only a "coved" or type I ECG segment elevation is presently considered diagnostic for the disease [11]. The other crucial aspect in the diagnosis of Brugada syndrome is the criterion for structurally normal hearts [11]. This case clearly does not demonstrate a structurally normal heart, as it demonstrates the false tendon-induced subaortic hypertrophy variant of hypertrophic cardiomyopathy. In order to accept a type II ECG ("saddle-back" elevation) as Brugada syndrome one needs genetic confirmation with a structurally normal heart [11].

Thirdly, hypertrophy is a mechanism (or response) of the heart to reduce stress on the ventricular wall [10]. It has been shown that mechanical stress on the ventricular wall can elicit a wide variety of auto-and paracrine responses, leading to the local secretion of a wide variety of growth factors, such as endothelin 1, angiotensin II and insulin like growth factor [10]. Therefore, scientifically it is clearly conceivable that a false tendon inserting itself in a subaortic location, will cause a localized stretch response at the implantation site and leading in some instances to a localized, hypertrophic response, as shown before [10]. It is therefore quite plausible that the localized, septal hypertrophic response is the reason for the observed repolarization changes.

In conclusion, a case report is presented of a young, healthy man with a "saddle back" ST-elevation of the precordial leads. The cause for this phenomenon is the sixth type of

false tendon, the subaortic false tendon [10] leading to a localized hypertrophic response. It is proposed that this is a totally benign phenomenon and that care should be taken in the young, healthy patient not to confuse this entity with serious disorders, like the Brugada syndrome.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The author declares that they have no competing interests.

Additional material

Additional file 1

Parasternal long axis view of muscular tendon. *This is a movie clip of the parasternal long axis view of the sub-aortic muscular tendon, attached to the interventricular septum.*

Click here for file

[http://www.biomedcentral.com/content/supplementary/1476-7120-7-13-S1.avi]

Additional file 2

Apical origin. *This image shows the apical origin of the muscular tendon.*

Click here for file

[http://www.biomedcentral.com/content/supplementary/1476-7120-7-13-S2.bmp]

Additional file 3

Muscular nature. *Image clearly demonstrates the muscular nature of the tendon.*

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[http://www.biomedcentral.com/content/supplementary/1476-7120-7-13-S3.bmp]

Additional file 4

Short axis view. *Short axis image. Note the localized hypertrophic response at the septal area of implantation.*

Click here for file

[http://www.biomedcentral.com/content/supplementary/1476-7120-7-13-S4.bmp]

Additional file 5

Localized hypertrophy. *Movie clip demonstrating the localized, hypertrophic response at the site of septal implantation.*

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[http://www.biomedcentral.com/content/supplementary/1476-7120-7-13-S5.avi]

Additional file 6

Septal implantation. *Image clearly showing the septal implantation of the muscular tendon.*

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[http://www.biomedcentral.com/content/supplementary/1476-7120-7-13-S6.bmp]

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Case report

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The subaortic tendon as a mimic of hypertrophic cardiomyopathy

James Ker

Address: Department of Physiology, University of Pretoria, Pretoria, South Africa, PO Box 24318, Gesina, Pretoria, South Africa 0031

Email: James Ker - jker@wol.co.za

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Abstract

Originally described by Brock and Teare, today hypertrophic cardiomyopathy is clinically defined as left (or right) ventricular hypertrophy without a known cardiac or systemic cause, such as systemic hypertension, Fabry's disease or aortic stenosis.

Also appreciated today is the enormous genotypic and phenotypic heterogeneity of this disease with more than 300 mutations over more than 24 genes, encoding various sarcomeric, mitochondrial and calcium-handling proteins, all as genetic causes for hypertrophic cardiomyopathy.

Phenotypically, the disease can vary from negligible to extreme hypertrophy, affecting either the left and/or right ventricle in an apical, midventricular or subaortic location.

Left ventricular false tendons are thin, fibrous or fibromuscular structures that traverse the left ventricular cavity. Recently, a case report was presented where it was shown that such a false tendon, originating from a subaortic location, was responsible for striking ST-segment elevation on the surface electrocardiogram.

In this case report, a case is presented where such a subaortic tendon led to the classic echocardiographic appearance of hypertrophic cardiomyopathy, thus in the assessment of hypertrophic cardiomyopathy, this entity needs to be excluded in order to prevent a false positive diagnosis of hypertrophic cardiomyopathy.

Introduction

Hypertrophic cardiomyopathy (HCM) was first described in 2 publications between 1957–1959 by Brock [1-3]. During this period Teare [1,4] also described the entity of asymmetrical septal hypertrophy in 8 autopsy cases.

HCM is the most prevalent genetic cardiovascular disease, as it affects one in 500 individuals and exhibits enormous genotypic and phenotypic heterogeneity [5].

Phenotypically, hypertrophy can vary from negligible to extreme – similarly fibrosis and myocyte disarray can also range from negligible to extreme [5]. This phenotypic variation is the result of the vast array of mutations present in the family of HCM [5].

These mutations can be inherited (familial) or can occur de novo (sporadic) [6].

Currently, more than 300 mutations, which are scattered over more than 24 genes are known as causes for HCM [5]. These involved genes encode various proteins of the sarcomere, mitochondria and the calcium-handling apparatus [5]. Sarcomeric mutations can affect the thick myo-

filament (beta-myosin heavy chain, regulatory myosin light chain and essential myosin light chain), the intermediate myofilament (myosin binding protein C) or the thin myofilament (cardiac troponins T and I, alpha-tropomyosin and actin) [5].

It is thus no wonder that the clinical presentation can range from apical hypertrophy, mid-ventricular hypertrophy, concentric hypertrophy and subaortic hypertrophy of the left and/or right ventricle [1,5-10].

Of all these variants, hypertrophic obstructive cardiomyopathy (HOCM) is the variant that has been studied the most [8]. In this entity (previously known as idiopathic, hypertrophic, subaortic stenosis) asymmetrical, septal hypertrophy is accompanied by the following three elements [8]: systolic anterior motion (SAM) of the anterior leaflet of the mitral valve; a left ventricular outflow tract (LVOT) gradient and mitral regurgitation.

Left ventricular false tendons are thin, fibrous or fibromuscular structures that traverse the left ventricular cavity and they may be single or multiple [11]. Recently, it was demonstrated that such a left ventricular false tendon, attached to the subaortic portion of the interventricular septum, led to striking ST-segment elevation on the surface electrocardiogram [12]. In this case report another possible diagnostic pitfall that can arise due to the presence of a subaortic tendon is presented.

Case report

A case report is presented where it is shown that a left ventricular false tendon, when attached to the subaortic portion of the interventricular septum – a subaortic tendon – can mimic the echocardiographic appearance of hypertrophic cardiomyopathy.

A 30-year old Caucasian male was referred for a cardiovascular examination by his primary care physician. The clinical reason for the referral was the presence of a soft, subaortic midsystolic murmur (Levine grade I). The patient was totally asymptomatic and no previous medical or surgical problems were present. Clinical examination confirmed the grade I, subaortic, midsystolic murmur. The rest of the clinical examination was normal.

Echocardiography demonstrated a classical parasternal long axis picture of hypertrophic cardiomyopathy, with the phenotype of subaortic hypertrophy (see additional file 1, 2, 3 and 4). However, no systolic anterior motion of the mitral valve (SAM) and no left ventricular outflow tract gradient were present.

However, further examination revealed the presence of a big, muscular, subaortic tendon, running parallel to the interventricular septum and giving the false impression of hypertrophic cardiomyopathy. See additional file 2 demonstrating this muscular tendon clearly as a separate structure.

Discussion

The echocardiographic assessment of ventricular hypertrophy is an extremely important component of the cardiovascular examination and it is also one of the most difficult clinical scenario's because of the vast array of pathologies, each one with a different prognosis.

Shapiro *et al* [13] performed a prospective, echocardiographic examination to determine the prevalence of localized, subaortic hypertrophy in 1000 consecutive patients presenting for a routine echocardiographic examination. They excluded patients with hypertrophic cardiomyopathy and 8 cases of such localized, subaortic hypertrophy were found. In their series, localized subaortic hypertrophy was diagnosed when the subaortic septum was 50% thicker than the mid-point of the septum.

Numerous diseases can lead to secondary left ventricular hypertrophy, which may then imitate hypertrophic cardiomyopathy [14] Jategaonkar *et al* described a case of HCM, with all the components of HOCM – asymmetric septal hypertrophy, SAM and mitral regurgitation – which turned out to be all due to an underlying pheochromocytoma [14]. Another important condition to exclude when localized, subaortic hypertrophy is found is hyperparathyroidism, as it has been shown that this condition is another important mimic of hypertrophic cardiomyopathy [15]. In the analysis of so-called "hypertrophic cardiac syndromes", they are often distinguished from one another by features such as: valvular abnormalities, outflow tract obstruction, electrocardiographic patterns, the presence or absence of diastolic dysfunction, as well as the degree and pattern of ventricular hypertrophy [16].

Amyloidosis causes the accumulation of amyloid in the myocardial interstitium and this process ultimately leads to a ventricle with a firm, rubbery consistency and ventricular hypertrophy [16]. Two-dimensional strain is a unique imaging mode that permits the objective analysis of myocardial motion throughout the entire cardiac cycle [16]. Sun *et al* [16] studied the ability of two-dimensional strain to assess global and regional function in patients with amyloidosis, hypertrophic cardiomyopathy and hypertrophy due to hypertension. They were able to demonstrate that patients with "amyloid cardiomyopathy" had significantly lower myocardial deformation as seen by two-dimensional strain imaging than patients with hypertrophic cardiomyopathy and hypertensive hypertrophy. Thus, two-dimensional strain imaging can be added

to the armamentarium of the echocardiographer in the assessment of idiopathic ventricular hypertrophy.

Another good example of how a meticulous echocardiographic examination can detect the presence of a specific and unusual cause for severe ventricular hypertrophy, is Fabry's disease – an X-linked metabolic storage disease where glycosphingolipid accumulates in the myocardium and other tissues, due to deficient activity of the enzyme alpha-galactosidase A [17]. The endocardium in Fabry's cardiomyopathy has a peculiar binary appearance, detectable by transthoracic echocardiography [17].

Thus, it is clear that not all cases of subaortic hypertrophy are due to hypertrophic cardiomyopathy.

This case report adds another mimic of hypertrophic cardiomyopathy to the list – that of the muscular subaortic tendon.

Authors' contributions

James Ker is the sole author

Competing interests

The author declares that they have no competing interests.

Additional material

Additional file 1

Parasternal long axis view. *This is a movie clip, demonstrating the classical echocardiographic picture of the subaortic hypertrophy variant of hypertrophic cardiomyopathy (HCM).*

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[http://www.biomedcentral.com/content/supplementary/1476-7120-7-31-S1.avi]

Additional file 2

Closer view of subaortic tendon. *This is a closer view of the basal interventricular septum. The thick, muscular subaortic tendon is clearly visible as a separate structure, giving the initial impression of hypertrophic cardiomyopathy.*

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Additional file 3

Parasternal long axis view. *Another movie clip, once again from the parasternal long axis view, demonstrating the subaortic hypertrophy.*

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Additional file 4

Subaortic hypertrophy. *Note the appearance of severe, subaortic hypertrophy.*

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Structural Causes of Right Bundle Branch Block—Time for a Closer Look?

James Ker*

Department of Physiology, University of Pretoria, Pretoria, South Africa, PO Box 24318, Gesina, Pretoria, South Africa, 0031

Abstract: Right bundle branch block is an electrocardiographic phenomenon with specific criteria.

Currently, two specific forms of right bundle branch block are acknowledged, a proximal and a distal variant. A vast array of pathologies can cause proximal, distal or even combined forms of right bundle branch block.

In this study it is suggested that a third type of right bundle branch block exist: one caused by a subaortic muscular tendon in the left ventricle, leading to an increased velocity of conduction in the left ventricle, with a resultant "relative" right bundle branch block. It is concluded that it is necessary (and time) to take a closer look at endoventricular structures in the assessment of structural causes of right bundle branch block.

Keywords: Right bundle branch block, subaortic, tendon, structural.

INTRODUCTION

Right bundle branch block (RBBB) is an electrocardiographic phenomenon with specific criteria [1, 2]: QRS duration > 120 msec; broad and/or notched R waves (rsr`, rsR` or rSR` pattern) in the right precordial leads (leads V1 and V2) and wide and/or deep S waves in leads I and V6.

RBBB is the electrocardiographic reflection of delayed conduction in the right ventricle, caused by sclerosis (Lenegre's disease), fibrosis (Lev's disease) or necrosis of the right bundle branch [3, 4]. Recently, Shah *et al.* [5] described a case of a septal branch aneurysm which caused a right bundle branch block by causing direct pressure on the right bundle branch near it's subendocardial course on the right ventricular side of the interventricular septum.

It has been established that there are two forms of RBBB [6-8]: In the first, there is interruption of conduction in the main right branch of the bundle of His—termed proximal RBBB and in the second, conduction in the terminal ramifications of the right bundle branch are delayed—termed distal RBBB or arborisation block.

Interestingly, it has been shown that the clinical examination can guide the clinician to distinghuish between proximal and distal RBBB [6, 9]. Brooks *et al.* [9] demonstrated echophonocardiographically that in patients with proximal RBBB the time interval between mitral valve and tricuspid valve closure was prolonged, whereas in patients with distal RBBB the time delay is between tricuspid valve closure and pulmonary valve opening.

In this study a third cause of RBBB is proposed—neither proximal, nor distal, but one caused by increased conduction to the left ventricle by a subaortic muscular tendon in this way causing a "pseudo" RBBB.

*Address correspondence to this author at the Department of Physiology, University of Pretoria, Pretoria, South Africa, PO Box 24318, Gesina, Pretoria, South Africa, 0031; Tel: +2712-3430078; Fax: +2712-3430079; E-mail: jker@wol.co.za

MATERIALS AND METHODS

This was a prospective, observational study. A total of 880 patients who presented for a cardiovascular examination were examined for the presence of right bundle branch block (RBBB). 880 patients were screened. The number of patients amounted to 880, due to the study protocol stipulating a time period of 6 months for enrollment.

All patients with RBBB with any history of structural heart disease and/or myocardial infarction were excluded from the study.

RESULTS

A total of 11 patients with RBBB were found. In this group of 11 patients 6 had a history of myocardial infarction and were excluded from the study. 2 of the remaining 5 had no detectable structural anomaly of the heart. However, in 3 of these 5 patients (Figs. **1**, **2**, **3**) a peculiar muscular tendon extended between the subaortic portion of the interventricular septum and the left ventricular apex (Figs. **4**, **5**, **6**).

DISCUSSION

Anatomically, the right bundle is composed of a single group of fibres which arborises only at the periphery [6]. Current physiological evidence demonstrates that the electrocardiographical pattern of RBBB is identical in both proximal and distal interruptions (block) of the right-sided His-Purkinje network [6, 10-12]. It has been shown that interruption of the proximal portion of the right-sided His-Purkinje network leads to a delay in the onset of right ventricular contraction (manifesting clinically as a delay between tricuspid and mitral valve closure) with a normal subsequent sequence of right ventricular contraction,

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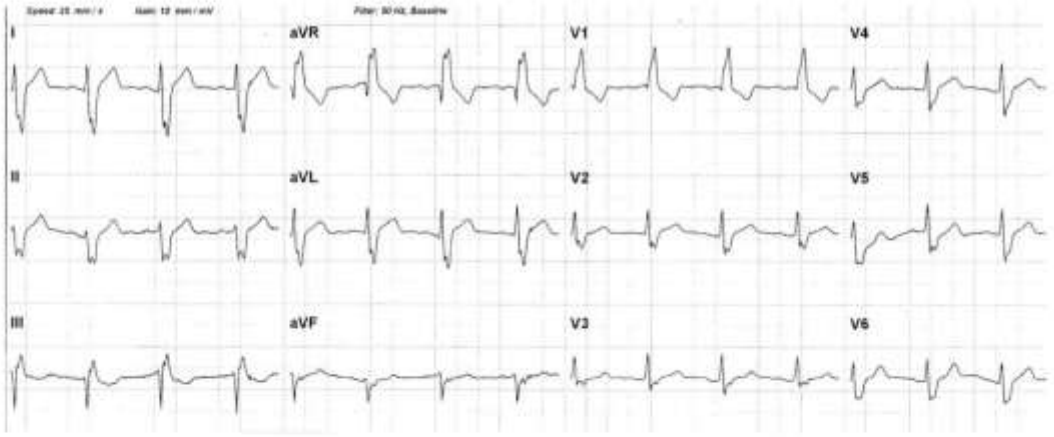

Fig. (1). The ECG clearly demonstrates a right bundle branch block.

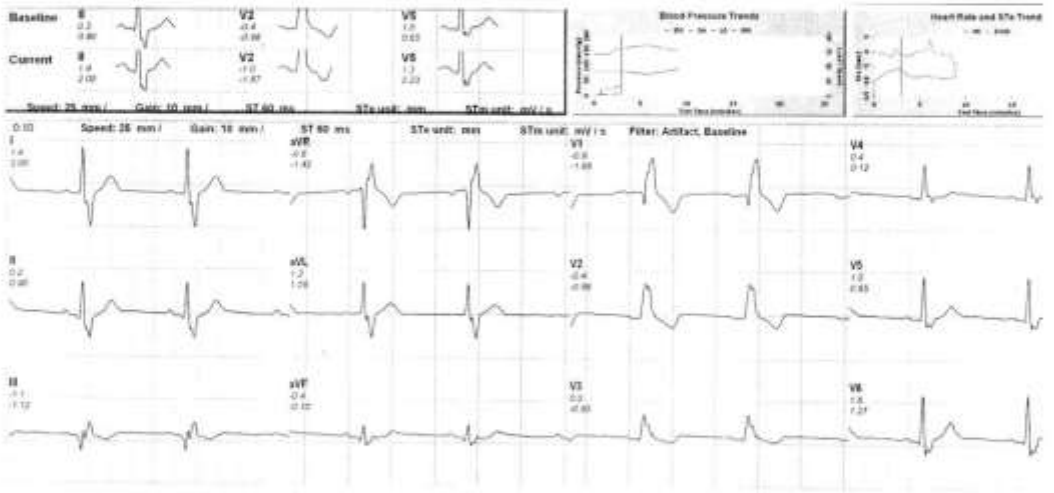

Fig. (2). Right bundle branch block is present.

whereas a distal block (disease affecting the distal branches of the His-Purkinje network) will cause asynchronous contraction of the right ventricle, thus slowing the rate of rise of pressure in the right ventricle, without delaying its onset, manifesting as a delay in the opening of the pulmonary valve[6, 10-12].

Combined disease is also possible in the same patient, with generalized disease affecting the right-sided conduction system, causing both proximal and distal RBBB [6].

Prognostically, it has been shown that this distinction is important, as proximal block caused by a single, localized lesion has an excellent long-term prognosis, whereas distal block caused by diffuse disease may be a manifestation of a progressive process [6, 13].

In this study, it is proposed that there exists a third type of right bundle branch block—neither proximal, nor distal, but one caused by an increased velocity of conduction to the left ventricle, effected by a muscular sub-aortic tendon coursing between the sub-aortic portion of the interventricular septum and the apex of the left ventricle, in this way leading to a "relative" RBBB as conduction in the right ventricle lags behind the increased conduction in the left ventricle.

Physiologically, this third type of RBBB behaves as a proximal block, with a delay in right ventricular contraction, manifested by a delay between mitral and tricuspid valve closure. This is not the first electrocardiographic

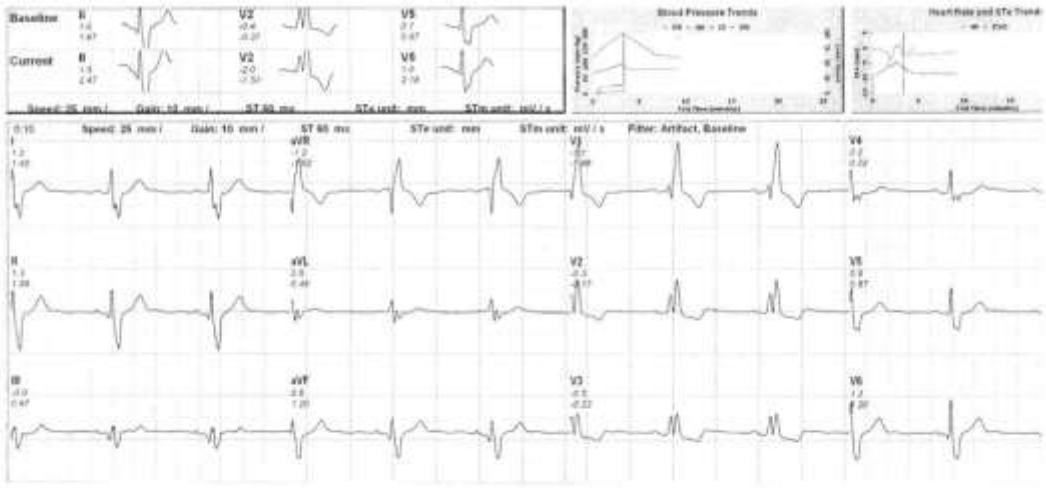

Fig. (3). Right bundle branch block is present.

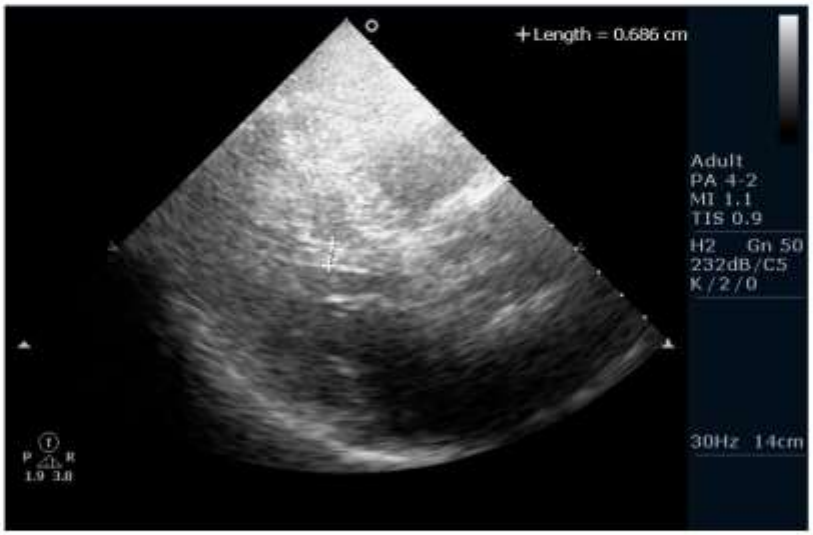

Fig. (4). Parasternal long axis view from patient 1, demonstrating the muscular subaortic tendon, arising from the subaortic area and implanting in the apex of the left ventricle.

manifestation of muscular, sub-aortic tendons: Ker [14] demonstrated that such a tendon can be responsible for striking ST-segment elevation on the electrocardiogram.

The electrocardiographic feature shared by all three these cases is a broad and notched R wave in lead aVR (Figs. **1**, **2** and **3**). Furthermore, they also share a deep and notched S wave in leads I, II, aVL and V4, 5 and 6 with a broad R wave in lead V1.

The echocardiographic feature (Figs. **4**, **5** and **6**) is that of a thick and muscular band or tendon like structure extending from the subaortic area to the left ventricular apex. These muscular tendons are different from the widely known thin tendon like structures as they appear much thicker and they always extend from the subaortic region to the left ventricular apex. As stated before they have been shown to be a cause of ST segment elevation [14] and recently

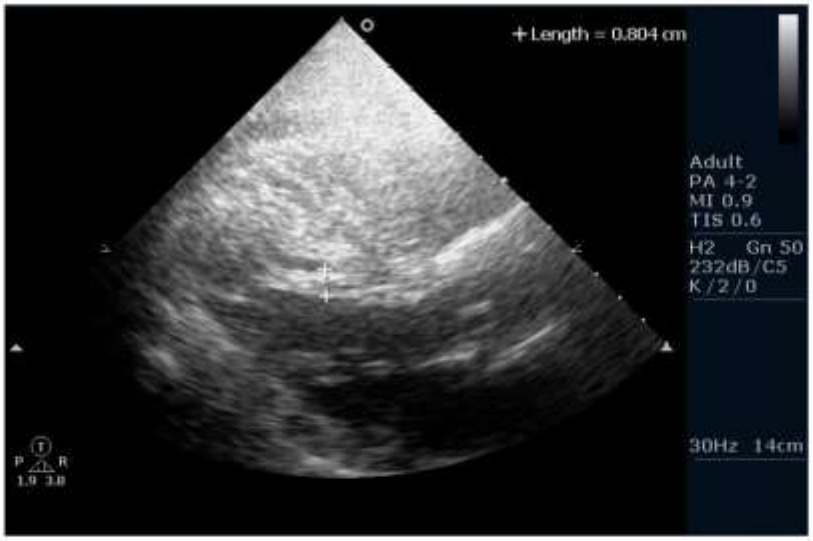

Fig. (5). Subaortic tendon in patient 2.

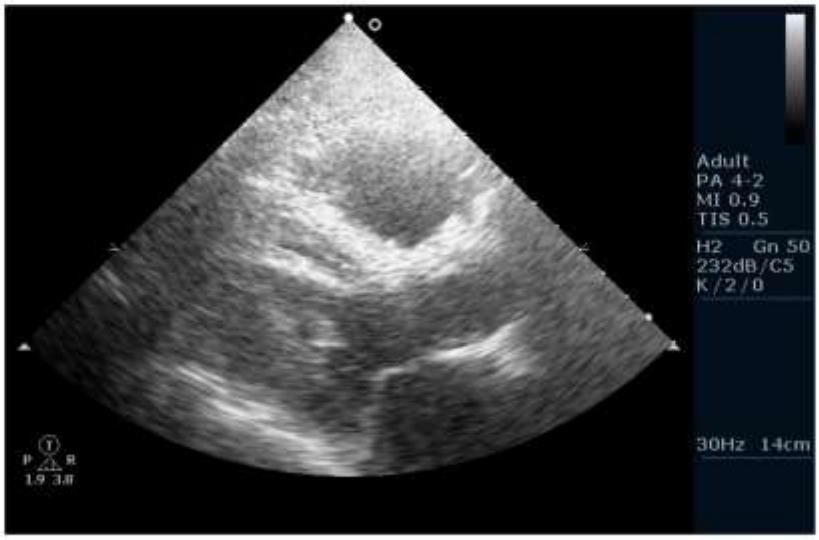

Fig. (6). Subaortic tendon in patient 3.

they have been shown to mimic hypertrophic cardiomyopathy [15].

Thus, in the assessment of structural causes for right bundle branch block it is suggested that it is time to take a closer look at endoventricular structures and specifically at muscular structures traversing the cavity of the left ventricle. Based on the demonstrated electrocardiograms it is suggested that a broad and notched R wave in lead aVR in patients with RBBB may serve as an electrocardiographic clue for an underlying endoventricular cause of RBBB.

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Clinical Medicine Insights: Cardiology

ORIGINAL RESEARCH

Subaortic (Type 6) Muscular Band—Innocent Bystander or Pathologic Structure?

J Ker

Department of Physiology, University of Pretoria, Gesina, Pretoria, South Africa.
Correspondence author email: jker@wol.co.za

Abstract: Intraventricular tendons are structures that was identified more than a hundred years ago. It has been suggested that they represent intracavitary radiations of the bundle of His and that they may be an isolated finding or be associated with structural cardiac abnormalities.

Loukas et al divided these structures into five categories and recently a sixth type have been added.

Various physiological disturbances have been observed due to the sixth type of tendon, such as ST segment elevation and right bundle branch block. It has been noted that this peculiar structure appears too thick to be called a tendon, thus the term band.

This retrospective analysis analyzed the incidence of the thick, subaortic (type 6) muscular band in a cardiovascular clinic.

Keywords: subaortic, band, type 6

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Introduction

Intraventricular tendons was first observed 115 years ago.[1] They are usually thin, fibrous or fibromuscular structures that traverse the left ventricular cavity.[2] They may be single or multiple and have no connection to the valvular cusps.[2]

False tendons can be an isolated finding or can be associated with cardiac abnormalities.[3]

Loukas et al[4] examined 200 formalin fixed, adult hearts and divided false tendons into five categories: In type I the false tendon is located between the posteromedial papillary muscle and the ventricular septum. In type II the false tendon is located between the two papillary muscles. In type III the false tendon is located between the anterolateral papillary muscle and the ventricular septum. In type IV the false tendon is located between the ventricular septum and the free wall. In type V the false tendons appear weblike and have three or more points of insertion.

After careful histological examination Abdulla et al[3] suggested that false tendons may be intracavitary radiations of the bundle of His and that their clinical significance may be more relevant than previously believed and merits further study.

Recently, various physiological effects due to a newly observed thick, subaortic muscular band have been described.[5–7]

The purpose of this study was to describe the incidence of this peculiar new type of muscular band in a cardiovascular clinic.

Methods

This study was a retrospective analysis. A total of 4900 adult echocardiograms, performed between 2004 and 2010 for various clinical indications—ranging from hypertension to cardiac murmurs and dyspnoea—were reviewed and analyzed for the presence of a left ventricular muscular band in the subaortic position.

Results

A total of 376 adult echocardiograms clearly demonstrated the presence of a muscular structure, located between the left ventricular inferior wall and the subaortic interventricular septum (see Figure 1 and 2 and movie clip 1 and 2). In all of these cases a striking local ventricular hypertrophic response was present at the site of septal implantation. In some of these cases the local hypertrophic response even mimics the echocardiographical appearance of hypertrophic cardiomyopathy[6] (see movie clip 1).

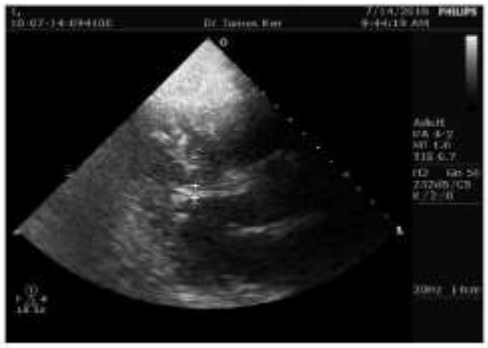

Figure 1 Parasternal, long-axis echocardiographical image, depicting a thick subaortic, muscular band, marked with X.

Discussion

A peculiar muscular structure, too thick in appearance to be called a tendon, extending between the subaortic portion of the interventricular septum and the inferior left ventricular wall is identified in this study. A striking feature is a localized area of ventricular hypertrophy at the site of subaortic implantation of the muscular structure.

Among these 376 patients with the muscular subaortic band present, the following physiological effects have been observed: ST-segment elevation of the anterior electrocardiographic leads, mimicking acute myocardial infarction,[4] echocardiographical mimicking of hypertropic cardiomyopathy[5] and right bundle branch block.[6]

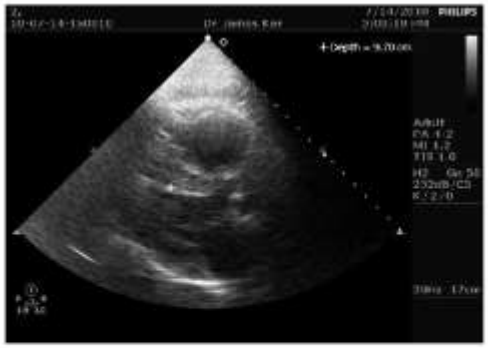

Figure 2 Another example of a thick subaortic muscular band, marked with X.

It has been proposed before that this muscular, subaortic band may represent a sixth type of ventricular false tendon.[8] The current clinical implication of the presence of this peculiar intracardiac structure is that it may mimic cardiac disease, such as myocardial infarction or Brugada syndrome in the case of ST segment elevation,[5] it may lead to the erroneous diagnosis of hypertrophic cardiomyopathy if the echocardiographer is not vigilant[6] and recently it has been described that a third type of right bundle branch block may result due to the presence of such a subaortic muscular band.[7]

Disclosures

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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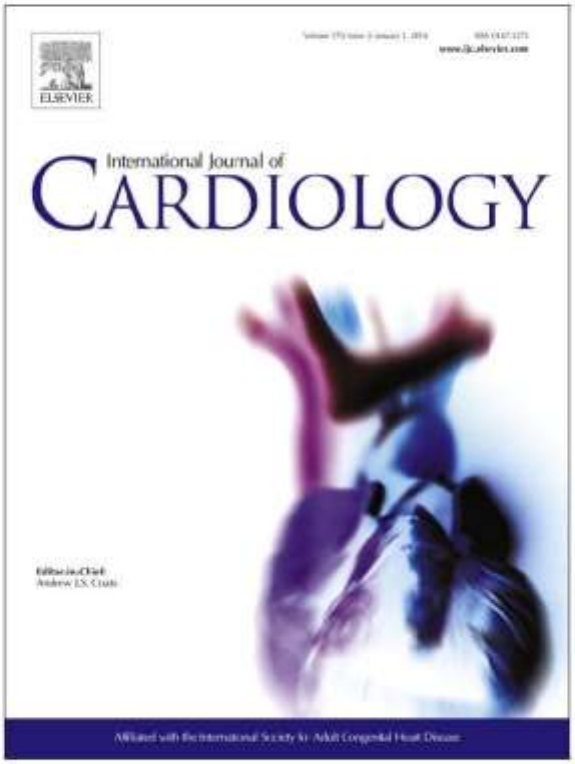

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Letter to the Editor

Hemochromatosis and the heart—Heavier than iron?

James Ker *

University of Pretoria, Department of Genetics, Hobday 36, Silver Lakes, Pretoria, Gauteng 0031, South Africa

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Recently a fascinating observation on increased height in HFE hemochromatosis was made by Cippa and Krayenbuehl [1]. The authors assessed height in a cohort of 176 patients with HFE hemochromatosis in Switzerland and they found that men with hemochromatosis were on average 4.3 cm taller than their reference population without hemochromatosis—in women the difference in height was 3.3 cm in those with versus those without hemochromatosis [1]. Note that all these patients were homozygous for C282Y (93%) or compound heterozygotes for C282Y-H63D (7%) and thus they all had hemochromatosis with iron overload.

Classic, hereditary hemochromatosis is an autosomal recessive iron overload disease due to mutations of the HFE gene, located on chromosome 6 [2]. In most cases the culprit mutation is C282Y, which may have originated in a Celtic (Viking) ancestor more than 2000 years ago [2]. Other, less common mutations are H63D and S65C [2].

The major-histocompatibility complex class I-like protein, HFE, affected by these mutations, has an ancestral peptide-binding groove that is too narrow for antigen presentation, but importantly it now seems that HFE might bind to other (as yet uncharacterized) proteins [2].

Recently, a subaortic muscular band inside the left ventricle with physiological sequelae have been described [3–5]. A total of 85 such patients were collected and screened for the three HFE mutations. Out of a total of 85 such patients 69 (81%) were heterozygous for one of these mutations. None of these patients had iron overload as may be expected in heterozygotes, as hemochromatosis is an autosomal recessive disease. Figs. 1 and 2 are examples of such subaortic muscular structures, observed in this series.

In the series by Cippa and Krayenbuehl all of the patients had verified iron overload and the authors attribute the increased height in these patients to a constantly enhanced iron supply during physical development [1]. However, one has to ask if this enhanced growth effect is really simply due to iron supply? As stated before HFE has an ancestral peptide binding groove too narrow for antigen presentation, but might bind to other proteins [2]. It is plausible that a mutated HFE might lead to some as yet uncharacterized cellular effect enhancing both skeletal and myocardial growth.

It is therefore suggested that it may be worthwhile to explore the concept that this mutated protein (HFE) may exert cellular effects far beyond that of iron absorption, such as causing myocardial growth/hypertrophy.

Will hemochromatosis in the future turn out to be heavier than iron in the human heart?

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* Tel.: +27 827897661; fax: +27 128090358.
E-mail address: jker@vetl.co.za.

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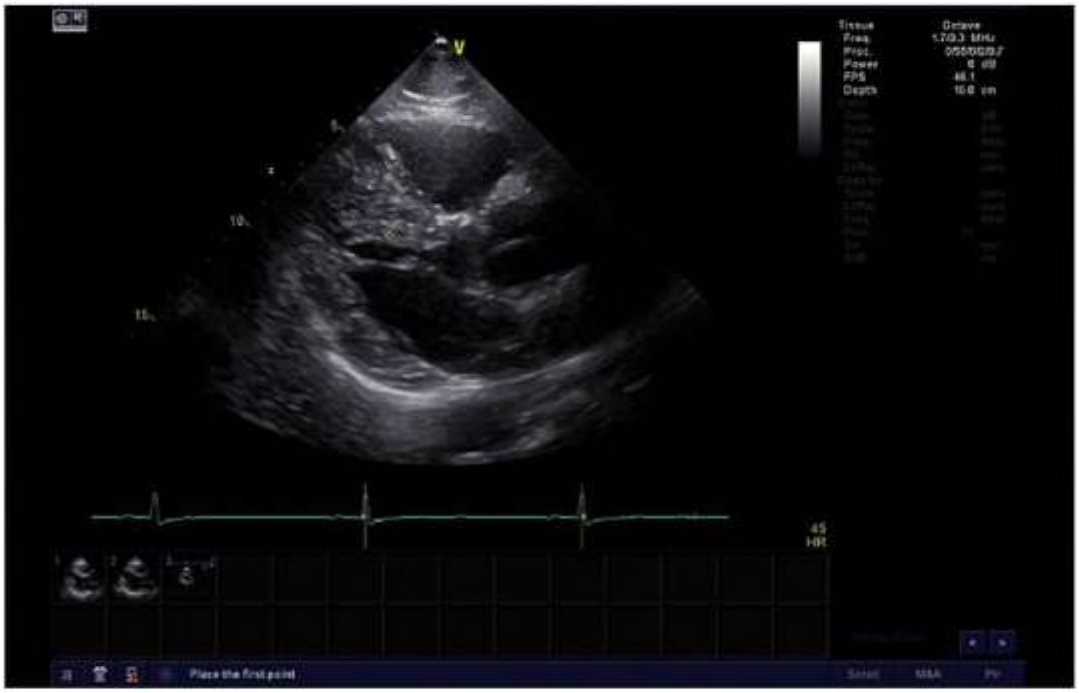

Fig. 1. Note the subaortic, muscular structure, marked with * in this patient heterozygous for the H63D mutation.

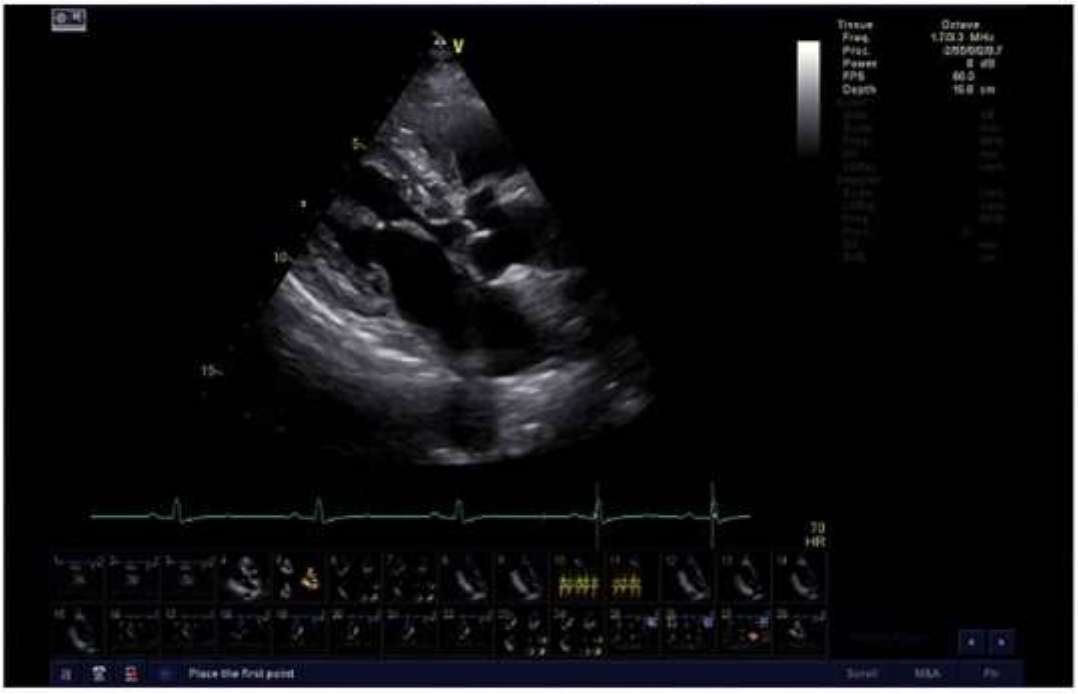

Fig. 2. Another example of a subaortic, muscular structure with a slightly different phenotype in another patient heterozygous for the H63D mutation.

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A new phenotypic marker of hypertrophic cardiomyopathy

"Life is a great bundle of little things."

Oliver Wendell Holmes (1809–94)

Hypertrophic cardiomyopathy (HCM) is a common cardiac disorder associated with sudden cardiac death, characterised by an unexplained increase in left ventricular wall thickness or mass.[1–3] The prevalence is about one in 500 of the general population, affecting men and women of all ages and ethnic backgrounds[2,3] who present with ventricular hypertrophy, left-ventricular outflow tract obstruction, heart failure, and potentially lethal arrhythmias.[4]

More than 1000 mutations in at least nine genes cause HCM.[4] The majority are missense alleles, encoding so-called poison peptides—dominant-negative, mutant peptides—which adversely affect cardiac sarcomere function.[4] Some mutations might also result in insufficient protein for normal function. The advent of cardiac imaging and genetic testing identified two distinct phenotypes, hypertrophic and non-hypertrophic HCM.[3] However, non-hypertrophic HCM is not equivalent to phenotype-negative HCM, as various non-hypertrophic stigmata of classic HCM are often present in genotype-positive, phenotype-negative patients.[3] These stigmata include redundant mitral valve leaflets, myocardial crypts, and anomalous papillary muscle insertions into the anterior mitral valve leaflet.[3] Individuals can express the hypertrophic phenotype as late as the sixth or seventh decade[3] and thus by identifying these stigmata HCM can be diagnosed before the development of classic ventricular hypertrophy, and appropriate management planned. Sudden cardiac death is a major concern in these patients, especially the young,[3] and identifying the phenotype can thus lead to recommendations on participation in competitive sports and interventions ranging from beta blockers to implantable cardioverter defibrillators.

Recently, Christiane Gruner and colleagues[6] described distinctive apical–basal muscle bundles in the hearts of HCM patients, as well as in genotype-positive, phenotype-negative relatives. The study cohort consisted of 230 genetically and phenotypically confirmed HCM patients who underwent cardiovascular magnetic resonance imaging at three tertiary centres, with 30 genotype-positive, phenotype-negative family members and 126 control individuals also studied. An accessory left-ventricular muscle bundle was defined as a single band of muscle extending through the left-ventricular cavity from the apex to the basal septum or the anterior wall of the left ventricle.[6] Such apical–basal muscle bundles were present in 145 (63%) of 230 HCM patients, with similar proportions in patients younger than 20 years and in those older than 60 years. Bundles were also seen in 18 (60%) of 30 genotype-positive, phenotype-negative family members, and in 12 (10%) of 126 controls. Although no association could be found between the presence of muscle bundles and left-ventricular outflow tract obstruction, in 22 patients who required surgery for relief of obstruction removal was deemed necessary.

Gruner and colleagues' study[6] adds another useful morphological marker to aid in the clinical diagnosis of a common inherited cardiac disease. Although MRI provides a comprehensive assessment of intracardiac anatomy in HCM patients, no single anatomical observation can be deemed completely specific for the disease. However, adding accessory apical–basal left-ventricular muscle bundles to established anatomical signs of HCM, such as redundant mitral valve leaflets, myocardial crypts, and anomalous papillary muscle insertions, will add to clinicians' confidence in identification of HCM.

James Ker
Department of Internal Medicine, University of Pretoria, Pretoria 0001, South Africa
jker@wol.co.za

I declare no competing interests.

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Solitary Papillary Muscle Hypertrophy: A New Echo-Electrocardiographic Syndrome? A Case Report

J. Ker

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Solitary Papillary Muscle Hypertrophy: A New Echo-Electrocardiographic Syndrome?

A Case Report

J. Ker, MRCP (Edinburgh), PhD, *Pretoria, South Africa*

Hypertrophic cardiomyopathy is the term for a heterogeneous group of disorders for which various mutations of genes involving proteins of the cardiac sarcomere lead to hypertrophy of various segments of the left ventricle. The hypertrophy can involve the left and/or right ventricle, be symmetric or asymmetric, involving the septum, free wall, mid-ventricle, or apex. The phenomenon of solitary papillary muscle hypertrophy is rare with only 2 references in the literature. Furthermore, giant negative T and U waves are 2 common electrocardiographic phenomena in hypertrophic cardiomyopathy and have been attributed to hypertrophy of the posterior papillary muscle. Solitary hypertrophy of the anterior papillary muscle might be a new echo-electrocardiographic syndrome.

Introduction

Hypertrophic cardiomyopathy (HCM) is genotypically and phenotypically a highly heterogeneous disorder.[1-3] In this condition, various mutations in genes coding for proteins of the cardiac sarcomere manifest as left ventricular hypertrophy without obvious cause.[1-3] In the Familial Hypertrophic Cardiomyopathy Database, more than 150 mutations, scattered throughout 10 genes encoding proteins of the cardiac sarcomere, are listed as causes of HCM.[3] The phenotypic manifestation of HCM is equally diverse: the hypertrophy may affect the left and/or right ventricle and can be symmetrical or asymmetrical.[1] Septal hypertrophy is the most common type of asymmetrical hypertrophy, with midventricular and apical hypertrophy being less common.[3]

Kobashi et al[4] noted that patients can present with isolated papillary muscle hypertrophy and suggested that this is either a newly identified subtype of HCM or, alternatively, that this is simply an early form of HCM. In that same year (1998), Reddy et al[5] described a case of apical hypertrophic cardiomyopathy. However, Suwa

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From the University of Pretoria and Pretoria Heart Hospital, Pretoria, South Africa.

Correspondence: J. Ker, MRCP (Edinburgh), PhD, PO Box 24318, Gesina, Pretoria, South Africa 0031; e-mail: jker@wol.co.za.

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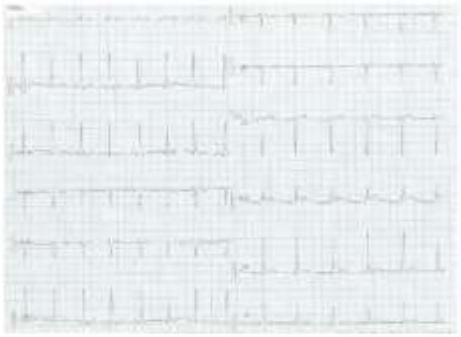

Figure 1. Twelve-lead electrocardiogram. Note the peculiar appearance of lead V4. There is notching of the QRS complex, ST elevation, and a prominent, positive U wave.

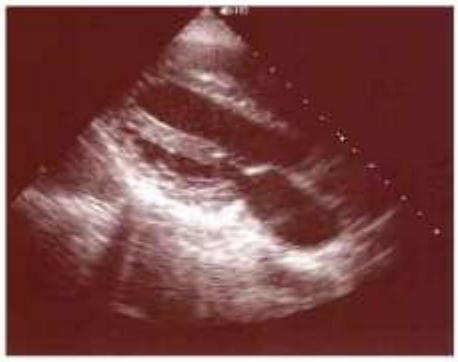

Figure 2. Echocardiogram: parasternal, long-axis view. Note the marked, isolated hypertrophy of the anterior papillary muscle.

and Kobashi[6] noted that the case actually had typical features of solitary papillary muscle hypertrophy. Since then, no case reports of solitary papillary muscle hypertrophy were found in the literature, and the question of whether this entity truly represents a subtype of HCM remains.

A 20-year-old Caucasian man was referred to our cardiology department because of an abnormal electrocardiogram (ECG) result (see Figure 1). The ECG revealed a peculiar pattern in lead V4: notching of the QRS complex with elevation of the ST segment and a prominent, positive U wave. The clinical examination, chest x-ray, blood urea nitrogen, full blood count, troponin-T, Pro–brain natriuretic peptide, and electrolyte levels were all normal.

Transthoracic, two-dimensional echocardiography revealed isolated hypertrophy of the anterolateral papillary muscle, with an otherwise normal left ventricle with no hypertrophy in any other segment (see Figure 2).

Giant negative T and U waves are two common electrocardiographic findings in HCM.[7] Hasegawa et al[7] reported 2 cases of HCM as a possible explanation for these electrocardiographic changes in HCM. In the first patient, giant negative T and U waves became evident only after the appearance of posterior papillary muscle hypertrophy, and in the second patient, these waves disappeared following posterior wall infarction, which involved the posterior papillary muscle.

In this case, a prominent, positive U wave was accompanied by ST elevation and notching of the QRS complex in lead V4, with marked hypertrophy of the anterior papillary muscle. Might this be the first of a new echo-electrocardiographic syndrome?

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Case Report

The U-wave and papillary muscle variants: revisiting an old association

JAMES KER

Summary

One of the earliest hypotheses on the origin of the U-wave was that these waves represent repolarisation of the papillary muscles and their neighboring structures. Various U-wave and TU-segment abnormalities have been described and ascribed to certain cardiac pathological conditions.

In this case report it is hypothesised that prominent U-waves in the inferior leads are caused by an accessory papillary muscle. Any possible long-term consequences are not known.

Department of Physiology, University of Pretoria, South Africa

JAMES KER, MRCP, PhD, FESC, FACC, jker@wol.co.za

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The U-wave, first described by Einthoven,[1] is still an electrocardiographic deflection of enigmatic origin. It is an additional low-amplitude wave that is sometimes visible after the T-wave. The U-wave is usually less than 0.1 mV in amplitude and normally has the same polarity as the preceding T-wave. It is usually best seen in the mid-precordial leads at slow heart rates.

The electrophysiological basis for U-wave generation is not certain. Any one (or more) of the following may be the cause of the U-wave: repolarisation of the papillary muscles,[2] repolarisation of the Purkinje fibers outlasting that of the contracting myocardium,[3] prolonged repolarisation in cells of the mid-myocardium – the 'M cells',[4] or after-potentials, caused by mechanical forces in the ventricular wall with termination of mechanical systole – the 'mechano-electrical feedback' hypothesis.[5]

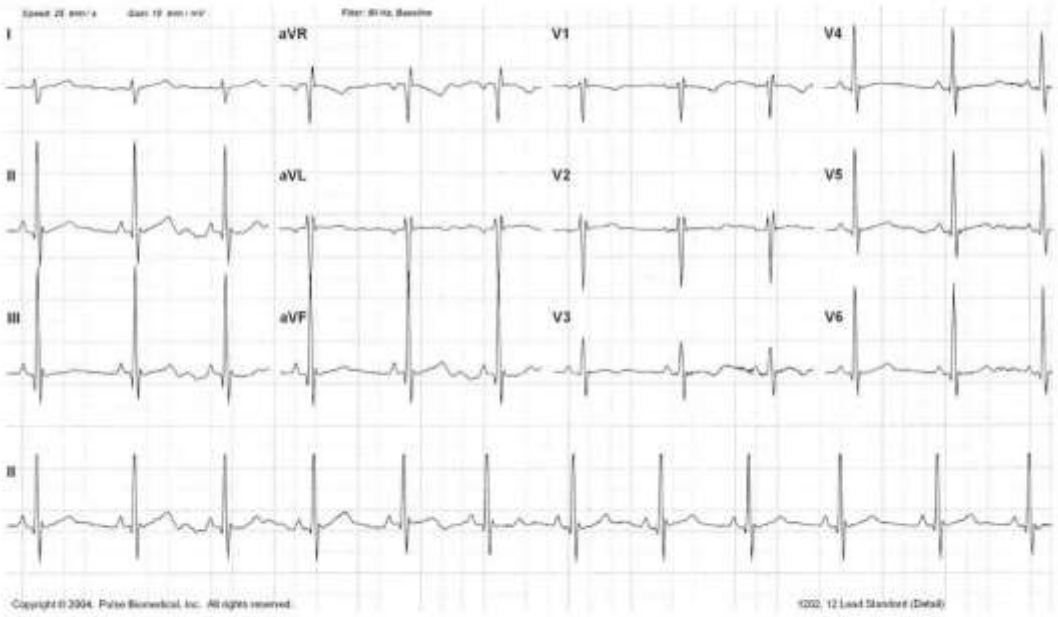

Fig. 1. Standard 12-lead electrocardiogram. Note the prominent U-waves in leads II, III and aVF. Interestingly, they are absent in the preceding beat with a longer R–R interval. A possible explanation for this phenomenon is the longer diastolic time with resultant increase in end-diastolic volume, leading to a greater degree of papillary muscle stretch with a possible augmentation of the U-wave of the following beat.

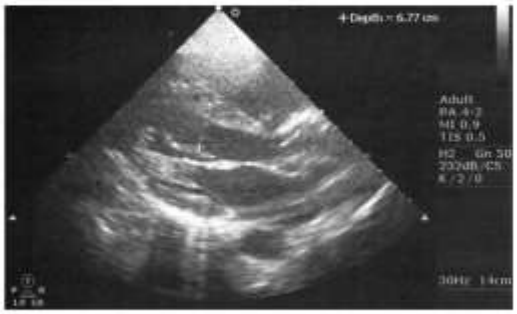

Fig. 2. This is the parasternal, long-axis view from a transthoracic echocardiogram. + marks the accessory papillary muscle. This accessory papillary muscle led to no obvious adverse sequelae. The mitral valve functioned normally and no intra-ventricular pressure gradient was present.

Recently, various primary abnormalities of the ventricular papillary muscles have been described.[6-10] These abnormalities include: haemangiomas,[6] solitary hypertrophy,[7] endodermal heterotopia (inclusion cysts),[8] papillary fibroelastoma,[9] and an octopus-shaped papillary muscle causing mid-ventricular obstruction.[10]

Ker[7] described a case of ST-elevation and QRS-notching with a prominent U-wave in lead V4 in a patient with solitary papillary muscle hypertrophy. Although the papillary muscle origin of the U-wave is only one of many theories (each one of them plausible but not conclusively proven), the current era in cardiology where echocardiography readily identifies variants (not necessarily pathological) of intra-ventricular structures is ideal for clinicians to try and correlate these variants with electrocardiographic changes.

Case report

A healthy 15-year-old girl was referred for a cardiovascular evaluation because of very prominent U-waves in the inferior leads of a 12-lead electrocardiogram (Fig. 1). She had no previous medical or surgical problems, clinical examination was normal and a comprehensive biochemical evaluation revealed no abnormalities.

Transthoracic echocardiography revealed a prominent accessory papillary muscle (Fig. 2). This accessory papillary muscle had no apparent functional consequences; the mitral valve functioned normally and no intra-ventricular pressure gradient was present.

Discussion

The U-wave is usually the most prominent in leads V2 or V3.[11] Two observations in this case merit discussion. Firstly, the prominent U-waves are noted in the inferior leads (II, III, aVF). It is therefore possible (and proposed) that in cases of prominent U-waves, which might be caused by accessory papillary muscles, that these U-waves will be noted only in the inferior leads. Therefore, it is proposed that the location of visible U-waves may be a clue to underlying papillary muscle variants.

Secondly, as is clearly visible in Fig. 1, the U-waves in leads II, III and aVF are seen in the beat following a beat with a longer R–R interval. It is proposed and hypothesised that this might be due to the following mechanism: The beat preceding the U-wave has a longer R–R interval, which will cause a longer diastolic interval, thus leading to a greater left ventricular end-diastolic volume and a consequently larger ejection fraction (Frank-Starling mechanism). This may cause a greater amount of papillary muscle stretch and torsion with a possible effect on the observed U-waves in the following beat. Therefore, this case report indirectly supports the mechano-electric feedback hypothesis for these visible U-waves and not repolarisation of the papillary muscles.

Lastly, it is hoped that this case report focuses attention on the possible correlation between a growing number of anatomical variants of the papillary muscles and possible variants of the U-wave, which might be identified on the standard 12-lead electrocardiogram.

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Cardiovascular Ultrasound

BioMed Central

Case report

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The accessory papillary muscle with inferior J-waves---peculiarity or hidden danger?

James Ker*[1] and Lorraine du Toit[2]

Address: [1]Department of Physiology, University of Pretoria, Pretoria, South Africa and [2]Department of Forensic Medicine, University of Pretoria, Pretoria, South Africa

Email: James Ker* - jker@wol.co.za; Lorraine du Toit - lorraine.dutoit@med.up.ac.za

* Corresponding author

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Abstract

Originally described in 1953, today the so-called J-wave is the source of much controversy. As a marker of so-called "early repolarization", this variant has been regarded as a totally benign variant since the 1960's. However, since then a wealth of data have indicated that the J-wave may be a marker of a highly arrhythmogenic substrate with a resultant high risk of sudden cardiac death.

In this case report a case of an accessory papillary muscle with a prominent J-wave is described. This may be the first of many possible cases where papillary muscle variants may be the cause of the J-wave.

Introduction

In 1953 the so-called "J-wave" was described by dr John Osborn (thus, also called the Osborn wave) [1]. This peculiar electrocardiographic deflection was initially described in experimental hypothermia--today realized as an "injury current" which is the result of the fact that hypothermia increases the epicardial potassium current relative to that in the endocardium during ventricular repolarization--this explains the risk of ventricular fibrillation in hypothermia [1].

However, another peculiar electrocardiographic pattern, known as "early repolarization" has been known for more than 60 years [2]. This electrocardiographic pattern is diverse [3], but all of it's variants have one characteristic in common: The "J-wave"--a characteristic slurring or notching, producing a positive hump, found at the junction of the end of the QRS complex and the beginning of the ST segment [2]. Until recently, this variant was considered benign [4] and epidemiologically is found in 2 to 5% of the population, usually in men, young adults, athletes and dark-skinned persons [2].

However, during the last decade, numerous publications appeared, describing J-waves in men with idiopathic ventricular fibrillation [5-10]. Basic electrophysiology have already suggested a critical role of the J-wave in the pathogenesis of idiopathic ventricular fibrillation [11]. Recently, Nam et al [12] examined the incidence of early repolarization among 1395 controls, representative of the general population, and 15 patients with idiopathic ventricular fibrillation. In these 15 patients with idiopathic ventricular fibrillation all known causes, including the long-and short QT-syndromes, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia have been excluded and 4 of these 15 patients presented with electrical storm (defined as four or more episodes of ventricular fibrillation in one day). Among the control group the incidence of early repolarization was 3.3% and among the idiopathic ventricular fibrillation group it was

a staggering 60% with all four patients with electrical storm having early repolarization [12]. Also recently, is the study by Ha ssaguerre [13] who found that 31% of 206 patients who were resuscitated after idiopathic ventricular fibrillation have early repolarization--as shown by the J-wave.

Thus, currently it is thought that early repolarization is not always benign as previously thought and that the J-wave is indicative of a highly arrhythmogenic substrate with a high risk of sudden death in some cases.

In this case report an accessory papillary muscle with inferior J-waves--corresponding to the area of the accessory papillary muscle--are shown. It is possible that this may be a uniquely newly discovered group of patients with J-waves.

Case report

A case report is presented which clearly demonstrates a J-wave in the inferior lead III on the electrocardiogram. An accessory, third papillary muscle is clearly present on the parasternal, short-axis view--corresponding to the area covered by the inferior lead III. It is suggested that this is a new phenotype of the J-wave--caused by accessory papillary muscles.

A 40-year old caucasian male was referred for a cardiovascular examination by his primary care physician due to a peculiar electrocardiogram. The patient was totally asymptomatic with no previous medical problems and the only previous surgical procedure was an appendicectomy. The patient sought medical advice from his primary care physician on yearly health screening tests as he recently reached the age of 40 years.

The clinical examination did not reveal any abnormalities. The electrocardiogram clearly demonstrated a J-wave in the inferior lead III. In addition, a bifid T-wave was present in lead III, consistent with electrocardiographic stigmata of early repolarization and in leads I and V2 striking ST-elevation was present (see additional file 1).

Echocardiography demonstrated an accessory (third) papillary muscle, clearly visible on both the parasternal long-axis (see additional file 2) and the parasternal short-axis view as a separate structure (see additional file 3 and 4).

Discussion

Various primary and secondary abnormalities of the ventricular papillary muscles has already been described [14]. These abnormalities include, hemangiomas, solitary hypertrophy, papillary fibroelastoma, inclusion cysts, inflammation in Takayasu's arteritis, isolated infarction, hypoplasia as part of ventricular non-compaction and the description of an octopus shaped papillary muscle, causing mid-ventricular obstruction [14]. A growing number of reports are focusing on the electrocardiographic effects of endoventricular structures [15,16].

As discussed, the J-wave is currently a topic of major interest as it is becoming increasingly plausible that this once benign thought marker of early repolarization may be indicative of a highly arrhythmogenic substrate with a high risk of sudden cardiac death.

As a possible anatomical explanation for the J-wave Boineau raised the possibility that the cause may be deep invagination of Purkinje fibers to the subepicardial level, which will result in increased transmural activation, followed by earlier repolarization [17].

This case report, showing a clear J-wave in the inferior lead III in association with an accessory papillary muscle, may be explained by one of two mechanisms: The accessory papillary muscle may be the endoventricular association of deep invagination of Purkinje fibers or the J-wave may be caused by the accessory papillary muscle itself. In light of the recently described arrhythmogenic associations of the J-wave, as discussed above, this case can be regarded as one with a high risk for idiopathic ventricular fibrillation and thus, sudden cardiac death. The whole spectrum of early repolarization consists of an elevation of the QRS-ST junction (the J-point), QRS notching or slurring (the J wave) and a tall, symmetric T-wave [4,12]. The only other published case report on an accessory papillary muscle with electrocardiographic effects is that of an asymptomatic and healthy 15-year old caucasian girl with prominent U-waves in the inferior leads of the electrocardiogram and an accessory papillary muscle, detected by transthoracic echocardiography [16]. It is quite plausible that the U-waves in that case may also represent repolarization abnormalities as the QRS-ST junction is often involved in repolarization abnormalities [4,12].

Therefore, the diagnostic implication for the echocardiographer is that the echocardiogram, which is an ideal diagnostic modality for the evaluation of endoventricular structures may also be utilized to assess the patient for the risk of idiopathic ventricular fibrillation and thus, sudden cardiac death.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JK and LD are the sole authors. JK performed the echocardiogram and electrocardiography. LD performed the literature search on the prognostic aspects of the J-wave. Both

authors participated in the design of the manuscript. JK wrote the case report. LD wrote the introduction and discussion.

Both authors read and approved the final manuscript.

Additional material

Additional file 1

Electrocardiogram depicting J-wave. *This is the 12-lead electrocardiogram, clearly demonstrating the J-wave in lead III. Also note the bifid T-wave and ST-segment elevation in leads I and V1-all possibly caused by the accessory papillary muscle.*

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[http://www.biomedcentral.com/content/supplementary/1476-7120-7-50-S1.jpeg]

Additional file 2

Parasternal, long-axis view. *This is the parasternal, long-axis view. Note the accessory papillary muscle, marked with +.*

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[http://www.biomedcentral.com/content/supplementary/1476-7120-7-50-S2.bmp]

Additional file 3

Parasternal, short-axis view. *This is the parasternal, short-axis view. The accessory papillary muscle is much clearer demonstrated as a separate structure, marked with +.*

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Additional file 4

Parasternal, short-axis view. *This is a movie clip from the parasternal, short-axis view, demonstrating the accessory papillary muscle as a separate structure.*

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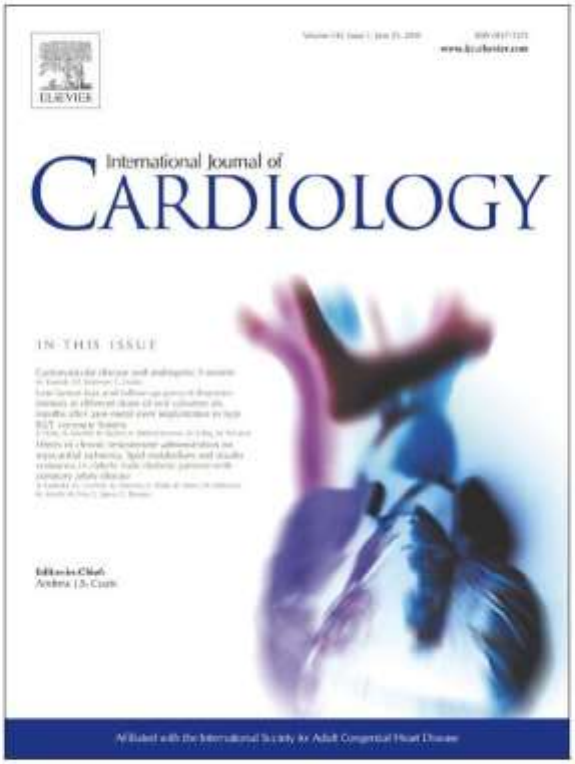

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Letter to the Editor

The "mirror" papillary muscle

James Ker*

Department of Physiology, University of Pretoria, Pretoria, South Africa, PO Box 24318, Gezina, Pretoria, South Africa, 0031

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Abstract

Various structural anomalies of the papillary muscles have been described in a variety of primary and secondary cardiovascular disorders. Some of these lead to intraventricular pressure gradients, while some has no obvious functional consequences at present.

A peculiar anterolateral papillary muscle anomaly with an accessory papillary muscle, causing the appearance of a mirror image on transthoracic echocardiography is described.

Keywords: Papillary muscle; Anomaly; Mirror

Various primary and secondary abnormalities of the ventricular papillary muscles has been described [1–10]. Nordblom et al. [1] recently described the normal ventricular positioning of the papillary muscles. Among the primary group of papillary muscle anomalies, some has been noted to be a cause of dynamic left ventricular obstruction [2]. The clinical implication(s) of the secondary group usually reflects those of the underlying cause of the papillary muscle abnormality. To date no case of a primary papillary muscle anomaly, resembling that of a "mirror" anterolateral papillary muscle has been described.

A 50-year old Caucasian male patient presented for a routine medical evaluation. He was asymptomatic, never had any previous surgery, never smoked and had no known allergies. He was taking ramipril 10 mg per day for uncomplicated hypertension.

His clinical evaluation did not reveal any abnormalities and his electrocardiogram was normal. A routine, transthoracic echocardiogram (TTE) was done to exclude the presence of left ventricular hypertrophy (LVH). This revealed the presence of a mirror image anterolateral papillary muscle with the chordae tendineae extending to the left ventricular apex (see Fig. 1).

This "mirror" papillary muscle did not have any clinical consequences, no electrocardiographic effects and specifically no mid-ventricular dynamic obstruction.

This is the first documented case of a "mirror" papillary muscle I could find in the Medline data base, adding to the growing number of primary papillary muscle anomalies described in the recent literature.

Recently, a growing number of publications [1–9], focused attention on a wide variety of pathologies and congenital anomalies afflicting the ventricular papillary muscles. These pathologies include: hemangiomas [3], solitary hypertrophy [4], endodermal heterotopia [5] (previously known as inclusion cysts), papillary fibroelastoma [6], an octopus shaped [7] papillary muscle, causing mid-ventricular obstruction, inflammation in Takayasu's arteritis [8], isolated infarction after cardiopulmonary resuscitation [9] and the finding of poorly formed papillary muscles in cases of left ventricular non-compaction [10].

The currently known clinical implication(s) of these papillary muscle anomalies are malfunction of the mitral valvular apparatus, causing valvular incompetence and/or dynamic mid-ventricular obstruction [2].

In this case of an accessory papillary muscle, which causes a mirror image of the anterolateral papillary muscle, there is no current functional impairment of the mitral valvular apparatus and no dynamic mid-ventricular obstruction.

* Tel.: +27 123414341; fax: +27 128090358.
E-mail address: jker@wol.co.za.

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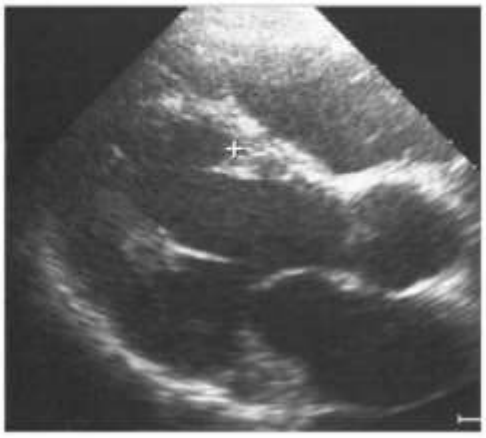

Fig. 1. This is the parasternal, long axis view on transthoracic echocardiography of the accessory papillary muscle (marked with a +). The accessory papillary muscle is noted to be attached to the interventricular septum, with the chordae extending to the apex of the left ventricle, leading to the appearance of a "mirror" image of the anterolateral papillary muscle.

However, there is no current data available to predict the possible future occurrence of any adverse long-term cardiac sequelae that might develop.

I sincerely hope that the future will shed more light on the pathogenesis and long-term sequelae of this growing number of primary papillary muscle anomalies.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [11].

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CARDIOVASCULAR ULTRASOUND

CASE REPORT Open Access

Bigeminy and the bifid papillary muscle

James Ker[1,2]

Abstract

Various structural anomalies of the left ventricular papillary muscles have been observed in recent years. Many of these have been linked to electrocardiographic aberrations.

Recently two reports have appeared where the base of the posterior papillary muscle was identified as the source of frequent premature ventricular complexes. In some of these patients these frequent premature ventricular complexes have led to left ventricular dysfunction.

In this report a newly discovered structural variant of the anterior papillary muscle is described--the bifid papillary muscle. Furthermore, it is proposed that this bifid papillary muscle is the source of frequent ventricular premature complexes, presenting as bigeminy in a patient with normal left ventricular function.

Introduction

In recent years various anomalies of the left ventricular papillary muscles have been observed [1]. These include: solitary hypertrophy [2] (as a variant of hypertrophic cardiomyopathy), accessory papillary muscles [1], inverted papillary muscles giving a "mirror" appearance [3], and an octopus-shaped variant, leading to mid-ventricular obstruction [4].

Interestingly, many of these papillary muscle variants have been linked to electrocardiographic aberrations [1,2,5]: These include: prominent U-waves in the inferior leads with an accessory papillary muscle [1], notching of the QRS-complex with ST-segment elevation and a prominent, positive U-wave, all in lead V4 with solitary hypertrophy of the anterolateral papillary muscle [2] and inferior J-waves with an accessory papillary muscle [5].

In this report, a new structural variant of the anterolateral papillary muscle is described--the bifid papillary muscle. In addition the patient had frequent premature ventricular complexes, presenting with pulsus bigeminy. It is proposed that the bifid papillary muscle is a newly discovered entity causing bigeminy.

Case report

A case report is presented depicting a new variant of the anterolateral papillary muscle--the bifid papillary muscle. Furthermore, there is a growing number of reports in the literature demonstrating various electrocardiographic aberrations caused by the papillary muscles and it's variants. Here it is proposed that the bifid papillary muscle is the cause of frequent premature ventricular complexes, presenting clinically with pulsus bigeminy.

A 51-year old Italian woman was referred for a cardiovascular examination by her primary care physician. The reason for the referral was the presence of an irregular pulse beat detected by the primary care physician. The patient herself was totally asymptomatic and was totally unaware of this irregularity. She never had any medical problems, never underwent any surgical procedures and was not taking any medication or illicit drugs. She also never smoked or has any known allergies. The reason for her visit to the primary care physician was for a routine medical examination to ensure that she was fit for travel and for advice on the prevention of influenza H1N1 as she was planning a boat cruise for vacation purposes.

Clinical examination revealed a pulsus bigeminy. The rest of the clinical examination did not reveal any pathological findings and the blood pressure was 115/75 mmHg. The electrocardiogram demonstrated frequent premature ventricular complexes with bigeminy (see additional file 1). The total number of premature ventricular complexes amounted to 21345 over a 24-hour period. A comprehensive biochemical screen did not reveal any pH, electrolyte or hematological abnormalities which could account for the rhythm disturbance. This biochemical screen specifically excluded thyroid abnormalities. Coronary artery disease was ruled out by means of a CT-angiogram. Although the patient had a low risk for atherosclerotic disease this was done to exclude the

* Correspondence: jker@wol.co.za
† Department of Physiology, University of Pretoria, Pretoria, South Africa
Full list of author information is available at the end of the article

possibility of alternative ischaemic etiologies, such as coronary artery anomalies.

Echocardiography demonstrated a peculiar anomaly of the anterolateral papillary muscle (see additional files 2, 3, 4 and 5). The apical, two chamber view revealed a bifid appearance of the anterolateral papillary muscle (see additional files 2 and 3).

The parasternal, short axis view also clearly demonstrates the bifid appearance (see additional files 4 and 5). The larger of the two heads are marked with +. Note the smaller head below. Additional files 6, 7 and 8 demonstrate additional apical two chamber images.

Due to the fact that papillary muscle abnormalities are frequent in patients with hypertrophic cardiomyopathy (HCM), it was specifically noted that there were no features of hypertrophic cardiomyopathy present in this case. There were no ventricular hypertrophy, systolic anterior motion of the mitral valve, septal immobility and the septal to free wall thickness ratio was < 1.3. Specifically there were also no apical hypertrophy or any T wave inversion, suggestive of apical HCM.

Discussion

Premature ventricular complexes (ventricular premature beats) is the most common arrhythmia detected by physicians during a physical examination [6].

Recently it was realized that the papillary muscles of the left ventricle may be the source of frequent premature ventricular complexes [7,8].

Doppalapudi et al [7] recently described a distinct new syndrome in seven patients. In this syndrome ventricular arrhythmia arises from the base of the posterior papillary muscle in the left ventricle. This entity presented as sustained ventricular tachycardia in two patients and as frequent premature ventricular complexes with salvos of non-sustained ventricular tachycardia in five patients [7]. Importantly, all these patients had a normal left ventricular function.

In contrast to this series with normal left ventricular function Sternick et al [8] published a case where frequent premature ventricular complexes, also arising from the base of the left posterior papillary muscle provoked significant left ventricular dysfunction. Furthermore, after cool-tip ablation with resultant elimination of these premature ventricular complexes, complete reversal of the left ventricular dysfunction occurred.

In conclusion, a case is presented of a newly described structural variant of the left anterolateral papillary muscle--the bifid papillary muscle. It is furthermore also proposed that this structural variant is the source of frequent premature ventricular complexes, presenting as bigeminy in a patient with normal left ventricular function. This adds to the cited two reports where the left ventricular posterior papillary muscle was the source of frequent premature ventricular complexes.

Additional material

Additional file 1 Electrocardiogram demonstrating frequent premature ventricular complexes with bigeminy. This is the 12 lead electrocardiogram, demonstrating frequent premature ventricular complexes with bigeminy.

Additional file 2 The bifid papillary muscle. This is an image from the apical two chamber view, clearly demonstrating the bifid anterolateral papillary muscle.

Additional file 3 Apical two chamber view. This is a movie clip from the apical two chamber view, demonstrating the bifid anterolateral papillary muscle.

Additional file 4 Parasternal short axis view. This is an image from the parasternal short axis view, clearly demonstrating the bifid anterolateral papillary muscle. The larger upper head is marked with +. Note the smaller head below.

Additional file 5 Parasternal short axis view. This is a movie clip from the parasternal short axis view, demonstrating the bifid anterolateral papillary muscle.

Additional file 6 Apical two chamber view. This is an additional movie clip from the apical two chamber view.

Additional file 7 Apical two chamber view. This is an additional movie clip from the apical two chamber view.

Additional file 8 Apical two chamber view. This is an additional movie clip from the apical two chamber view.

Competing interests

The author declares that they have no competing interests.

Authors' contributions

JK is the sole author.

Author Details

[1]Department of Physiology, University of Pretoria, Pretoria, South Africa and [2]PO Box 24318, Gesina, Pretoria, 0031, South Africa

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Clinical Medicine Insights: Cardiology

CASE REPORT

Right Ventricular Variants and Pulmonary Embolism—Association or Coincidence?

James Ker

Department of Physiology, University of Pretoria, Pretoria, South Africa. Corresponding author email: jker@wol.co.za

Abstract: It has been stated that the interior of the right ventricle is as unique to each individual as one's fingerprint. This statement is backed by numerous publications which demonstrates considerable variation in the number, shape and configuration of papillary muscles inside the normal right ventricle.

It has also been shown that these variants may be the cause of cardiac rhythm disorders.

In this case report another potential complication of such right ventricular papillary muscle variants is proposed—these muscles may be the source of pulmonary emboli.

The pathogenesis may be that of local stasis around these aberrant muscular structures and/or emboli may form inside the right ventricle as a result of cardiac rhythm disorders, induced by these muscles.

It is proposed that in future the role of the right ventricle as the source of pulmonary emboli will become more apparent and an important part of the diagnostic work up in cases of idiopathic pulmonary embolism.

Keywords: Pulmonary embolism, right ventricle, papillary muscle, variants

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This article is available from http://www.la-press.com.

Introduction

According to Victor and Nayak[1] the interior of the right ventricle is as unique to each individual as one's fingerprint. Numerous publications[2–6] has shown that inside the normal right ventricle considerable variation exists in the number of papillary muscles, the number of heads of individual papillary muscles, the number of papillae on the heads of papillary muscles and also the shape of individual papillary muscles.

Wenink[2] examined 100 normal hearts and concluded that the medial papillary muscle of the right ventricle, also known as the papillary muscle of the conus, the muscle of Luschka and the muscle of Lancisi, displays such wide morphological variations that the value of the muscle as an anatomical landmark in the right ventricle is very restricted. Due to this wide morphological variations he proposed the name the medial papillary complex.

Restivo et al[3] studied fetal hearts—81 subjects, ranging in age from 20 weeks of gestation to 13 months—and also found considerable variability in the papillary muscles of the right ventricle.

Nigri et al[4] studied the morphological characteristics of the right ventricular papillary muscles and their chordae tendineae in 79 normal human hearts—aged from 14 to 68 years— and found the following:

The anterior and posterior papillary muscles were present in all of the 79 hearts. The septal papillary muscle was absent in 21.5% of cases. The anterior papillary muscle had one head in 81% of cases and two heads in 19% of cases. A head of a papillary muscle was defined as a muscle that is directly attached to the ventricular wall. The average length of the anterior papillary muscle was 19.16 mm. The septal papillary muscle had one head in 41.7% of cases, two heads in 16.5% of cases, three heads in 12.7% of cases and four heads in 7.6% of cases and the average length of the septal papillary muscle was 5.59 mm. The posterior papillary muscle had one head in 25.4% of cases, two heads in 46.8% of cases, three heads in 21.5% of cases and four heads in 6.3% of cases. Its average length was 11.53 mm. The chordae tendineae also displayed enormous variation: From one to eleven originated from the anterior papillary muscle, from one to eight from the posterior papillary muscle and from one to five from the septal papillary muscle.

Skwarek et al[5] separates the conal papillary muscle and the papillary muscles of the posterior angle of the right ventricle from the classically described papillary muscles of the right ventricle, referred to in anatomical nomenclature—the anterior, posterior and septal papillary muscles. They found the conal papillary muscle—also described by Luschka in the seventeenth century—as the most constant of the septal papillary muscles. Furthermore, they found papillary muscles in the posterior angle of the right ventricle which could not be clearly classified as either septal or posterior muscles—thus, called the muscles of the posterior angle of the right ventricle.

Similar to Nigri et al,[4] Begum et al[6] studied fifty hearts—aged from 20 to 70 years—from the Bangladesh population and found the following:

The right ventricle had a single anterior papillary muscle in 92% of cases. The posterior papillary muscle was single in 28% of cases and double in 32%. The septal papillary muscle was single in 46% of cases and absent in 30% of cases. They found the anterior papillary muscles the longest and the septal papillary muscles the shortest.

Case report

A case report is presented where a large papillary muscle complex is present in the apical part of the lateral wall of the right ventricle in a 44 year old Caucasian woman. This aberrant papillary muscle complex is thought to be the source of recurrent pulmonary emboli.

A 44 year old Caucasian woman presented with a 3 month history of pleuritic chest pain. During and after all three her pregnancies she also experienced the same pleuritic chest pain for variable periods, ranging from one to four months.

She was taking levothyroxine for hypothyroidism, which had been diagnosed two years earlier. No other medical problems were present.

The clinical examination was normal. A 12-lead electrocardiogram and chest radiograph were also normal. A ventilation-perfusion (V/Q) scan demonstrated multiple pulmonary emboli in both lungs.

A comprehensive search did not reveal any known cause for these multiple pulmonary emboli: No deep venous thromboses of the lower and upper limbs or

pelvic veins were present, no malignant process were present and the following biochemical measurements were all normal: Antithrombin and proteins C and S levels were within normal limits, factor IX levels were within normal limits and factor V Leiden was negative, lipoprotein(a) and homocyteine levels were normal, anti-nuclear factor was absent, antiphospholipid antibodies were absent, and the prothrombin mutation PT G20210A was absent.

Echocardiography revealed the presence of a large, papillary muscle complex in the apical part of the lateral wall of the right ventricle (Fig. 1). Figures 2 and 3 demonstrate that this papillary muscle complex consists of a base with a single, tall head flanked by a smaller head on either side. In supplementary Figure 1, it is clear that this muscular complex is papillary muscle, as chordae tendineae extends from the papillary muscle complex.

Discussion

What might be the potential clinical complications of these various variants of papillary muscles in the right ventricle?

They may be the source of cardiac rhythm disorders.[7] Lazzari et al[7] examined the short-term behavior of extrasystoles, arising from the anterior papillary muscle of the right ventricle. 20 subjects were studied with Holter recordings and exercise data. According to the authors a right ventricular anterior papillary muscle extrasystole has a left bundle branch block morphology with a downward oriented QRS axis in the frontal plane, a slurred r wave in lead V1 and an R/S ratio less that 1 in lead V1. They concluded that this entity can be found in otherwise normal hearts with an uncomplicated outcome in the short-term.

Aktas et al[8] investigated papillary muscle variants around the tricuspid valve in cases of sudden death. 400 hearts were studied and a great variability in the number of papillary muscles in the right ventricle was found, ranging from two to nine. The authors also observed a striking incidence of conical and flat topped configurations of the posterior papillary muscle in these deaths. The authors concluded that these pap-

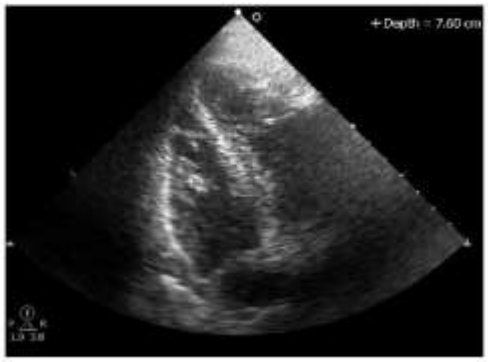

Figure 2. Papillary muscle complex.
Note: Another view of the aberrant papillary muscle complex.

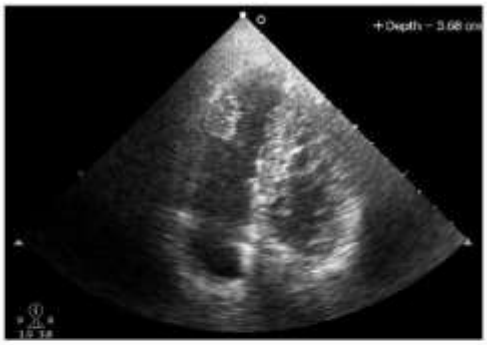

Figure 1. Aberrant papillary muscle complex in the lateral wall of the right ventricle.
Note: This is an apical, four chamber view demonstrating a large papillary muscle complex, with its origin from the lateral wall of the right ventricle.

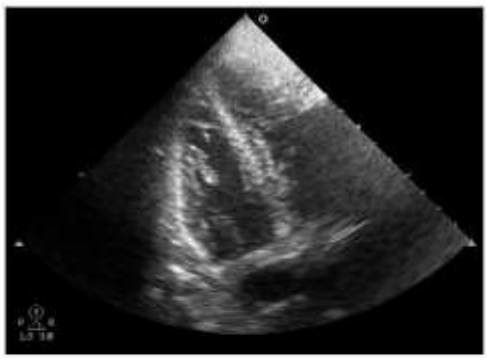

Figure 3. Three headed papillary muscle complex.
Note: This is an apical view which demonstrates that the papillary muscle complex consists of a base with a single, tall head flanked by a smaller head on either side.

illary muscle variants may be the cause of sudden cardiac death. However, there is a paucity of data on the existence and possible mechanisms of arrhythmia in patients with papillary muscle variants.

In this case report another potential complication of such papillary muscle variants in the right ventricle is proposed—these variants may be the source of pulmonary emboli.

The physiological basis of this may be due to stasis of blood around these structures with resultant emboli or these muscles may be the source of brief episodes of cardiac rhythm disorders in the right ventricle, as previously described,[7] with resultant episodes of stasis and consequent emboli.

The right side of the heart as the source of pulmonary emboli is not a new concept: Various primary and secondary cardiac tumors have been shown to be a potential source of pulmonary emboli.[9–12] The primary tumors include myxomas[9] and papillary fibroelastomas,[10] whereas testicular embryonal carcinoma[11] and squamous cervical carcinoma[12] are examples of metastatic right ventricular tumors with resultant pulmonary emboli.

Possible mimics of such a papillary muscle variant in the right ventricle include: valvular vegetations, a papillary fibroelastoma, thrombus and metastatic tumors. A valvular vegetation was not considered due to the fact that there is no continuity between the mass and the tricuspid valve. The unique echocardiographic features of papillary fibroelastomas include small size, attachment to the endocardium via a stalk or pedicle that is highly mobile, a refractive appearance and areas of echolucency within the tumor itself.[10] No evidence of any primary malignancy could be found and therefore the possibility of a cardiac metastasis was not considered. Endocardial metastases are extremely rare and this has been attributed to the strong kneading action of the heart, the metabolic peculiarities of the myocardium, the rapidity of coronary blood flow and the lymphatic connections that drain afferently from the heart.[13]

Lastly, Maron et al[14] have shown that there may be a "spillover" of the primary left ventricular hypertrophic process from the septum into adjacent segments of the right ventricular wall in patients with hypertrophic cardiomyopathy. However, in this case the muscular complex is seen in the lateral wall and no echocardiographic stigmata of hypertrophic cardiomyopathy were present in the left ventricle. However, it is possible that pulmonary embolism may arise from this right ventricular apical muscular complex by the same mechanism as that seen in patients with left ventricular apical hypertrophic cardiomyopathy.

It is hoped that this report will lead to more focus on the right ventricle as the possible source in cases of unexplained pulmonary emboli. It is proposed that in the future of clinical cardiology the right ventricle will become an important area of investigation in cases of unexplained pulmonary embolism.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient for publication of this study.

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Clinical Medicine Insights: Cardiology

ORINIGAL RESEARCH

The Double U Wave—Should the Electrocardiogram be Interpreted Echocardiographically?

James Ker

Department of Physiology, University of Pretoria, Pretoria, South Africa. Corresponding author email: jker@wol.co.za

Abstract: The U wave is still an electrocardiographic deflection of enigmatic origin. Numerous hypotheses on its origin have been formulated, but to date none has been conclusively proven. Recently, a report described the first case of bifid (or notched) U waves. Until then this phenomenon has only been described in the T wave. This is the first report of double U waves—two separate deflections, ascribed to an accessory papillary muscle.

Hypothesis: The presence of a double U wave will be associated with an accessory papillary muscle (s).

Materials and methods: This is a retrospective analysis of 4729 patient files of patients who were evaluated at a cardiology practice. The 12-lead surface electrocardiogram was evaluated for the possible presence of a double U wave. In cases where a double U wave was found, the transthoracic echocardiogram was then scrutinized for the presence of an accessory papillary muscle.

Results: A total of 3 cases of a double U wave were found. In every case an accessory papillary muscle was clearly seen on the transthoracic echocardiogram.

Conclusion: A double U wave is a new variant of an old electrocardiographic deflection of enigmatic origin. This variant may be associated with an accessory papillary muscle.

Keywords: U wave, double, papillary muscle

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Introduction

The electrocardiographic deflection, which is sometimes seen at the end of ventricular repolarisation and which was named the U wave by Einthoven, is often seen in normal subjects, but is still of enigmatic origin.[1,2] The electrophysiological basis of U wave generation is still elusive with numerous cited hypotheses,[3,4] such as: repolarisation of the papillary muscles,[5] repolarisation of the Purkinje fibers outlasting that of the contracting myocardium,[6] prolonged repolarisation in cells of the mid-myocardium—the "M cells"[7] or it may be due to after-potentials, caused by mechanical forces in the ventricular wall with termination of mechanical systole—the "mechano-electrical feedback hypothesis".[8]

Equally interesting is the new focus on variation in morphology of the U wave: "Normal" U waves are usually upright, <1 mm and of similar polarity of the preceding T wave.[4] Recently, Ariyarajah et al[4] described the first report of "notched" or "bifid" U waves—until this report only T wave bifidity have been described. But is it possible to observe two separate U waves—a true "double U wave"?

This study describes the first observation of double U waves—a new variant of a known electrocardiographic deflection of enigmatic origin, possibly associated with an accessory papillary muscle.

Materials and Methods

This is a retrospective analysis. A total of 4729 files of patients evaluated at a cardiology practice were evaluated for the presence of a double U wave, seen on a 12-lead surface electrocardiogram.

Case 1

A 46-year-old Caucasian male with no previous medical or surgical history presented for a routine medical evaluation to exclude any possible underlying disease.

He was completely asymptomatic and was not using any medical treatment.

The clinical examination did not reveal any abnormalities. The electrocardiogram (Fig. 1) demonstrated striking double U waves in leads II, III, aVF and V3–V6. An effort electrocardiogram (Bruce protocol via treadmill exercise) was within normal limits.

The echocardiogram demonstrated a structurally normal heart, but with a prominent accessory papillary muscle, situated between the left ventricular apex and interventricular septum (Figs. 2 and 3). No intra-ventricular pressure gradient or mitral valve dysfunction were present. Figure 2 is an echocardiographic image from the parasternal, long axis view, demonstrating the accessory papillary muscle (marked with +). Figure 3 is an echocardiographic image, taken from the apical, four-chamber view, also demonstrating the accessory papillary muscle, also marked with +. A comprehensive biochemical evaluation, which included thyroid function, serum glucose level, serum electrolytes, iron and ferritin levels and a full blood count did not reveal any abnormalities which could explain the double U wave.

Case 2

A 33-year-old Caucasian woman with no previous medical or surgical history also presented for a cardiovascular examination to exclude any possible underlying cardiovascular disease due to the presence of a family history of ischaemic heart disease. She was not taking any medicine and was completely asymptomatic. The clinical examination was completely normal and a biochemical screen did not reveal any abnormalities. The electrocardiogram (Fig. 4) revealed a double U wave in leads II, III, aVF and V3–V6. An effort electrocardiogram (Bruce protocol via treadmill exercise) was within normal limits. The transthoracic echocardiogram also revealed an accessory papillary muscle. No intra-ventricular pressure gradient or mitral valve dysfunction were present. Figure 5 is the parasternal, short-axis view—note the accessory papillary muscle marked with +. The accessory papillary muscle can be clearly seen, situated between the anterolateral and posteromedial papillary muscles. All serum electrolytes were within normal limits.

Case 3

A 67-year-old Caucasian male with hyperlipidaemia presented for a cardiovascular examination. He was asymptomatic and was taking 10 mg of atorvastatin daily. His surgical history included a prostatectomy for benign prostatic hyperplasia.

The clinical examination was completely normal and a biochemical screen did not reveal any abnormalities. The electrocardiogram revealed a double U wave in leads II, III, aVF and V3–V6 (Fig. 6). An effort electrocardiogram (Bruce protocol via treadmill exercise) was within normal limits.

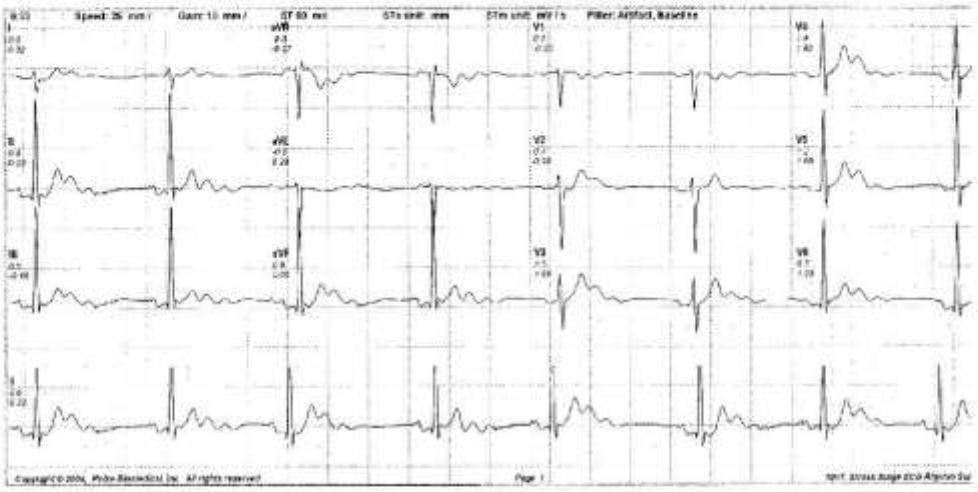

Figure 1. Electrocardiogram of case 1. Note the striking double U waves in leads II, III, aVF and V3–V6.

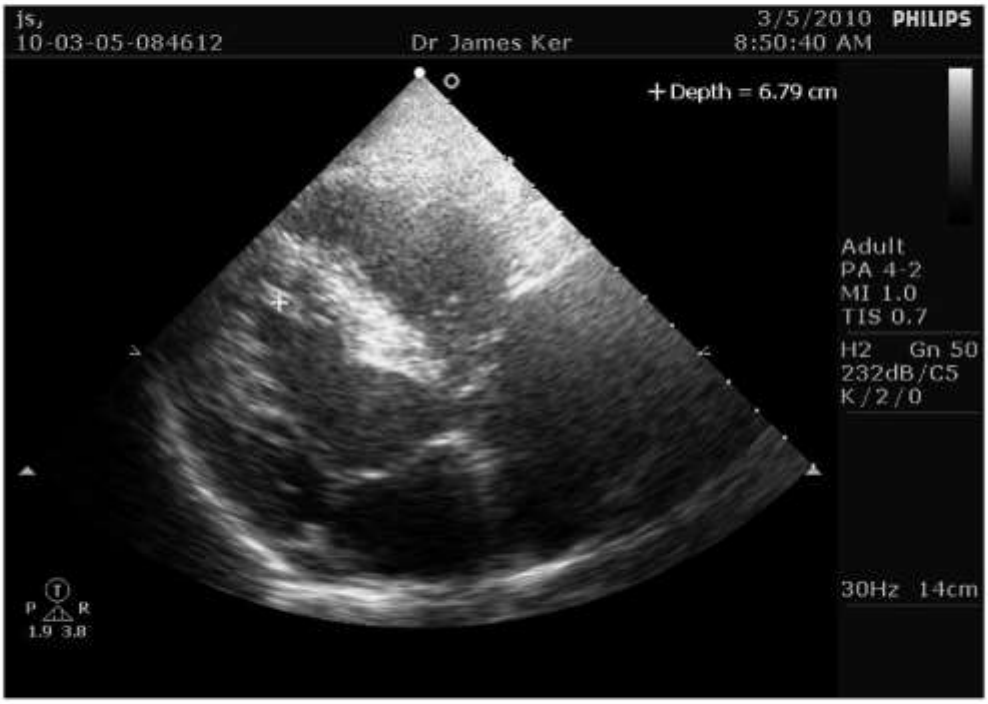

Figure 2. Echocardiogram. Echocardiographic image demonstrating the accessory papillary muscle of case 1.

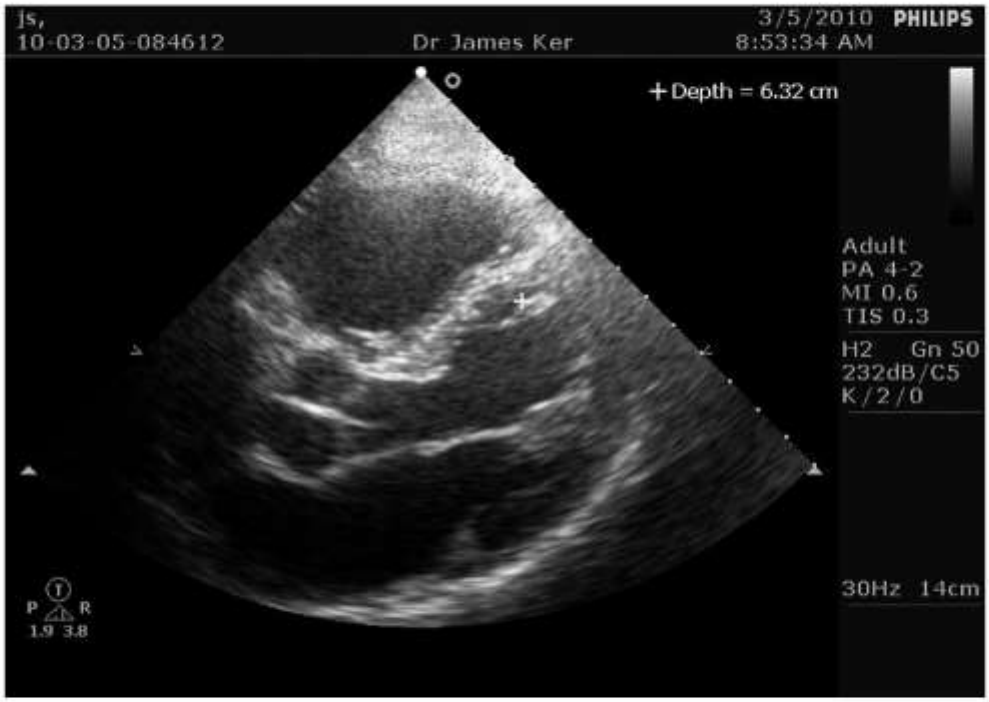

Figure 3. Echocardiogram. Additional echocardiographic image demonstrating the accessory papillary muscle of case 1.

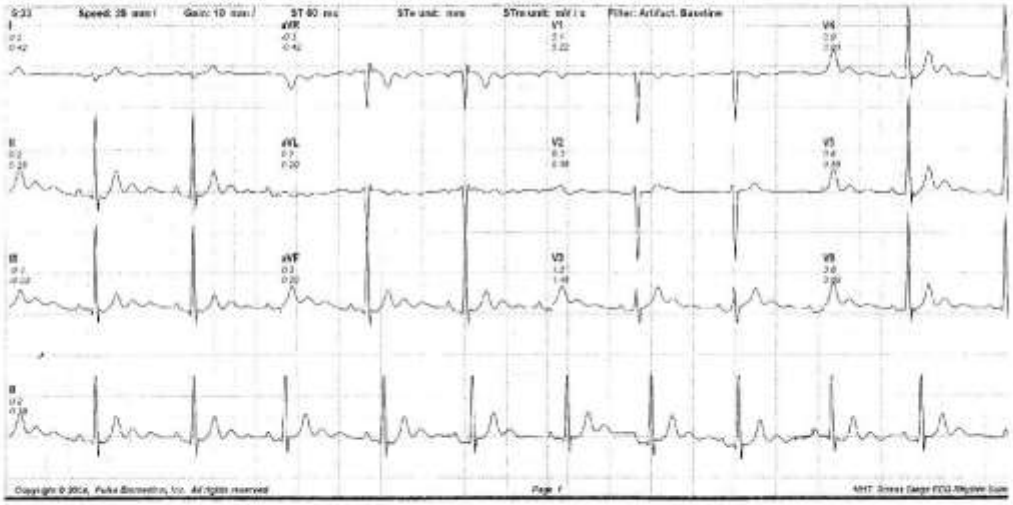

Figure 4. Electrocardiogram of case 2. Electrocardiogram demonstrating double U waves in leads II, III, aVF and V3–V6.

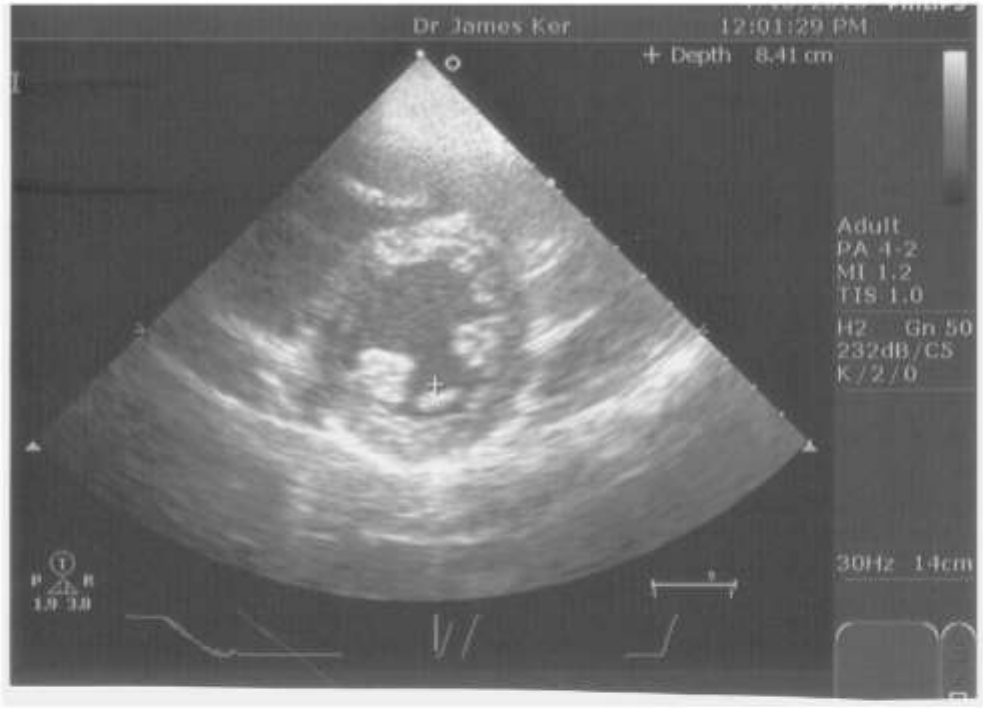

Figure 5. Echocardiogram. Parasternal, short-axis view of case 2. Note the accessory papillary muscle, marked with +.

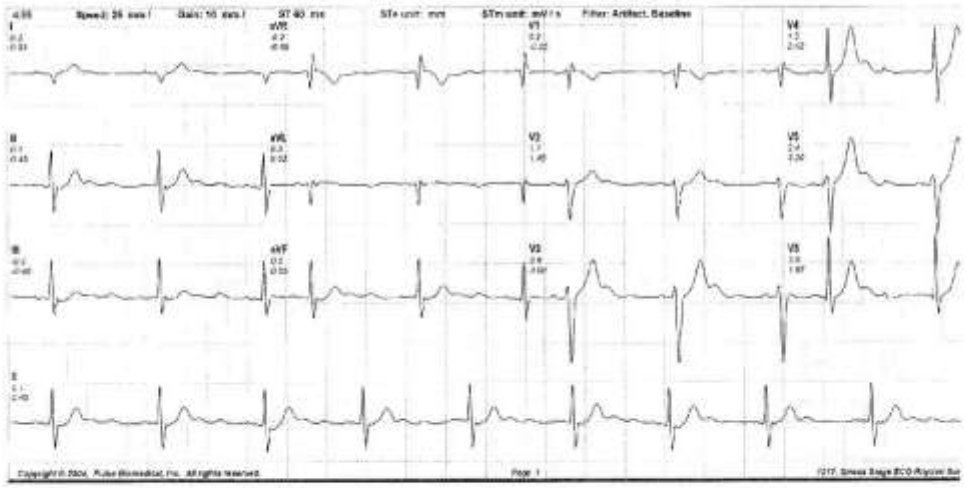

Figure 6. Electrocardiogram of case 3. Electrocardiogram demonstrating double U waves in leads II, III, aVF and V3–V6.

The echocardiogram demonstrated an accessory papillary muscle—Figure 7 is a parasternal, long-axis view, demonstrating the accessory papillary muscle just below the interventricular septum, marked with +. No intra-ventricular pressure gradient or mitral valve dysfunction were present. All serum electrolytes were within normal limits.

Discussion

This study clearly demonstrates the presence of double U waves. As these are visible on separate ECG leads (II, III, aVF and V3–V6) they are unlikely artefactual. Furthermore, as there is a clear return to baseline between these U waves, they cannot be considered bifid (or notched).

In all of these leads with a double U wave, a following P wave is clearly seen, thus the second U wave is also not a mistaken P wave. It is proposed that the second U wave is caused by the accessory papillary muscle.

Interestingly, this is not the first report linking U waves to papillary muscle anomalies. A case of ST segment elevation with QRS notching and a prominent U wave in lead V4 have been described in a patient with solitary papillary muscle hypertrophy[9] and another case linked an accessory papillary muscle to prominent U waves in the inferior leads.[3]

In the era of readily available echocardiographic examinations, numerous other electrocardiographic phenomena have been explained by underlying endoventricular structural anomalies. These include: premature ventricular complexes with bigeminy due to a bifid papillary muscle,[10] inferior J-waves due to an accessory papillary muscle,[11] ST segment elevation due to a sub aortic tendon[12] and a new variant of right bundle branch block due to the presence of a sub aortic tendon, leading to an increased velocity of conduction in the left ventricle.[13] However, not all observed papillary muscle anomalies are associated with electrocardiographic changes—a case of a "mirror" papillary muscle had no electrocardiographic abnormalities.[14]

It is proposed that the double U wave is a newly observed electrocardiographic entity, possibly and most probably caused by an accessory papillary muscle. Peculiarly, this is observed in leads II, III, aVF and V3–V6 in

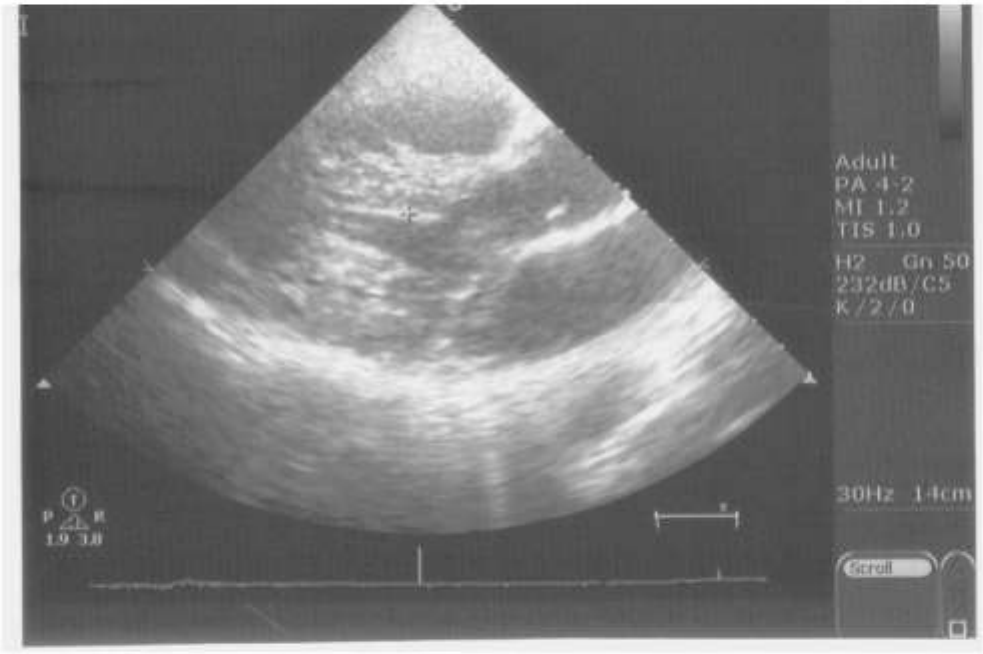

Figure 7. Echocardiogram. Parasternal, long-axis view of case 3, demonstrating the accessory papillary muscle just below the interventricular septum.

all of the observed cases. Whether or not there may be any associated arrhythmia risk is not known.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material. Written consent was obtained from the patients for publication of this study.

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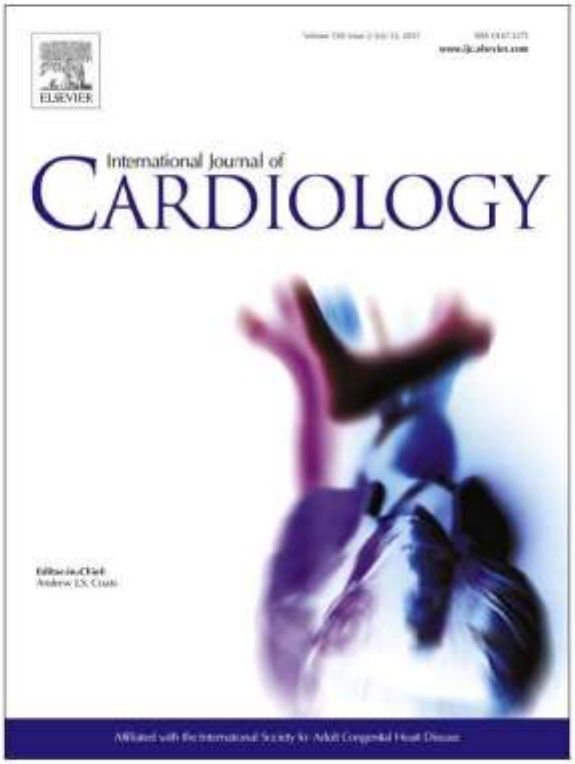

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Electrocardiographic intricacies clarified by echocardiography—Should the electrocardiogram be interpreted echocardiographically?

James Ker *

Department of Physiology, University of Pretoria, Pretoria, South Africa, PO Box 24318, Gezina, Pretoria, 0031 South Africa

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ABSTRACT

Background: During the past century the electrocardiogram (ECG) has established itself as an integral part of the cardiovascular examination. Since the first direct recordings of cardiac potentials by Waller in 1887, to the invention of the string galvanometer by Willem Einthoven in 1901, to use in the clinic by 1910, the electrocardiogram has become the most widely used clinical tool in the diagnosis of virtually every type of heart disease. Currently up to 20 million ECGs are performed annually in the United States alone.

Hypothesis: However, in this era of readily available echocardiography, an important caveat in the interpretation of the electrocardiogram has emerged: variants of intracardiac structures which might mimic disease on the ECG.

Methods: In this perspective various structural variants of intracardiac structures, specifically variants of papillary muscles and subaortic muscular bands, will be shown, together with their associated electrocardiographic changes, mimicking disease.

Conclusion: It is concluded that in this era of readily available echocardiography, the electrocardiogram should be interpreted echocardiographically in instances where intricate variations are seen on the surface electrocardiogram.

1. Introduction

During the past century the electrocardiogram (ECG) has established itself as an integral part of the cardiovascular examination. Since the first direct recordings of cardiac potentials by Waller in 1887, to the invention of the string galvanometer by Willem Einthoven in 1901, to use in the clinic by 1910, the electrocardiogram has become the most widely used clinical tool in the diagnosis of virtually every type of heart disease [1].

Currently up to 20 million ECGs are performed annually in the United States alone [1].

However, in this era of readily available echocardiography, an important caveat in the interpretation of the electrocardiogram has emerged: variants of intracardiac structures which might mimic disease on the ECG.

In this perspective various structural variants of intracardiac structures will be shown, together with their associated electrocardiographic aberrations, mimicking disease.

2. Subaortic tendon induced ST-segment elevation

Fig. 1 is the 12-lead electrocardiogram of a 34-year old, healthy caucasian male. Note the striking ST-segment elevation in leads V3 and V4. The differential diagnosis of ST-segment elevation is wide and diverse and includes the following [2]: myocardial ischemia or infarction, Prinzmetal angina pattern, Takotsubo cardiomyopathy, ventricular aneurysm, pericarditis, early repolarisation pattern, left ventricular hypertrophy, left bundle branch block, other causes of myocardial injury, such as myocarditis, trauma or a tumor invading the left ventricle, hypothermia, after DC cardioversion, hyperkalemia, hypercalcemia, type 1C antiarrhythmic drugs, intracranial hemorrhage and the Brugada pattern. In this particular case none of the above were present and the only explanation found was the presence of a peculiar muscular band, extending between the interventricular septum and the left ventricular apex [2] (Fig. 2). The characteristics of this peculiar subaortic muscular band have been described before [3]. The possible pathophysiological mechanisms of this phenomenon of subaortic tendon induced ST-segment elevation have been described in detail [2].

3. Solitary papillary muscle hypertrophy with QRS-and ST-segment changes

Fig. 3 is the 12-lead electrocardiogram of a healthy 20-year old, caucasian male. Note the notching of the ascending limb of the QRS-complex in lead V4, together with ST-segment elevation and a prominent, positive U wave, also in lead V4. Echocardiography revealed isolated hypertrophy of the anterolateral papillary muscle (Fig. 4). Isolated papillary muscle hypertrophy is a rare entity and in

* Tel.: +27 12 3430078; fax: +27 12 3430079.
E-mail address: jker@wol.co.za.

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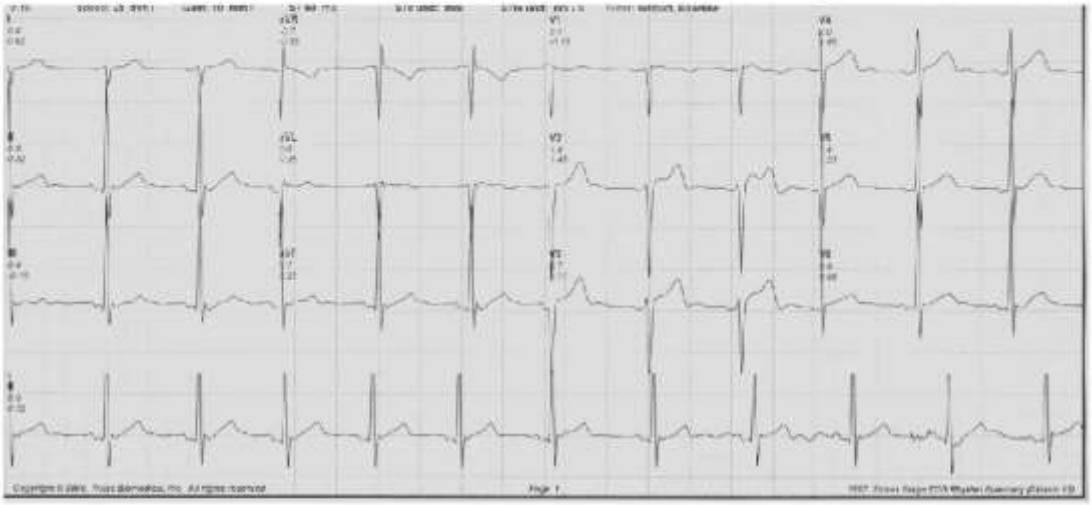

Fig. 1. 12-lead electrocardiogram of a healthy 34-year old Caucasian male. Note the ST-segment elevation in leads V3 and V4.

this case it was proposed that isolated hypertrophy of the anterolateral papillary muscle with notching of the ascending limb of the QRS complex, with ST-segment elevation and a prominent, positive U wave, all in lead V4 is a new echo-electrocardiographic syndrome [4].

4. Papillary muscle variants and the U wave

One of the earliest hypotheses on the origin of the U wave involved repolarisation of the papillary muscles and their neighboring structures [5]. Today the U wave is still an electrocardiographic deflection of enigmatic origin with none of the current theories on the genesis of the U wave accepted as factual. These theories include the following [5]: repolarisation of the papillary muscles, repolarisation of the Purkinje fibers outlasting that of the contracting myocardium, prolonged repolarisation in cells of the mid-myocardium—the "M cells", and the so-called "mechano-electrical feedback hypothesis"—after-potentials, caused by mechanical forces in the ventricular wall with termination of mechanical systole.

Fig. 5 is the 12-lead electrocardiogram of a healthy 15-year old caucasian girl. Note the prominent U waves in the inferior leads (II, III and aVF). The only anomaly found in this case was the presence of two prominent, accessory papillary muscles (Fig. 6). Fig. 6 is the echocardiographic image demonstrating this accessory papillary muscles (marked with +). In this case it was proposed that the prominent inferior U waves are caused by the presence of the

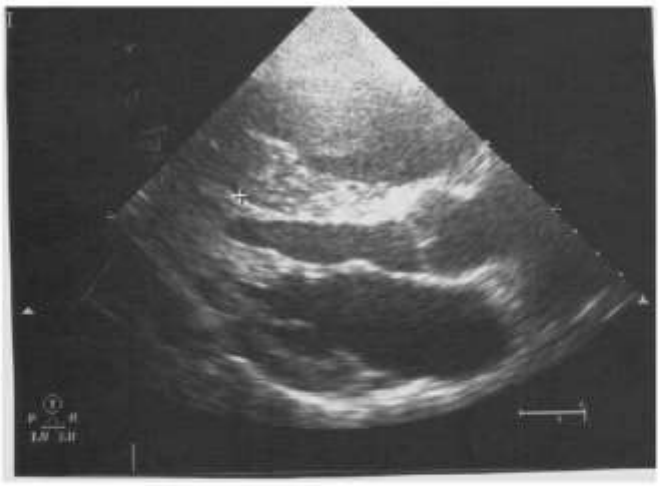

Fig. 2. Transthoracic echocardiographic image, taken from the parasternal, long-axis view. Note the presence of a peculiar muscular band which extends between the interventricular septum and the left ventricular apex.

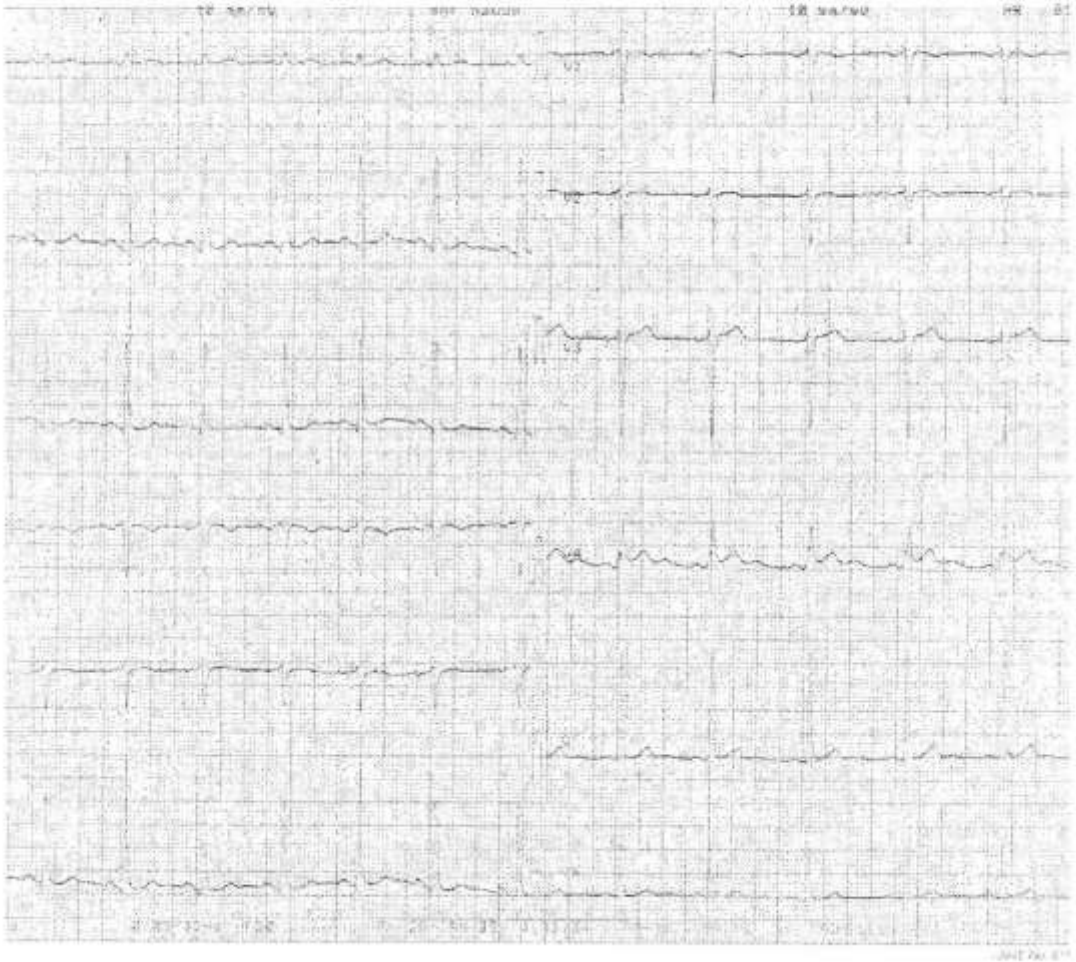

Fig. 3. 12-lead electrocardiogram of a healthy, 20-year old Caucasian male. Note the notching of the ascending limb of the QRS-complex in lead V4. ST-segment elevation and a prominent, positive U wave are also present in lead V4.

accessory papillary muscles and the pathophysiological mechanisms were discussed [5].

Currently, there is a new focus on the morphology of the U wave [6]. Usually U waves are upright, <1 mm in amplitude and of similar polarity than that of the preceding T wave [7]. The first report of "notched" or "bifid" U waves was recently described [7]. Until this report only T wave bifidity has been described.

5. Accessory papillary muscles and the double U wave

Fig. 7 is a 12-lead electrocardiogram which clearly demonstrates the presence of double U waves. A recent retrospective analysis identified 3 cases of double U waves in a database of 4729 patients [6]. In all three these cases of double U waves, an accessory papillary muscle was clearly demonstrated [6]. Fig. 8 is an echocardiographic image, taken from the patient in Fig. 7. This is a transverse section of the left ventricle, demonstrating two accessory papillary muscles—one in the 7 o'clock position and the other one just before the 3 o'clock position. Fig. 9 is a longitudinal section of the left ventricle, demonstrating the same accessory papillary muscles in another plane (marked with +). It is proposed that the double U wave is a newly observed electrocardiographic entity which is possibly and most probably the result of an accessory papillary muscle [6].

6. Bigeminy and the bifid papillary muscle

Fig. 10 is the 12-lead electrocardiogram of a 51-year old Italian woman, presenting with ventricular bigeminy. After a comprehensive evaluation the only explanation found for the electrocardiographic abnormality was the presence of a peculiar structural variant of the anterolateral papillary muscle—the "bifid" papillary muscle (Fig. 11) [8].

It was recently realized that the papillary muscles of the left ventricle may be the source of frequent premature ventricular complexes [9,10]. Doppalapudi et al. [9] recently described a distinct new syndrome of ventricular arrhythmia arising from the base of the

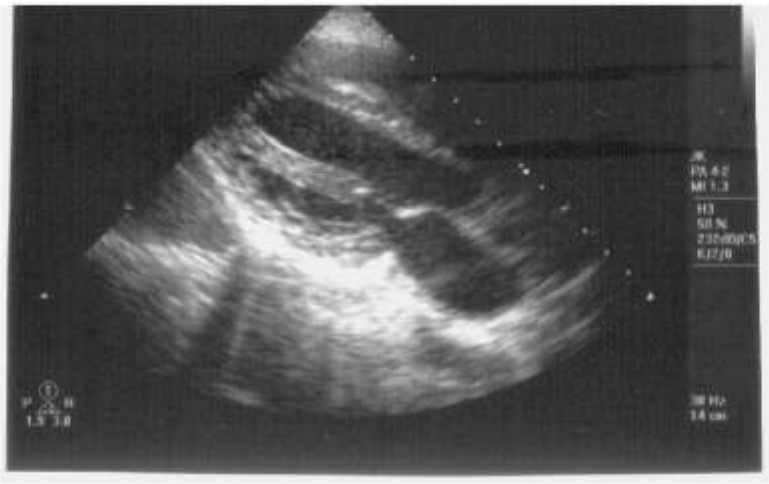

Fig. 4. Transthoracic echocardiographic image, taken from the parasternal, long-axis view. Note the isolated hypertrophy of the anterolateral papillary muscle.

posterior papillary muscle, presenting clinically as sustained ventricular tachycardia in two patients and as frequent premature ventricular complexes with salvos of non-sustained ventricular tachycardia in another five patients. This report added to the two already cited reports of the left ventricular papillary muscle(s) as the source of ventricular arrhythmia [8].

7. Conclusion

The papillary muscles have already been identified as potential sites of reentry, contributing to the maintenance of ventricular fibrillation in animal models [11]. Recently, the left ventricular papillary muscles have been shown to be arrhythmogenic in the human heart after myocardial infarction [11–13]. In addition to this papillary muscle arrhythmogenic entity as a complication of structural heart disease, idiopathic ventricular arrhythmia, originating from the posterior papillary muscle has also been described as a novel clinical syndrome [9]. In addition to this a distinct subgroup of idiopathic ventricular arrhythmias, arising from the anterior papillary muscle has also been described [11]. Both the anterior and posterior papillary muscles have thus been shown to be the source of ventricular arrhythmias in the human heart, without any underlying structural heart disease. The left ventricular papillary muscles are conical projections of myocardium into the left ventricular cavity, covered by endothelium [14]. A peripheral Purkinje network extends on to the surface of the papillary muscles and may serve as either a focal point of origin of arrhythmia or it may form part of a macroreentrant circuit [14].

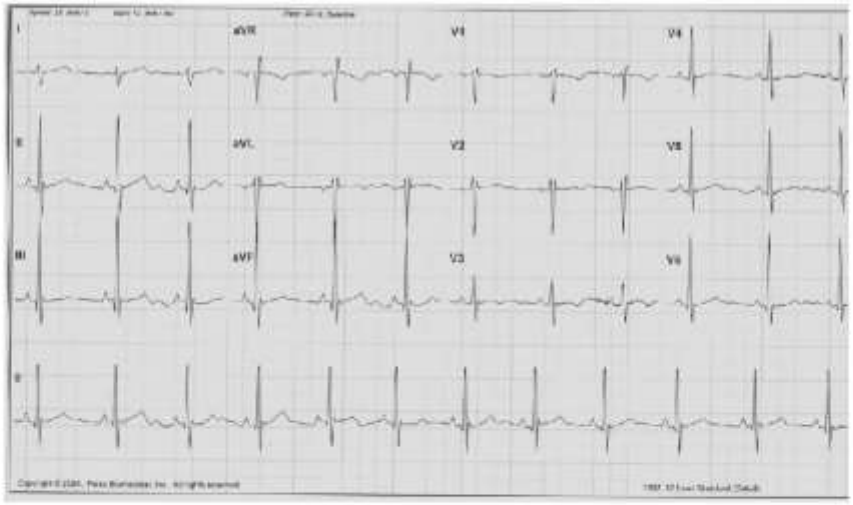

Fig. 5. 12-lead electrocardiogram of a healthy 15-year old Caucasian girl. Note the prominent U waves in the inferior leads (II, III and aVF).

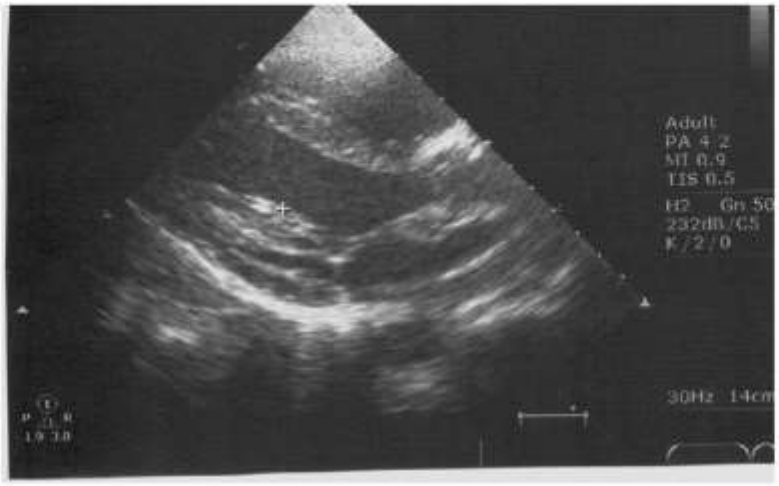

Fig. 6. Note the two prominent, accessory papillary muscles, marked with +.

In this perspective, various variants of the left ventricular papillary muscles, together with their associated electrocardiographic changes were demonstrated.

As discussed, the left ventricular papillary muscles have emerged as established role players in ventricular arrhythmias and as echocardiography is an established and excellent clinical tool to evaluate the structure, number and position of papillary muscles, it is proposed that the electrocardiogram should be interpreted according to structural data given by the echocardiogram.

Competing interests

The author declares that no competing interests are present.

Acknowledgements

The author declares that he complied with the ethical principles of publishing of the International Journal of Cardiology [15].

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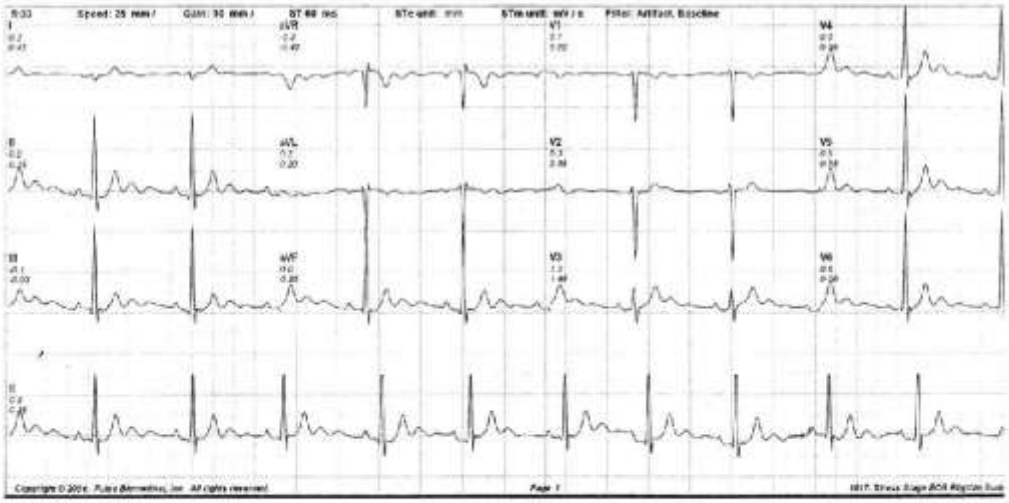

Fig. 7. 12-lead electrocardiogram. Note the presence of double U waves.

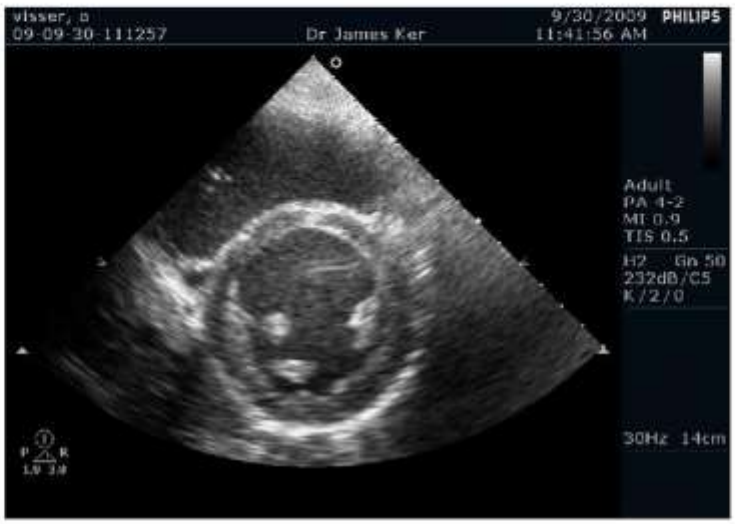

Fig. 8. Echocardiographic image demonstrating a transverse section of the left ventricle. Note the presence of two accessory papillary muscles—one in the 7 o'clock position and the other one just before the 3 o'clock position.

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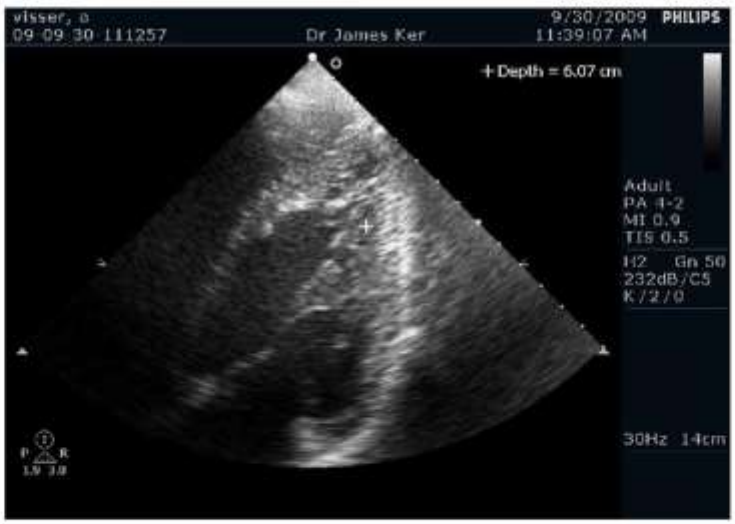

Fig. 9. This is a longitudinal section of the same ventricle as in figure 8, demonstrating the same accessory papillary muscles in another plane (marked with +).

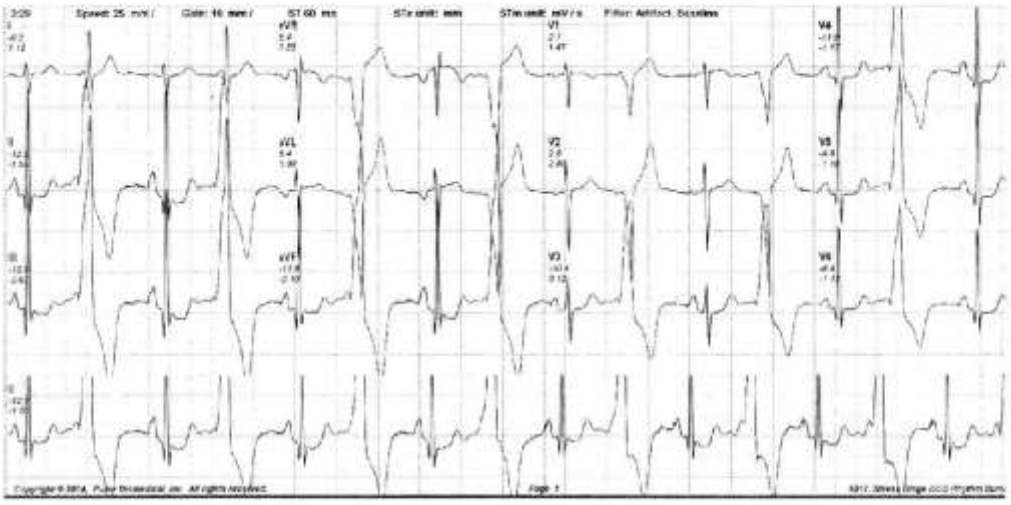

Fig. 10. 12-lead electrocardiogram of a 51-year old Italian woman, presenting with ventricular bigeminy.

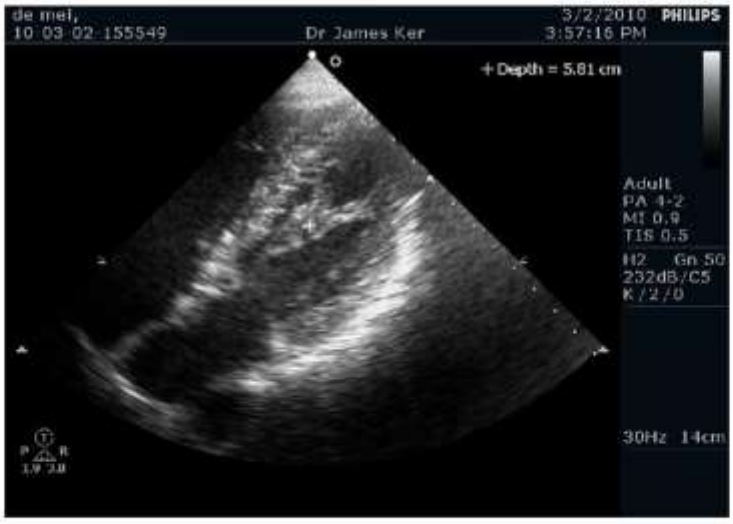

Fig. 11. Echocardiographic image demonstrating the presence of a "bifid" papillary muscle (marked with +).

Case Report

Isolated left ventricular non-compaction as a cause of thrombo-embolic stroke: a case report and review

J KER, C VAN DER MERWE

Summary

Isolated left ventricular non-compaction is the result of incomplete myocardial morphogenesis, leading to persistence of the embryonic myocardium. The condition is recognised by an excessively prominent trabecular meshwork and deep intertrabecular recesses of the left ventricle. These intertrabecular recesses are prone to thrombus formation, with resultant embolic sequelae. We describe a case of cerebral thrombo-embolism in a young woman due to isolated left ventricular non-compaction.

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Case report

A 42-year-old woman was referred for a cardiac evaluation after a second episode of cerebral thrombo-embolism, involving the left mid-cerebral artery distribution. The patient had a history of ulcerative colitis, which was in remission due to 5-aminosalicylic acid use. The clinical examination, electrocardiography, biochemical profile and chest roentgenography were all within normal limits.

Two-dimensional echocardiography was then performed. This revealed the presence of numerous, excessively prominent trabeculations and deep intertrabecular recesses in the mid- and apical segments of the left ventricle (Fig. 1). During systole, the ratio of the non-compacted to compacted layer was above two, a characteristic finding in isolated left ventricular non-compaction (Fig. 2).

The diagnosis of isolated left ventricular non-compaction was made, based on fulfillment of four echocardiographic criteria, as described by Jenni *et al.* (see Discussion): (1) coexisting cardiac abnormalities were absent, (2) a trabecular meshwork with deep, endomyocardial spaces was present, (3) an end-systolic ratio of more than two of non-compacted to compacted layer was present, and (4) colour Doppler demonstrated deep, perfused intertrabecular recesses. Systolic function was normal with a left ventricular ejection fraction of 64% and a normal pro-BNP level. No electrocardiographic manifestations of dysrhythmia were present.

It was decided that the patient needed long-term anticoagulation with warfarin in order to prevent any thromboembolic recurrences. Echocardiography of first-degree relatives did not reveal any other cases of non-compaction.

Department of Physiology, University of Pretoria and Pretoria Heart Hospital, Pretoria

J. KER, MB ChB (Pret), MMed (Pret), MRCP (Edinburgh)

Department of Radiology, Pretoria Heart Hospital, Pretoria

C VAN DER MERWE, MB ChB (Pret), MMED (Pret)

Discussion

Isolated left ventricular non-compaction is a rare congenital condition that is the result of an intrauterine developmental arrest, which stops the compaction of the loose, myocardial fibre meshwork of the left ventricle.[1] The resultant non-compacted myocardium has a spongy appearance with prominent trabeculations and deep, intertrabecular recesses that communicate with the ventricular cavity, predisposing to local thrombus formation.[2] The condition is currently listed by the World Health Organisation as an unclassified cardiomyopathy,[3] with only a few case reports in the literature.[1]

A non-isolated form associated with other congenital heart defects, and an isolated form, often undetected, have been described.[1] The risk for thrombo-embolic episodes is high.[1,4] Severe heart failure and life-threatening ventricular arrhythmias can also complicate this condition[2] and it has been advocated that cardiac transplantation should be aggressively pursued once heart failure occurs.[1] It is therefore clear that a diagnosis of isolated left ventricular non-compaction is associated with a high morbidity and mortality and the diagnosis should be made with care, as prominent ventricular trabeculation can be found in healthy hearts as well as in hypertrophied hearts, due to dilated, hypertrophic, valvular

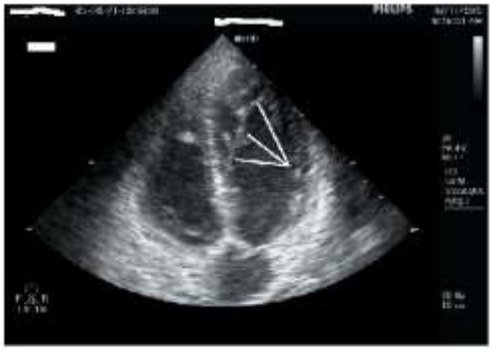

Fig. 1. Two-dimensional echocardiography. Note the excessively prominent trabeculations (white lines) and deep intratrabecular recesses in the mid- and apical segments of the left ventricle.

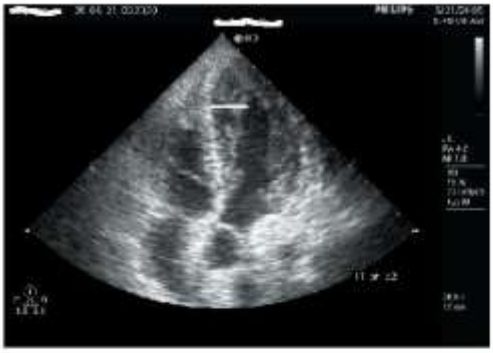

Fig. 2. Two-dimensional echocardiography. Note the characteristic ratio of non-compacted (long white line) to compacted layer (short white line) > 2 during systole.

or hypertensive cardiomyopathy.[2] However, in a recent study by Murphy *et al.*,[5] it was found that isolated left ventricular non-compaction is associated with a better prognosis than previously thought.

Since our patient did not have heart failure, which was shown by normal LVEF and a normal pro-BNP level as well as the absence of any dysrhythmias, one tends to think that the prognosis might not be so grave as that reported in the literature. Because this is such a rare condition with few documented case reports, it is fair to speculate that there might be a continuum of severity, with not all patients progressing to heart failure. Only time will tell, as more case reports will undoubtedly appear in future.

Echocardiographic criteria have been established[2] and include the following: the characteristic appearance of numerous, excessively prominent trabeculations and deep, intertrabecular recesses; intertrabecular spaces filled by blood from the ventricular cavity; and an end-systolic ratio of more than two of non-compacted to compacted layers. This last criterion differentiates isolated left ventricular non-compaction from the trabeculations seen in left ventricular hypertrophy, hypertrophic cardiomyopathy and dilated cardiomyopathy. In summary, we describe an unusual cause of thrombo-embolic stroke and this case should highlight the importance of meticulous echocardiography in patients with thrombo-embolic stroke.

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Clinical Medicine Insights: Cardiology

CASE REPORT

Post-Mortem Echocardiography as a Guide to Cardiac Autopsy—A Worthwhile Concept?

J. Ker[1], L. Du Toit-Prinsloo[2], WFP. Van Heerden[3] and G Saayman[2]

[1]Department of Physiology, University of Pretoria, Pretoria, South Africa. [2]Department of Forensic Medicine, University of Pretoria, Pretoria, South Africa. [3]Department of Oral Pathology and Oral Biology, University of Pretoria, Pretoria, South Africa. Corresponding author email: jker@wol.co.za

Abstract: Sudden and unexpected death in the young is a common and worldwide problem. Sudden, unexpected death in infancy (SUDI), clinically unexpected death in an infant between one week and one year of age, affects around 1 in 1000 infants. Autopsy will reveal a specific cause of death in only one third of cases. This has led to various ancillary examinations in an effort to increase the diagnostic yield of the autopsy.

In this case report it is suggested that another diagnostic modality, that of the post-mortem echocardiogram might be a worthwhile concept to explore.

Keywords: autopsy, echocardiogram, SUDI

Clinical Medicine Insights: Cardiology 2010:4 59–61

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Introduction

Every year thousands of infants, children, adolescents and young adults die suddenly and unexpectedly.[1] Of these a significant proportion are autopsy negative and are classified as autopsy negative sudden, unexplained death.[1] Sudden unexpected death in infancy (SUDI) is defined as clinically unexpected death in infants from one week to one year of age.[2] SUDI affects around 1 in 1000 infants, with a peak prevalence at three months of age.[2]

Detailed autopsy examinations, including various ancillary examinations reveal a specific cause of death in only about one third of cases.[2,3] These ancillary examinations include radiological skeletal surveys to identify rib fractures,[4] bacteriological examination,[5,6] post-mortem genetic testing to identify the subset of channelopathic SUDI, known as the cardiac channel molecular autopsy,[1] as well as DNA and RNA extraction from a variety of tissues to detect serotonin transporter gene polymorphisms.[7]

Various cardiovascular abnormalities, isolated or associated with central nervous system alterations have been observed in cases of SUDI.[5] These include: accessory atrioventricular pathways (mostly Mahaim fibres), hypoplasia of the cardiac conduction system or the central fibrous body, splitting of the atrioventricular node or the His bundle and a Zahn node.[5]

In this proof of concept study we aimed to explore the feasibility of post-mortem echocardiography in order to alert the pathologist to any possible underlying cardiovascular anomalies before the actual dissection of the heart, in order to avoid any possible damage to underlying delicate structures.

Materials and Methods

This proof of concept study was undertaken with approval of the ethical committee of the Faculty of Health Sciences, University of Pretoria.

The heart of a three month old male infant, whose death fulfilled the criteria for SUDI was used. At autopsy, the heart was removed, irrigated and filled with buffered formalin. The major vessels were tied of with string, in order to maintain the filling of the left ventricle with formalin to facilitate the subsequent echocardiogram.

Echocardiography was performed with a Philips Envisor C echocardiography system. The heart was dissected afterwards.

Results

Echocardiography revealed the presence of a subaortic muscular band (see Figure 1). The muscular tendon is marked with +. The left ventricle was then dissected by cutting it open from the lateral aspect in order to prevent any damage to the observed muscular band. The presence of a thick muscular band was confirmed macroscopically (see Figure 2).

Discussion

Autopsy has a very low yield for a specific diagnosis in cases of SUDI.[2,3] Weber et al performed the largest single-institution autopsy study of SUDI.[3] They analyzed 1516 paediatric post-mortem examinations and found 546 SUDI cases. Death could be explained in 37% of these cases by the autopsy findings implying that 63% of SUDI cases remained unexplained. The authors suggest that alternative and/or additional diagnostic techniques are needed to improve the detection rate of an identifiable cause of death at autopsy in an attempt to lower the high number of unexplained SUDI cases.

An intriguing new concept is the so-called "molecular autopsy" where post-mortem genetic analysis in cases of SUDI explores the prevalence of channelopathies as the pathogenic basis for sudden unexplained death in infants.[8]

We propose that post-mortem echocardiography is an additional concept worth exploring. This single case report merits a larger study to determine whether post-mortem echocardiography can ultimately guide the cardiac dissection method in order to preserve delicate underlying cardiac anomalous structures

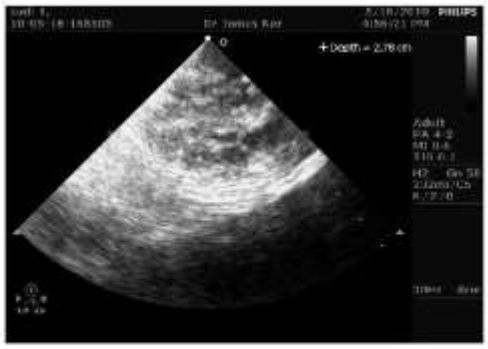

Figure 1. Post-mortem echocardiogram. Note the subaortic muscular band marked with +.

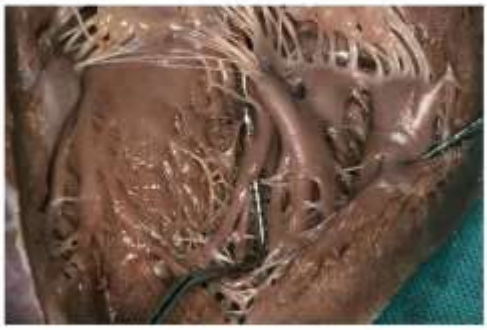

Figure 2. The dissected left ventricle. Note the thick muscular band.

which may ultimately turn out to play a causal role in cases of SUDI.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patients parents for publication of this study.

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Clinical Medicine Insights: Cardiology

SHORT REPORT

Sudden Infant Death Syndrome and Left Ventricular Hypertrabeculation-Hidden Arrhythmogenic Entity?

J. Ker[1], L. Du Toit-Prinsloo[2], W.F.P. van Heerden[3] and G. Saayman[2]

[1]Department of Physiology, University of Pretoria, Pretoria, South Africa. [2]Department of Forensic Medicine, University of Pretoria, Pretoria, South Africa. [3]Department of Oral Pathology and Oral Biology, University of Pretoria, Pretoria, South Africa. Corresponding author email: jker@wol.co.za

Abstract: Left ventricular noncompaction/hypertrabeculation is a condition which is characterized by a highly trabeculated, "spongy" myocardium.
It can present at any age with heart failure, arrhythmia and/or thromboembolic events.
A wide variety of mutations have been found to be a cause of hypertrabeculation and it is possible that there is a continuum of hypertrophic cardiomyopathy, dilated cardiomyopathy and hypertrabeculation/noncompaction.
We present a case of left ventricular hypertrabeculation which presented as sudden infant death syndrome and we propose that this entity may be a hidden cause of arrhythmic death in some infants presenting as sudden infant death syndrome.

Keywords: sudden infant death syndrome, hypertrabeculation, noncompaction

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Introduction

The cardiac syndrome of isolated, left ventricular noncompaction is characterized by a persistence of the embryonic pattern of a highly trabeculated myocardium in the left ventricle.[1] This condition can be familial or sporadic and can be due to a variety of mutations in any one of the following proteins: mitochondrial, cytoskeletal, Z-line or sarcomeric.[1]

Chin et al[2] were the first to describe the entity and the complications of heart failure, ventricular arrhythmias and thromboembolic events. An association with Wolff-Parkinson-White syndrome was also noted.[2]

This condition can present during early life as fetal hydrops[1] or as sudden infant death syndrome due to neonatal heart failure and/or ventricular fibrillation.[1,3–6]

Case Report and Discussion

We present a case report of a three month old male infant who presented with sudden infant death syndrome. This three month old non-caucasian died suddenly and unexpectedly at his day care centre. He did not have any known medical problems and no surgical procedures were ever performed. No known allergies were present and no known family history of sudden, unexpected death were present. Unfortunately the family members were lost to follow up, before electrocardiographic and echocardiographic screening could be performed to assess the risk for sudden unexpected death.

Postmortem examination of the heart revealed numerous apical trabeculations of the left ventricle (see Fig. 1). The right ventricle appeared perfectly normal. The left ventricular wall thickness measured 1 cm and the histological assessment was perfectly normal. No abnormalities were detected in any other organs during the postmortem examination and no thrombi were detected in the arterial system or the left ventricle.

Current consensus on the mechanism of left ventricular noncompaction is that an arrest of myocardial maturation occurs during embryogenesis.[7] Before the eighth week of fetal life the myocardium consists of a network of fibres, washed by deep recesses, communicating with the left ventricular cavity.[1] The reason for this is that there is no coronary vasculature yet, therefore the trabeculations of myocardial tissue increases the myocardial surface area in contact with the ventricular lumen, as the myocardium is nourished directly from the endoventricular column of blood at this stage.[1]

Figure 1. Left ventricular hypertrabeculation in a three month old infant, presenting as sudden infant death syndrome. It is postulated that the apical area of hypertrabeculation acted as the source of a fatal arrhythmia.

The coronary vasculature develops during the fifth to eighth week of fetal life and after this the meshwork of myocardial fibres will become compacted.[1] This "compaction process" advances from the base of the heart to the apex and from the epicardium to the endocardium as this is the direction of coronary arterial development.[1]

Various echocardiographic criteria have been proposed for the diagnosis of left ventricular noncompaction.[2,8] In reaction to these proposed echocardiographic criteria Stöllberger et al[1,9,10] named this peculiar left ventricular phenotype "left ventricular hypertrabeculation" and defined the condition as the presence of more than three trabeculations in the left ventricle in a location distal (apical) to the papillary muscles. A postmortem study by Boyd et al[1,11] in 474 normal human hearts have shown that while 68% of these hearts displayed prominent trabeculations, only 4% of these hearts had more than three and none had more than five trabeculations.

Left ventricular noncompaction/hypertrabeculation can occur in a sporadic or familial form and both types can be due to a variety of mutations in various sarcomere, mitochondrial, Z-line or cytoskeletal proteins.[1,12–15]

Figure 1 clearly demonstrates more than three trabeculations in the left ventricle in a location apical to the papillary muscles. According to

Boyd et al[11] this case which presented as a sudden infant death syndrome thus fulfills the criterion for left ventricular hypertrabeculation. The association of hypertrabeculation/noncompaction with various sarcomere mutations supports the concept that this entity is a cardiomyopathy and furthermore, that there is a spectrum from hypertrophic cardiomyopathy, especially apical hypertrophic cardiomyopathy, dilated cardiomyopathy and hypertrabeculation/noncompaction.[14]

The natural history of left ventricular hypertrabeculation/noncompaction varies widely. Presentation with heart failure, arrhythmias and/or thromboembolism is described in patients of all ages.[15] Mild cases may remain asymptomatic.

We propose that this case of sudden infant death syndrome is due to an episode of fatal arrhythmia due to underlying left ventricular hypertrabeculation and that the presence of more than three trabeculations apical to the papillary muscles should be specifically excluded during postmortem examination in cases of sudden infant death syndrome.

We acknowledge the possibility that the left ventricular hypertrabeculation may be an incidental finding as this entity may be found in asymptomatic, "healthy" individuals, but due to the observation that arrhythmias may occur at any age[15] we propose that this may be an underrecognized cause of sudden, unexpected death, mimicking sudden infant death syndrome.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patients parents for publication of this study.

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Clinical Medicine Insights: Cardiology

CASE REPORT

Subendocardial Fibrosis in Left Ventricular Hypertrabeculation-Cause or Consequence?

J. Ker[1], L. Du Toit-Prinsloo[2], W.F.P. Van Heerden[3] and G. Saayman[2]

[1]Department of Physiology, University of Pretoria, Pretoria, South Africa. [2]Department of Forensic Medicine, University of Pretoria, Pretoria, South Africa. [3]Department of Oral Pathology and Oral Biology, University of Pretoria, Pretoria, South Africa. Corresponding author email: jker@wol.co.za

Abstract: Left ventricular noncompaction has been classified as a primary cardiomyopathy with a genetic origin. This condition is morphologically characterized by a thickened, two-layered myocardium with numerous prominent trabeculations and deep, intertrabecular recesses. Recently, it has become clear that these pathological characteristics extend across a continuum with left ventricular hypertrabeculation at one end of the spectrum.
The histological findings include areas of interstitial fibrosis.
We present a case of left ventricular hypertrabeculation which presented as sudden infant death syndrome. Histologically areas of subendocardial fibrosis was prominent and we propose that this entity may be a hidden cause of arrhythmic death in some infants presenting as sudden infant death syndrome., with areas of subendocardial fibrosis as possible arrhythmogenic foci.

Keywords: sudden infant death syndrome, hypertrabeculation, noncompaction, fibrosis

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Introduction

Left ventricular noncompaction has been classified as a primary cardiomyopathy with a genetic origin.[1] Morphologically, this condition is characterized by a thickened, two-layered myocardium with numerous and prominent trabeculations and deep, intertrabecular recesses.[1–3] Left ventricular noncompaction may be an isolated finding or it may be associated with a variety of other congenital heart defects.[1] Left ventricular noncompaction is associated with numerous sarcomere mutations and this fact created the view that there is a spectrum spanning hypertrophic cardiomyopathy (especially apical HCM), dilated cardiomyopathy and left ventricular noncompaction.[4]

Current diagnostic criteria for left ventricular noncompaction require the visualization of two distinct myocardial layers.[5] The work of Stöllberger departs from this stipulation and he coined the term "left ventricular hypertrabeculation".[5] This entity, which can be viewed as a less severe form of noncompaction, is characterized by the presence of more than three trabeculations located apically to the papillary muscles.[5]

Case Report and Discussion

We present a case report of a three month old male infant who presented with sudden infant death syndrome. The macroscopical characteristics of this case was reported before.[6] This three month old non-caucasian died suddenly and unexpectedly at his day care centre. He did not have any known medical problems and no surgical procedures were ever performed. No known allergies were present and no known family history of sudden, unexpected death were present. Unfortunately the family members were lost to follow up, before electrocardiographic and echocardiographic screening could be performed to assess their risk for sudden unexpected death.

Postmortem examination of the heart revealed numerous apical trabeculations of the left ventricle (see Fig. 1). The right ventricle appeared perfectly normal. The left ventricular wall thickness measured 1 cm. No abnormalities were detected in any other organs during the postmortem examination and no thrombi were detected in the arterial system or the left ventricle.

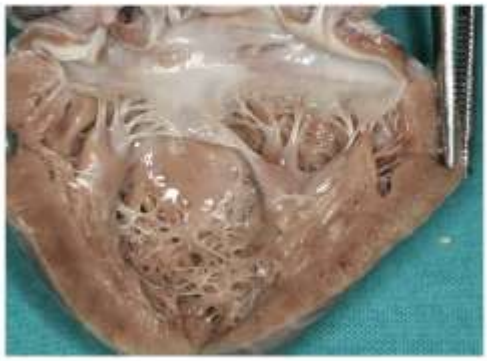

Figure 1. Note the numerous trabeculations in the apex of the left ventricle. More than three trabeculations distal to the level of the papillary muscles is present, thus fulfilling the criterion for the diagnosis of left ventricular hypertrabeculation.

Figure 1 clearly demonstrates more than three trabeculations in the left ventricle in a location apical to the papillary muscles. According to Stöllberger[7,8] this case which presented as a sudden infant death syndrome thus fulfills the criterion for left ventricular hypertrabeculation. Histological assessment of sections underlying the left ventricular trabeculae revealed prominent areas of subendocardial fibrosis (see Figs. 2, 3 and 4).

Figure 5 is a histological section of the apex of the left ventricle of a three month old male infant who also presented as a sudden infant death syndrome, but without left ventricular hypertrabeculation to serve as a control.

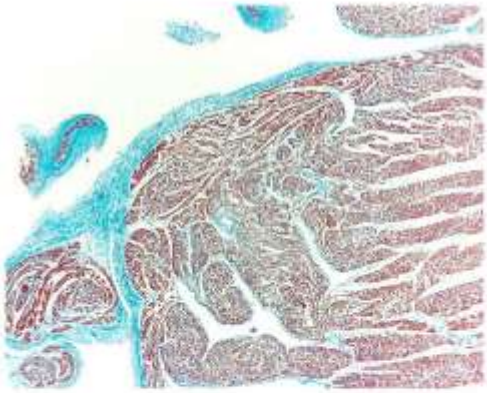

Figure 2. Histological sections with a Masson stain of the apex of the left ventricle. Note the areas of subendocardial and interstitial fibrosis.

Figure 3. Histological sections with a Masson stain of the apex of the left ventricle. Note the areas of subendocardial and interstitial fibrosis.

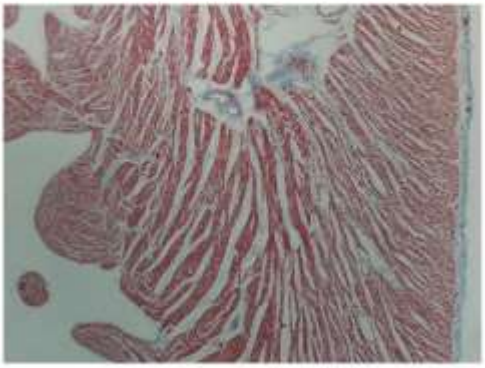

Figure 5. Histological section with a Masson stain of the apex of the left ventricle of the control case of sudden infant death syndrome, but without left ventricular hypertrabeculation.

Endocardial fibrosis with prominent elastin deposition have been described in cases of left ventricular noncompaction.[5,9,10] Currently, it is thought that ischaemia may play a major role in the pathogenesis of left ventricular noncompaction: MRI and thallium-201 scintigraphy has shown subendocardial and transmural perfusion defects which corresponds to areas of noncompacted myocardium.[5,11–14] Reduced coronary flow reserve, indicating microvascular dysfunction has also been shown to be present in isolated ventricular noncompaction by PET.[12] Currently, a "chicken and egg" dilemma exists regarding the pathogenesis of isolated ventricular noncompaction: either an impairment in the development of the myocardial microcirculation impairs the normal compaction process of the myocardium or vice versa.

In this case report we describe subendocardial fibrosis in a three month old infant with left ventricular hypertrabeculation. Current literature notes the presence of fibrosis in cases of ventricular noncompaction, this is the first case describing fibrosis in ventricular hypertrabeculation—the less severe form of noncompaction. Secondly, the presence of such striking subendocardial fibrosis implies that the involved areas in the left ventricle must experience ischaemia already in utero. Lastly, we propose that these fibrotic areas may act as the foci of ventricular arrhythmia as the underlying cause of death.

Figure 4. Histological sections with a Masson stain of the apex of the left ventricle. Note the areas of subendocardial and interstitial fibrosis.

Contribution from Different Authors

J Ker did the literature review and writing. L Du-Toit-Prinsloo, WFP Van Heerden and G Saayman did the post-mortem analysis and histological assessment.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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Case Report Open Access

The Enigma of Bulging to the Left—A Case Report of An Unusual Atrial Septal Aneurysm

James Ker*

Department of Physiology, University of Pretoria, PO Box 24318, Gesina, Pretoria, South Africa

Abstract

An atrial septal aneurysm (ASA) can be defined as a localized segment of the interatrial septum that bulges into either (or both of) the right or left atrium. It is still not certain whether this is a congenital or an acquired lesion and the natural history is unknown.

An ASA can occasionally be found in association with various disturbances of intracardiac hemodynamics, thus raising the question of a cause effect relationship.

Marazanof et al. found that in 90% of cases the atrial septal aneurysm protruded into the right atrium and that in half of the 10% of cases where it bulged into the left atrium this could not be explained by a raised right atrial pressure. To date this phenomenon remains unexplained.

In this case report such an unusual presentation of an atrial septal aneurysm is presented and discussed.

Keywords: Atrium; Septal; Aneurysm

Introduction

An atrial septal aneurysm (ASA) can be defined as a localized segment of the interatrial septum that bulges into either (or both of) the right or left atrium [1]. It is still not certain whether this is a congenital or an acquired lesion and the natural history is unknown [2].

Furthermore, an ASA can be an isolated lesion or it can be associated with a variety of other cardiac anomalies, such as a patent foramen ovale, atrial septal defect and mitral valve prolapse [1,3-6].

Of even more importance is the fact that an ASA can occasionally be found in association with various disturbances of intracardiac hemodynamics, thus raising the question of a cause effect relationship [2]. An ASA has been reported in association with the following alterations of intracardiac hemodynamics: tricuspid atresia [7,8], premature closure of the foramen ovale [2], mitral stenosis [9], hypoplastic right heart syndrome [10], spontaneous closure of an atrial septal defect [11], severe aortic stenosis in a 68 year old man [9], in a 4 year old boy undergoing revision of a Waterston shunt [9] and even in a case of pulmonary tuberculosis with pulmonary hypertension [2].

Marazanof et al. [12] studied the echocardiographic characteristics of atrial septal aneurysms in 259 patients. They found that in 90% of cases the atrial septal aneurysm protruded into the right atrium and that in half of the 10% of cases where it bulged into the left atrium this could not be explained by a raised right atrial pressure [12]. To date this phenomenon remains unexplained.

In this case report such an unusual presentation of an atrial septal aneurysm is presented and discussed.

Case Report

A 51 year old Caucasian male presented for a cardiovascular examination. He was asymptomatic with no prior surgical or medical problems. He did not use any prescription medication, never smoked and had no known allergies. The reason for the presentation for a cardiovascular examination was the presence of a midsystolic click, auscultated by his primary care provider.

Clinical examination confirmed the presence of a midsystolic click, no murmur was present. No other abnormalities were detectable. Transthoracic, two dimensional echocardiography revealed the cause of the midsystolic click to be a prominent atrial septal aneurysm (Figures 1-3).

Note the absence of the aneurysm during ventricular diastole with the mitral valve at maximal opening (Figure 4). Figure 1-3 demonstrate

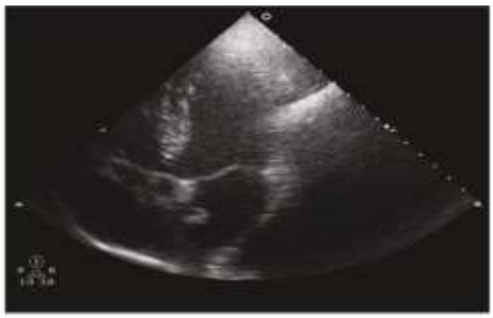

Figure 1: Title: Atrial septal aneurysm during early ventricular systole. Description: Transthoracic echocardiographic image. Note the atrial septal aneurysm bulging into the left atrium early in ventricular systole. Sequential images will show the prolapse to become more pronounced.

***Corresponding author:** Prof. James Ker MRCP, Ph.D, FESC, FACC, Department of Physiology, University of Pretoria, PO Box 24318, Gesina, Pretoria, 0031 South Africa, Tel: +2712-3430078; Fax: +2712-3430079; E-mail: jker@wol.co.za

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the progressive bulge of the interatrial septum into the left atrium as ventricular systole progresses. No other cardiac anomalies were detectable.

Due to the peculiarity that the interatrial septum bulged into the left atrium a comprehensive investigation to rule out any possible cause for pulmonary hypertension was done. A chest radiograph, arterial blood gas analysis, flow-volume loop and ventilation perfusion scintigraph were all within normal limits.

No medical or surgical intervention was done and the patient remains well after 12 months of the initial examination.

Discussion

An atrial septal aneurysm is a known cause of a midsystolic click [13]. Alexander et al. [13] used phonocardiography to show that the click coincides with the sudden bulging of the interatrial septum. As shown in this case the bulging of the interatrial septum is maximal during midventricular systole (Figures 1-4), coinciding with the audible midsystolic click.

Tei et al. [14] have shown that even in normal individuals slight shifts of the interatrial septum can be observed echocardiographically and that these interatrial septal shifts can be greatly exaggerated in the setting of a large interatrial pressure gradient as can be found in mitral stenosis, mitral regurgitation and tricuspid regurgitation.

Pressure changes inside the atria are characterized by the " a, c and v" waves on the atrial pressure curve [15]. In the atrial pressure curve the "a" wave is caused by atrial contraction and ordinarily the right atrial pressure rises to 4-6 mmHg and the left atrial pressure to about 7-8 mmHg during atrial contraction [15]. The "c" wave occurs when the ventricles begin to contract and is caused mainly by the bulging of the atrioventricular valves backward into the atria [15]. The "v" wave occurs at the end of ventricular contraction and is the result of blood flowing into the atria while the atrioventricular valves are still closed [15]. In the normal individual left atrial pressure exceeds right atrial pressure, so why then the bulging into the left atrium? This phenomenon was already noted by Marazanof et al. [12] in 1995, but remains unexplained. In that study 259 cases of atrial septal aneurysms were studied and 90% of these protruded into the right atrium. As in this case half of the 10% of cases where the aneurysm protruded into the left atrium the phenomenon could not be explained by an increased right atrial pressure [12].

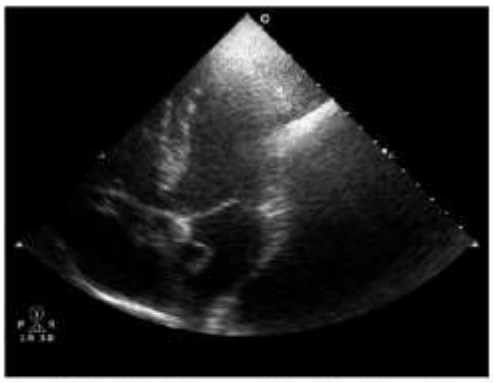

Figure 2: Title: Atrial septal aneurysm during mid ventricular systole. Description: Transthoracic echocardiographic image. Note the more pronounced bulging of the atrial septal aneurysm into the left atrium as ventricular systole progresses.

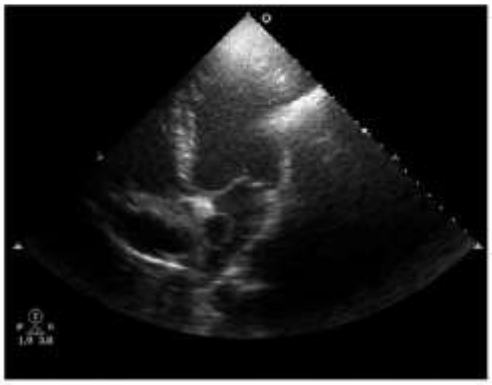

Figure 3: Title: Atrial septal aneurysm during late ventricular systole. Description: Transthoracic echocardiographic image. Note the maximal bulge into the left atrium during late ventricular systole.

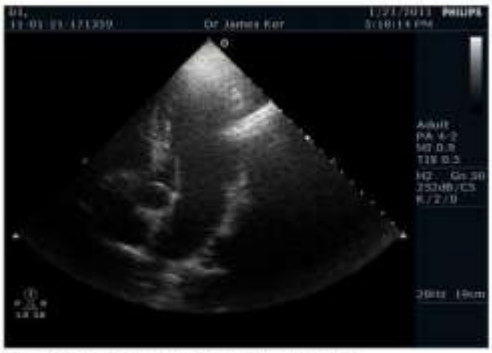

Figure 4: Title: Atrial septum during ventricular diastole. Description: The atrial septum during ventricular diastole. Note that there is no bulging of the septum into the left atrium.

In the same study by Marazanof et al. [12] it was noted that in all patients the fossa ovalis was involved in the aneurysm, but that in 55% of cases the aneurysm extended to the distal two thirds of the interatrial septum, thus creating a similar thin and outpouching membrane. Currently, no data on the genetical aspects of interatrial septal aneurysms are available. There is a possibility that this entity may be the result of an abnormality of connective tissue or a congenital abnormality of interatrial septation [12].

These are important questions to answer as an interatrial septal aneurysm may be a major cause of ischemic stroke in young adults [16] with recent reports suggesting that an atrial septal aneurysm associated with a patent foramen ovale might be a common cause of stroke even in patients older than 55 years [17,18]. An atrial septal aneurysm frequently co-exists with an atrial septal defect and/or a patent foramen

ovale [19] and this combination of lesions is more strongly associated with cryptogenic stroke and also more likely to lead to recurrent stroke than a patent foramen ovale in isolation [20,21].

Previous dogma held that stroke risk was due to paradoxical embolism through a patent foramen ovale, yet this risk remains undefined as deep venous thrombosis is infrequently detected in such patients [19]. An alternative and currently plausible mechanism for systemic embolism in these patients entails the presence of left atrial dysfunction and intermittent atrial arrhythmias, such as atrial fibrillation [19,22,23]. The incidence of atrial fibrillation in patients with atrial septal aneurysm ranges from 0% to 23% [5,24,25,].

In conclusion, it is suggested that there are many aspects of atrial septal aneurysms still to be elucidated and specifically that the stroke risk may be more related to atrial arrhythmia than currently realized. It can be hypothesized that atrial septal aneurysms bulging into the left atrium may be more prone to systemic embolism purely due to the left atrial bulge.

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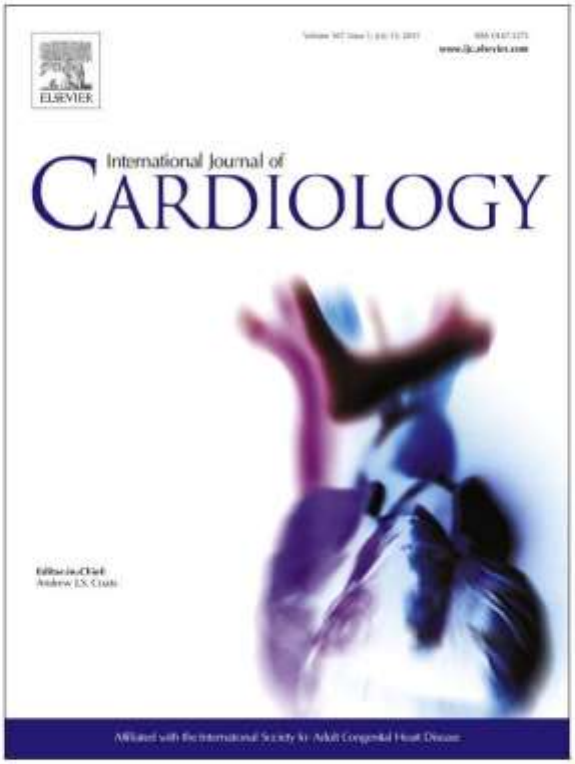

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Letter to the Editor

Cor triatriatum sinister presenting with adult onset atrial fibrillation—Another rare cause for a common clinical problem

James Ker *

Department of Physiology, University of Pretoria, Pretoria, South Africa

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Cor triatriatum – which may present as classical cor triatriatum or cor triatriatum sinister – is a rare form of congenital heart disease where the left atrium is divided by a fibromuscular septum [1]. First described by Church in 1868 [2], this is an entity which is rarely found in adults and accounts for approximately 0.1% of cases of congenital heart disease [3].

Patients with cor triatriatum classically present in infancy due to the obstructive nature of the left atrial membrane, with the creation of a pressure gradient with resultant elevation in pulmonary venous and arterial pressures [4]. However, some cases may present in adulthood [4].

A few classifications of cor triatriatum exist and may explain why some cases only present in later life [1,5–7]: In 1949 Loeffler divided cor triatriatum into 3 groups, based on the number and size of membrane fenestrations [6] – group I has no opening, group II has one or more small openings and group III has a wide opening. Marin-Garcia et al. [7] classify cor triatriatum on the appearance of the accessory left atrial chamber, with diaphragmatic, hour-glass and tubular subtypes.

As stated before cor triatriatum most commonly presents in infancy or childhood [1] and there are only a few reports of "subtotal" cor triatriatum presenting in adulthood in the literature – so-called cor triatriatum sinister [5]. Such adults may be asymptomatic where the diagnosis is incidental or the presenting clinical picture may be dyspnea, hemoptysis and/or atrial fibrillation. The rarity of the sinister variant in adults is illustrated by the following: in the laboratory of Buchholz and Jenni [5] only one classic cor triatriatum sinister was diagnosed in the 1980's out of a total of 12,576 Doppler echocardiographic studies and from 1994 to 1999 there were only three newly diagnosed cases in the literature [5].

Fig. 1 is a transthoracic echocardiographic image demonstrating an accessory left atrial chamber in the lateral wall of the left atrium above the posterior mitral valve cusp (marked with +). Fig. 2 is an MRI image of the left atrium and left ventricle, clearly demonstrating this accessory left atrial chamber. These figures are from a 43 year old Caucasian male. He was perfectly healthy until two years ago, when he presented with atrial fibrillation. After extensive diagnostic work up, which did not reveal any known cause for atrial fibrillation, he was sent for an ablation procedure which failed. Afterwards another two failed ablation attempts were performed. He was sent to our institution for a second opinion and a diagnosis of cor triatriatum sinister was made.

Another classification by Lucas and Krabill [7] divides cor triatriatum into type I with an accessory left atrial chamber where all the pulmonary veins communicate with the left atrium, type II where the pulmonary veins do not communicate directly with the left atrium and type III, the "subtotal" variant where some pulmonary veins communicate with the left atrium and some communicate with the accessory chamber.

Currently the embryologic basis of this anomaly is controversial, with three main theories at present [1]: the malseptation, malincorporation and entrapment theories. The malseptation hypothesis proposes that the dividing septum in the left atrium is an abnormal growth of the septum primum. The malincorporation hypothesis proposes that the septum results from incomplete incorporation of the embryonic common pulmonary vein into the left atrium. The entrapment hypothesis proposes that the left horn of the sinus venosus entraps the common pulmonary vein and thereby prevents its incorporation into the left atrium.

In conclusion, cor triatriatum sinister is a rare form of congenital heart disease which can present with adult onset atrial fibrillation. In this era of advanced diagnostic imaging this entity might be diagnosed with increasing frequency in the coming years and thus adds another rare cause for a common clinical entity, the patient with atrial fibrillation.

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* Tel.: +27 123430078; fax: +27 123430079.
E-mail address: jker@wol.co.za.

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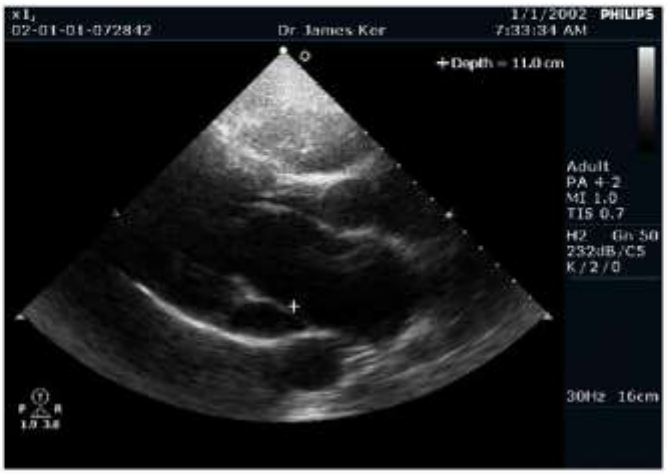

Fig. 1. Transthoracic echocardiographic image demonstrating the membrane in the lateral wall of the left atrium.

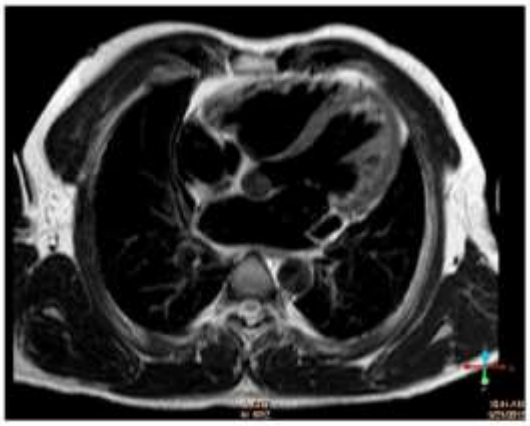

Fig. 2. MRI image confirms the accessory chamber formed in the lateral wall of the left atrium by the membrane.

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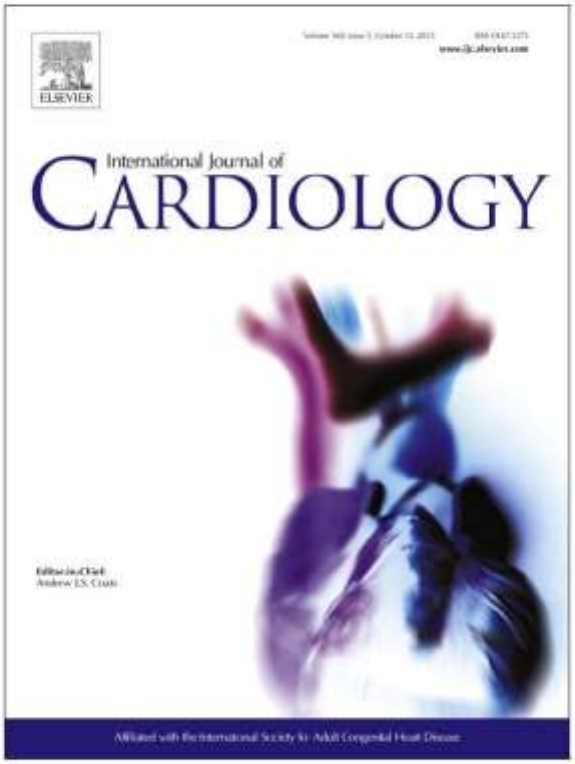

On the many possible futures of atrial fibrillation

James Ker *

Department of Physiology, University of Pretoria, PO Box 24318, Gezina, Pretoria 0031, South Africa

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Dear Editor,

After reading the latest report of yet another case of adult cor triatriatum sinister complicated by atrial fibrillation by Siniorakis et al. [1] the following quote by the bestselling British author of heroic fantasy, David Andrew Gemmell sprang into my mind: "Life is not so simple. There are many futures. The life of a single person is like a great tree: every branch, every twig, every leaf is a possible future" [2].

This is especially true in the clinical scenario of atrial fibrillation. Clearly a multifactorial disease with many possible causes…many branches, many twigs, many leaves….

Clearly we can add adult cor triatriatum sinister as yet another leaf to the tree of atrial fibrillation. However, we are faced with numerous clinical questions on this fairly newly discovered adult clinical entity.

Why do these adult patients present so late? It can be assumed that they had fairly asymptomatic childhood years as they would present as adults with extensive clinical investigations as children otherwise, which certainly is not the case if one looks at all the currently available case reports.

Secondly, by merely assuming that this entity is as simple as a congenital membrane separating various parts of the left atrium one is left with a hypothesis which is fraught with many errors and open to criticism. If this was truly the case, then why the late presentation as adults. Therefore, a reasonable question is if this presumed developmental anomaly involves the whole atrial wall with abnormal atrial musculature as a whole affecting all structural components.

Thirdly, we have to ask the question if whether they may all have had atrial fibrillation since birth which was simply not diagnosed before their adulthood years. This will imply that this particular subset of atrial fibrillation is more benign than the other subsets of adult onset cases with their respective diverse causes.

Fourthly, how should these cases be treated, if at all? At present we do not have any evidence based medicine on this subset of patients.

Lastly, in my opinion it is essential to obtain a proper imaging study of every single case of atrial fibrillation. I still see patients in my clinic who underwent unsuccessful ablation procedures where no imaging study of the left atrium was ever performed and hence with no specific diagnosis—my published case report of adult cor triatriatum sinister with adult onset atrial fibrillation is an example of such an unacceptable scenario [3]. In my opinion this can be compared to performing a thoracotomy on a coughing patient without obtaining a chest radiograph first to look for a possible reason for the symptom of cough.

In conclusion, we are left with a fairly newly discovered clinical entity with still many unanswered clinical questions. I look forward to these being answered and adding yet another leaf to the complex tree of atrial fibrillation.

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* Tel.: +27 12 3430078; fax: +27 12 3430079.
E-mail address: jker@wol.co.za.

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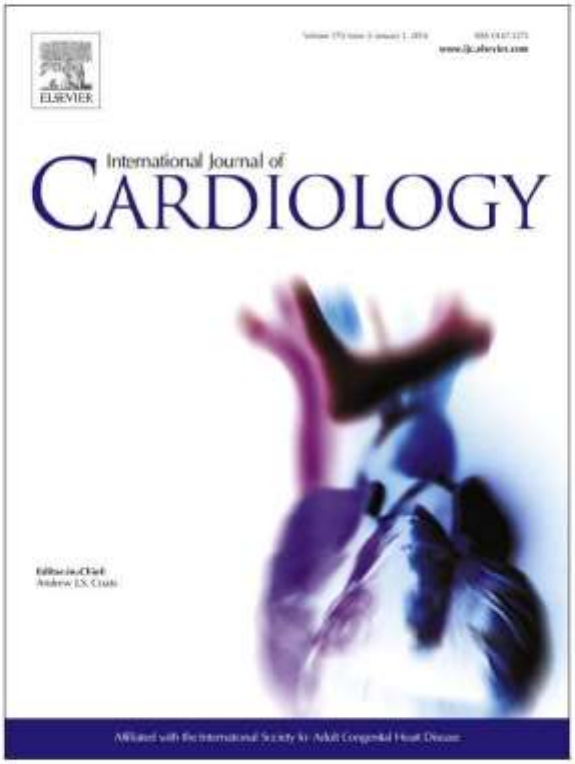

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Letter to the Editor

Congenital left atrial bands and cardioembolic events

James Ker *

University of Pretoria, Department of Genetics Hobday 36, Silver Lakes, Pretoria, Gauteng 0031, South Africa

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Congenital left atrial bands (CLAB) is a known entity [1–4]. However, the clinical importance of these anomalous muscular bands in the left atrium is still not clearly defined and they should not be confused with left ventricular false tendons [2]. It has been found that the incidence of supraventricular arrhythmias is increased in patients with such left atrial bands [3].

Until the report of two cases where cardioembolic events, resulted in stroke by Ozer et al. [1] this association was never published. To date, these two cases remain the only ones in the literature where stroke resulted from a cardioembolic event from such a CLAB.

I want to add two more cases of such cardioembolic events: One is a 29-year old male and the other a 43-year old male. Both presented with transient left sided hemiplegia which resolved completely. In both cases the only possible explanation found was the presence of a congenital left atrial band (Figs. 1 and 2). Figs. 1 and 2 is a 2D and 4D-transthoracic echocardiographic image respectively, demonstrating the presence of a congenital left atrial band from one of these cases.

In an autopsy series it was found that the incidence of CLAB is 2% [3]. These bands are composed of fibrous and muscular tissue and can be associated with a Chiari's network, a patent foramen ovale, mitral valve prolapse, mitral regurgitation and supraventricular arrhythmias [1,3]. Of note, none of these patients with stroke and transient neurological deficits due to cardioembolic events had any one of these associations present.

It is important that this entity is not confused with that of cor triatriatum sinister in which the left atrium is divided or compartmentalized by a septum [4,5].

As cryptogenic stroke is a diagnosis of exclusion I want to concur with Ozer et al. [1] that the presence of a congenital left atrial band should be added to the growing list of cardiac conditions to exclude in patients presenting with sudden neurological deficits.

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* Tel.: +27 827897661; fax: +27 128090358.
E-mail address: jker@worldcn.za.

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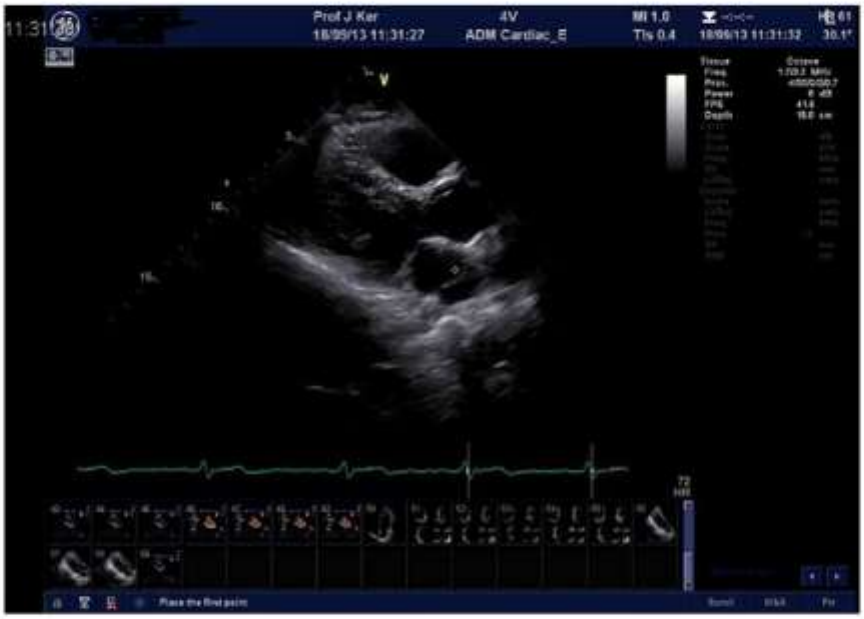

Fig. 1. 2 dimensional, transthoracic image depicting the left atrial band, marked with *.

Fig. 2. 4 dimensional, transthoracic image depicting the left atrial band, marked with *.

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Interatrial septal aneurysm with mitral valve prolapse in a patient with Marfan syndrome—a caveat of note

An interatrial septal aneurysm is a localized segment of the interatrial septum that bulges into either or both the left and right atrium [1,2]. The clinical importance of such an interatrial septal aneurysm is that it may be confused with an atrial tumor [2], it may be the cause of supraventricular arrhythmias [3] and it has a strong association with cryptogenic stroke in the young [4]. A review of the Medline database revealed only two case reports of an interatrial septal aneurysm in Marfan syndrome [3,5].

A patient with Marfan syndrome with mitral valve prolapse, as well as an interatrial septal aneurysm is presented. In this presentation an important caveat in such patients, which may lead to unnecessary mitral valve replacement, will be highlighted.

An asymptomatic 58-year old Caucasian woman requested a second opinion prior to mitral valve replacement due to severe mitral valve prolapse and apparent severe left atrial enlargement. Atrial fibrillation and stigmata of Marfan syndrome was noted, but no other clinical abnormalities were present. Fig. 1 is a two-dimensional, transthoracic echocardiographic image of the left atrium which demonstrates mitral valve prolapse of both the anterior and posterior mitral valve leaflets, as well as a prominent interatrial septal aneurysm which bulges into the right atrium. No echocardiographic stigmata of left ventricular dysfunction were present.

This case demonstrates an important, although unusual, caveat in clinical cardiology. The simultaneous presence of an interatrial septal aneurysm created the erroneous impression of severe left atrial enlargement. The dotted line in Fig. 2 indicates the actual position of the interatrial septum if one needs to measure the transverse diameter.

In this particular case, normal left ventricular function was present, no actual left atrial enlargement was present and the patient was advised that mitral valve replacement is not currently indicated.

Recently, a significant increase in the incidence of interatrial septal aneurysms was noted in young adults who were born prematurely with an extremely low birth weight (<1000 g) [6]. It is therefore foreseen that more such patients may be seen in the near future and it is hoped that this publication will aid the clinician in avoiding this important caveat in patients with severe mitral valve prolapse and simultaneous interatrial septal aneurysms.

Conflict of interest

The author declare that no conflict of interest is present.

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James Ker
Department of Internal Medicine and Genetics, University of Pretoria, Pretoria, South Africa
E-mail address: jker@wol.co.za

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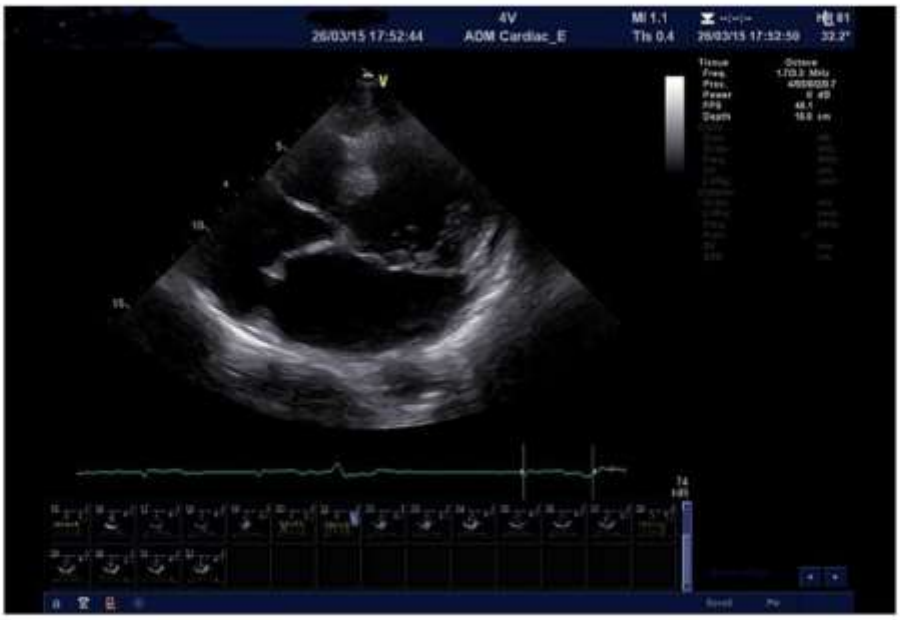

Fig. 1. Transthoracic, two-dimensional echocardiographic image demonstrating prolapse of both the anterior and posterior mitral valve leaflets with an interatrial septal aneurysm which bulges into the right atrium.

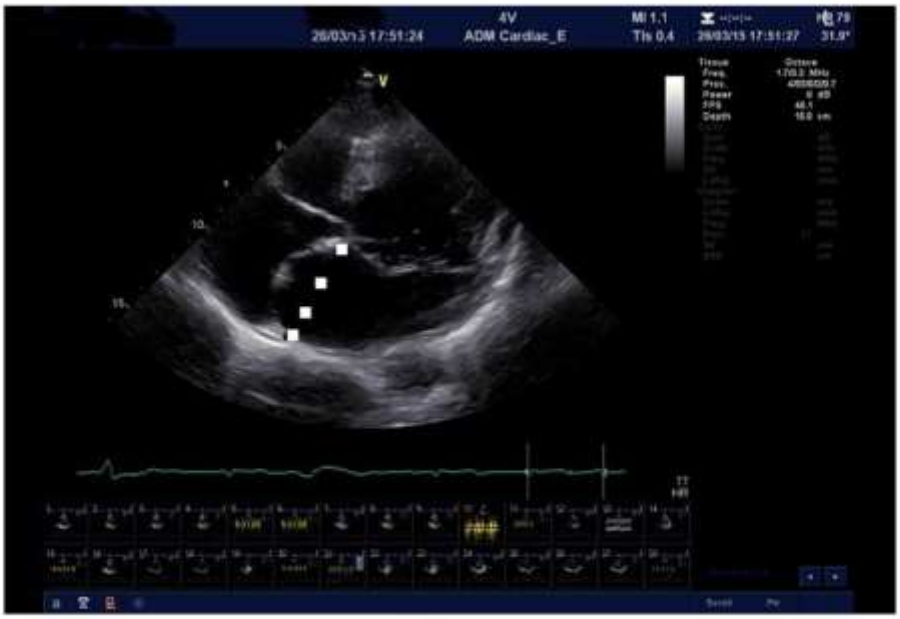

Fig. 2. The dotted line indicates the actual position of the interatrial septum when one needs to measure the transverse diameter of the left atrium.

Short Report

Tropical Doctor

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The interatrial septal aneurysm as a diagnostic aid in pulmonary embolism

James Ker

Keywords
Interatrial, septal, aneurysm, pulmonary hypertension

Introduction

An interatrial septal aneurysm is a localised segment of the interatrial septum that bulges into either or both the left and right atrium.[1,2] Such an aneurysm may be an isolated phenomenon, or it may be associated with other cardiac anomalies, such as a patent formamen ovale, atrial septal defects or mitral valve prolapse.

Hanley's diagnostic criteria for an interatrial septal aneurysm dictates that such a protrusion of the dilated part of the interatrial septum must be at least 1.5 cm beyond its plane or that it must have a phasic excursion during the cardiac cycle of at least 1.1 cm in total amplitude, with a diameter at its base of at least 1.5 cm.[3,4] There is no certainty yet if this is a congenital or an acquired lesion.[1,5]

It is known that young adults who were born prematurely are vulnerable to cardiovascular mishaps.[6] Recently, Bassareo et al.[6] observed a significantly increased incidence of interatrial septal aneurysms in young adults who were born prematurely with an extremely low birthweight (<1000 g). This important observation suggests that all young adults who were born prematurely should be screened for the presence of such.[6]

Much has been written about interatrial septal aneurysms, focusing on their associations, possible genetic associations, location, direction of bulging and clinical presentations, but to date this is the first report that the interatrial septal aneurysm can serve as a diagnostic aid in the diagnosis of pulmonary embolism.

Case report

A case of a 55-year-old man with recent onset exertional dyspnoea and prominent bulging of an interatrial septal aneurysm into the left atrium is described and how this finding led to the diagnosis of pulmonary embolism.

Figure 1. Prominent bulging into the left atrium (arrow). This a two-dimensional, transthoracic echocardiographic image of an interatrial septal aneurysm in a 55-year-old man with recent onset exertional dyspnoea.

Discussion

An echocardiographic study by Marazanof et al.[7] revealed that in 90% of cases the interatrial septal aneurysm will bulge into the right atrium,[7] which makes sense, as left atrial pressure exceeds right atrial pressure in the normal individual.[1] Interestingly, in half of the 10% of cases in Marazanof's study, where the interatrial septal aneurysm bulged into the left atrium, it could not be explained by an elevated right atrial pressure and to date this phenomenon remains unexplained.[1,7] However, from a clinical perspective, it is important to realise that half of such cases do display elevated right atrial pressure[7] and indeed various disturbances in intracardiac haemodynamics may be associated with an interatrial septal aneurysm.[1,5,8–10] These include tricuspid atresia, hypoplastic right heart syndrome, premature closure of the foramen ovale, mitral stenosis, aortic stenosis and even a case of pulmonary hypertension due to tuberculosis.[1,5,8–10]

In this case of a 55-year-old man with recent onset exertional dyspnoea, the prominent bulging of the interatrial septal aneurysm into the left atrium was

Professor, Department of Internal Medicine, University of Pretoria, Pretoria, South Africa

Corresponding author:
James Ker, Professor, University of Pretoria, PO Box 24138, Gesina pretoria, Gauteng 0031, South Africa.
Email: jker@wol.co.za

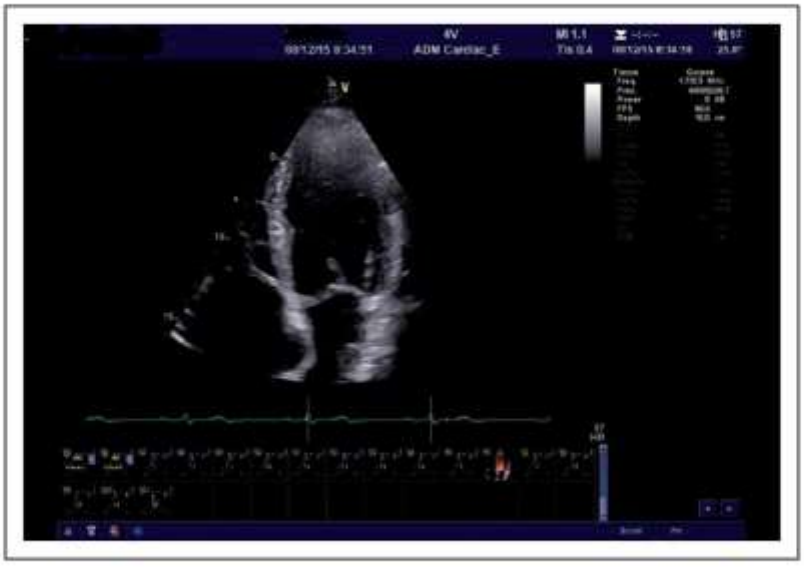

Figure 1. The prominent interatrial septal aneurysm, bulging into the left atrium.

Figure 2. The enlarged right atrium.

considered to be abnormal, especially in light of the enlarged right atrium. Of note, in light of the prominent dilatation of the right atrium, the pulmonary pressure was clearly elevated and it was concluded that ventilation-perfusion scintigraphy would be useful. This very clearly demonstrated multiple pulmonary emboli, thus no interventional procedures to measure pulmonary pressure was undertaken.

Conclusion

The presence of an interatrial septal aneurysm, apart from associations with various cardiac abnormalities mentioned may aid in the diagnosis of pulmonary embolism.

Competing interests

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Unilateral atrial fibrillation – how common is atrial divorce?

J Ker[1]

Abstract

Atrial fibrillation is the most common pathologic supraventricular tachycardia. It has many causes, is an expensive disease, impairs quality of life and leads to an increased risk of death. Atrial dissociation is characterised by the presence of two independent sets of P-waves. This peculiar abnormality may give rise to the scenario where one atrium is in atrial fibrillation while the other is in sinus rhythm. This is the first published case of atrial dissociation where the phenomenon is demonstrated by transmitral and transtricuspid pulsed wave Doppler.

Correspondence to:
J Ker
Department of Internal Medicine
University of Pretoria
Pretoria
South Africa

Email:
jker@wol.co.za

Keywords: atrial, dissociation, fibrillation, unilateral

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Atrial fibrillation (AF) is the most common pathologic supraventricular tachycardia, affecting 3 million people in the USA alone.[1,2] AF is caused by multiple electrical wavelets, appearing in the atria simultaneously, resembling the wavelets that would be produced if one dropped several pebbles in a bucket of water at the same time.[1]

AF is usually a progressive disease;[3] it often begins with infrequent episodes of limited duration which is termed paroxysmal AF (often defined as episodes of AF that terminate spontaneously within 1 week).[3] Such episodes tend to become more frequent and longer in duration, progressing to persistent AF (persistent AF fails to terminate spontaneously within 7 days and may require cardioversion) or permanent AF (permanent if the AF lasts for more than 1 year and cardioversion either has not been attempted or has failed).[3]

The electrophysiological basis of AF requires both a trigger that initiates the dysrhythmia and a substrate that can sustain it.[3,4] The most common trigger of AF is ectopic atrial beats that arise from the muscle sleeves around the pulmonary veins.[4,5] These triggers (ectopic beats) may be provoked by the intrinsic activity of cardiac ganglionic plexuses which are clustered in the vicinity of the pulmonary vein-left atrial junction.[3,5] The pulmonary vein-left atrial junction together with an enlarged atrium, harbouring fibrosis and inflammation, then serve as the substrate for sustaining wavelets of atrial fibrillation.[3]

With persistence of AF, further electrophysiological changes occur in the atria, which include shortening of the refractory period of the atrial muscle and this in turn predisposes to the development of other triggers and wavelets.[3] Consequently, this process results in a greater predisposition to AF, as well as the perpetuation of existing AF.[3] Maintenance of sinus rhythm can reverse these changes;[3] hence the saying 'AF begets AF and sinus rhythm begets sinus rhythm'.[3]

AF is an important disease as the rate of death is about double when compared to patients in sinus rhythm; it has an adverse effect on the quality of life and is expensive to treat (more than $6.5 billion per year in the USA alone).[3]

Atrial dissociation which presents as unilateral AF has been described previously.[6,7] Doubted by some, further evidence supporting the existence of atrial dissociation was presented by Chung in 1971.[8]

Figure 1 is the electrocardiogram of a 60-year-old Caucasian male with pulmonary hypertension and an enlarged right atrium due to idiopathic pulmonary fibrosis. The rhythm strip (lead II) reveals atrial flutter-fibrillation. However, if one looks at lead V1, two distinct sets of P-waves are seen. Figure 2 is the transtricuspid pulsed wave Doppler appearance. This clearly reflects AF. However, the transmitral pulsed wave Doppler (Figure 3) reflects sinus rhythm with E-A waves. There are two filling phases during ventricular filling: early and late. These two phases are represented by the E and A waves, respectively. These two waves represent the velocity of flow through the atrioventricular valve during early (E wave) and late (A wave) ventricular filling respectively. Late ventricular filling is caused by atrial contraction. Thus, when AF is present, no A wave will be seen. If one looks closely at Figures 2 and 3 this difference is striking: there is only an E wave in Figure 2 but E and A waves in Figure 3.

Atrial dissociation is characterised by the presence of two independent sets of P-waves.5 In extremely rare instances

[1]Professor of Internal Medicine, Department of Internal Medicine, University of Pretoria, Pretoria, South Africa

Figure 1 Electrocardiogram depicting atrial flutter-fibrillation. Note the distinct two sets of P waves in lead V1

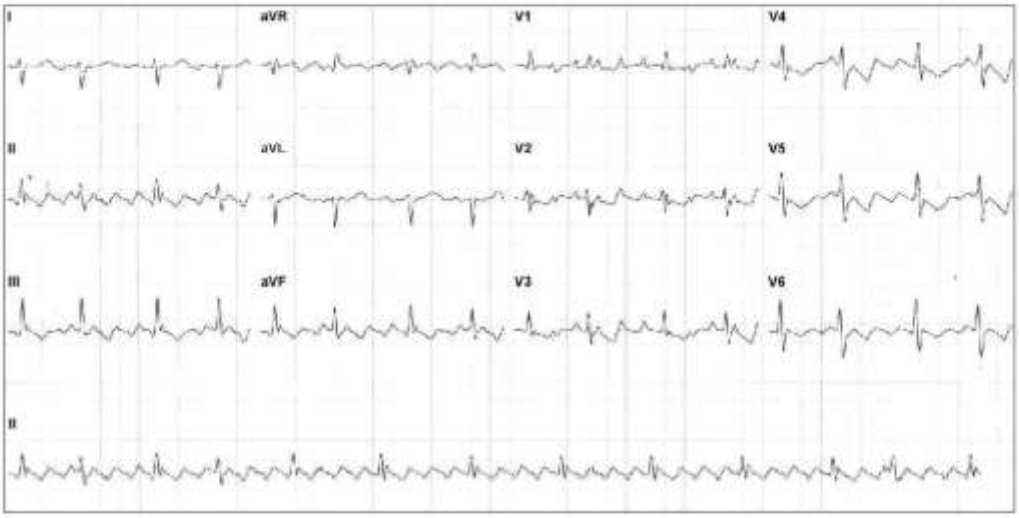


Figure 2 Pulsed wave Doppler over the tricuspid valve. This is the appearance of AF

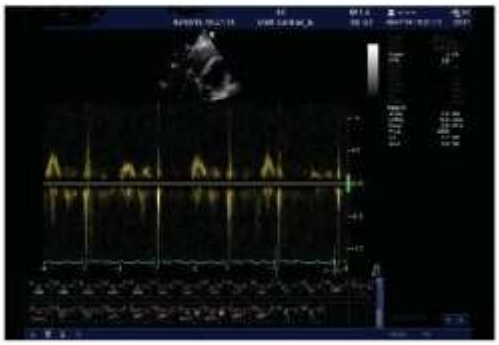
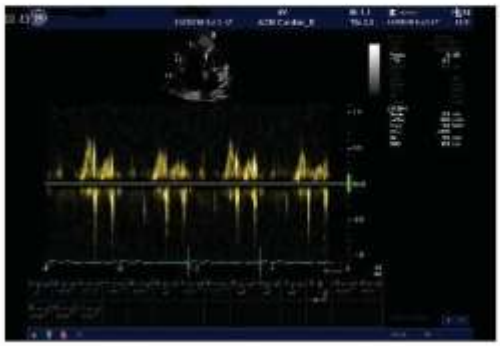


Figure 3 Pulsed wave Doppler over the mitral valve. This demonstrates normal sinus rhythm



of atrial dissociation it has clearly been described that one atrium or only a portion of one may have atrial tachycardia, atrial flutter or AF while the other atrium is still in sinus rhythm.[5,9–12]

The first observation of atrial dissociation was by Hering in an experimental study. Wenckebach was the first to report the phenomenon in a patient in 1906.[9] Since then, atrial dissociation was observed by numerous authors in various clinical settings, such as congestive heart failure, rheumatic heart disease, hypertension, uraemia, pneumonia, glomerulonephritis, myocardial infarction, congenital heart disease, diphtheria and digitalis intoxication.[5]

This is the first published case of atrial dissociation where the phenomenon is demonstrated by transmitral and transtricuspid pulsed wave Doppler demonstrating one atrium in sinus rhythm and one in atrial fibrillation.

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Case Report

Diaphragmatic hernia mimicking an atrial mass: a two-dimensional echocardiographic pitfall and a cause of postprandial syncope

J. KER, J. VAN BELJON

Summary

A large hiatal hernia constitutes a form of posterior mediastinal mass that can encroach on the posterior aspects of the heart. During two-dimensional echocardiography this phenomenon may be confused with an intra-atrial mass or various other posterior mediastinal masses. Furthermore, such a large hiatal hernia encroaching on the heart may cause syncope. We present such a case and the various possible mechanisms of syncope, as well as review the two-dimensional echocardiographic pitfalls in these patients.

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We present a case of postprandial syncope in which a large diaphragmatic hernia produced the two-dimensional echocardiographic appearance of an obstructing left atrial mass. Surgical correction of the hernia completely prevented any further syncope episodes.

Case Report

A 64-year-old man was admitted to hospital following an episode of postprandial syncope, accompanied by severe chest pain. The patient had a one-year history of postprandial syncope, accompanied by chest pain that increased progressively in intensity and frequency over this period. The only prior history was that of a left bundle branch block that was diagnosed 10 years previously. The patient was not taking any medication. Physical examination and blood and biochemical profiles, including troponin T levels, were all normal. The ECG showed left bundle branch block.

Department of Physiology, University of Pretoria and Pretoria Heart Hospital, Pretoria

J. KER, M.B. Ch.B., M.Med. (Int Med)

Department of Surgery, University of Pretoria, Pretoria

J. VAN BELJON, M.B. Ch.B., M.Med. (Surg), F.C.S.

Two-dimensional echocardiography was then performed. This revealed the presence of a large, amorphous mass impinging on the posterior left atrial wall (Fig. 1). An M-mode scan revealed an almost total obliteration of the left atrial cavity (Fig. 2).

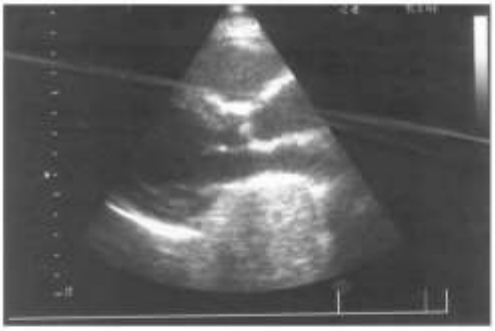

Fig. 1. A long-axis view demonstrating a large mass that appears to fill the cavity of the left atrium. It is not possible to distinguish between an intra-atrial and an extra-atrial mass with extrinsic compression of the left atrium.

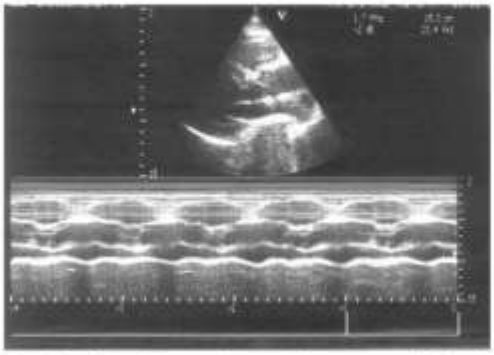

Fig. 2. An M-mode scan through the aorta and left atrium. This demonstrates almost total obliteration of the left atrial cavity, which is worse during diastole.

A chest roentgenogram demonstrated a massive hiatal hernia with a large portion of the stomach in the posterior mediastinum. A computed tomographic (CT) scan, following the oral administration of contrast, confirmed the posterior mediastinal mass to be the stomach. An endoscopic Nissen fundoplication was performed and no further episodes of postprandial syncope or chest pain occurred.

Discussion

Two-dimensional echocardiography is a valuable diagnostic tool for the detection of various intra-atrial masses, such as thrombus and tumours.[1] However, various adjacent extracardiac structures may closely mimic intracardiac masses on a two-dimensional echocardiogram.[2] The echocardiographic appearances of various anomalies of these adjoining structures have been described and these include mediastinal spread of bronchogenic carcinoma, various other mediastinal tumours, descending thoracic aortic aneurysms and even oesophageal carcinoma.[2,3]

In 1985 Nishimura *et al*.[2] were the first to describe five cases of a previously unrecognised phenomenon of diaphragmatic hernias mimicking intra-atrial masses. Since then, a surprisingly small number of single case reports of this peculiar phenomenon have appeared.

'Swallow syncope' is not an unknown phenomenon[4] and may have an electrical or mechanical pathophysiology.[5] An oesophagocardiac reflex, selectively triggered by deglutition, may induce various cardiac dysrhythmias.[5] This abnormal reflex starts from tensoreceptors localised deep in the oesophageal wall and a distention of the oesophageal wall is necessary for their activation.[4,6] The afferent pathway of this reflex is unknown, whereas the efferent pathway is cholinergic and vagal, and able to cause sinus or nodal bradycardia, sinus arrest, or second-degree atrioventricular block.[5] In a report of three cases, it has also been proposed that stimulation of epicardial receptors by a hiatal hernia may cause bradycardia.[7]

Recently, Akdemir *et al*[8] described a case of postprandial syncope where a hiatal hernia stimulated epicardial receptors and consequently triggered non-sustained ventricular tachycardia. A mechanical aetiology of postprandial syncope has also been proposed in patients with hiatal hernia – by compressing the heart from outside, a hiatal hernia may cause an obstructive cardiac lesion.[8]

Several features may help to distinguish between a large hiatal hernia and an atrial mass on two-dimensional echocardiography.[2] The echo density of a hiatal hernia will extend beyond the margins of the atria. With angulation of the transducer, the mass will not be confined to one atrium, but may appear to be in either atrium because the hernia is a posterior structure separate from the heart. The swirling effect is a very useful feature. The echo reflections from a hiatal hernia that contains stomach contents and air will demonstrate changing echo densities within the mass. If the patient drinks a carbonated beverage during the examination this phenomenon will be augmented.

D'Cruz *et al*.[3] described a few useful features in a series of 20 patients with large hiatal hernias. In parasternal views there was respiratory fluctuation in the degree of encroachment of the mass on the left atrium due to motion of the hiatal hernia along with the diaphragm during the respiratory cycle. In the apical four-chamber and long-axis views the descending thoracic aorta was obscured by the large echogenic mass. The hiatal hernia mass could be visualised in the subcostal view superior to the liver and posterior to the atria.

In conclusion, we present a case of postprandial syncope in a patient with a large hiatal hernia that almost completely obliterated the left atrial cavity, thus causing an obstructive cardiac lesion with resultant syncope. The possibility of various brady- and tachydysrhythmias caused during meals by the stimulation of various epicardial receptors by the mass cannot be excluded, as we did not perform any electrocardiographic monitoring during meals.

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Clinical Medicine Insights: Cardiology

CASE REPORT

The Violin Heart

James Ker

Department of Physiology, University of Pretoria, Pretoria, South Africa. Corresponding author email: jker@wol.co.za

Abstract: Left ventricular false tendons are thin, fibromuscular structures which traverse the left ventricular cavity. They are thought to be intracavitary radiations of the bundle of His. Usually these tendons span between the interventricular septum and the lateral wall or a papillary muscle. They have been known to be a source of innocent and musical murmurs.

In this case report a peculiar left ventricular false tendon is shown—one extending between the two papillary muscles, giving the appearance of a musical note. During ventricular diastole the tendon is pulled taut between the two heads of the papillary muscles and during ventricular systole the tendon relaxes. The echocardiographic characteristics and possible long term implications are discussed.

Keywords: false tendon, papillary muscle

Clinical Medicine Insights: Cardiology 2010:4 49–51

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Introduction

Left ventricular myocardial bands—also called false tendons—are anomalous fibromuscular structures which traverse the left ventricular cavity.[1] They originate in the interventricular septum and stretch across the left ventricular cavity, implanting in either the lateral wall or a papillary muscle.[2]

They may be associated with cardiac pathology or they may be an isolated finding.[2]

Echocardiographically these structures may mimic pathologic structures, such as intraventricular chorda rupture, vegetation or thrombus.[3]

These tendons may be a cause of murmurs—a musical murmur has been described when they are pulled taut by ventricular dilatation.[4] A substudy from the Framingham Heart Study have confirmed the association of false tendons with innocent, precordial murmurs, but they were not associated with a risk of mortality.[5]

In this case report a peculiar left ventricular false tendon is shown—the tendon extends between the two papillary muscles, giving the papillary muscle-tendon complex the appearance of a musical note. During the cardiac cycle the tendon is continuously being pulled taut and relaxed during ventricular diastole and systole respectively, thus leading to the echocardiographical impression of the playing of a musical cord, thus the term the "violin heart".

Case Report

A 23-year old, healthy Caucasian male was referred for an echocardiogram by his primary care physician who suspected the presence of a prolapsing mitral valve, based on his auscultation of a midsystolic click.

The patient never had any previous medical or surgical problems and he was completely asymptomatic. The midsystolic click was heard during an examination done during a bout of flu.

During the clinical examination of the patient the midsystolic click was not audible. No clinical abnormalities were detected and theelectrocardiogram was normal.

Echocardiography revealed a peculiar left ventricular false tendon which was clearly visible on the parasternal, short-axis view between the two papillary muscles (see Fig. 1- the tendon is marked with +). Also note the clear relaxation of tension on the tendon during left ventricular contraction (see Fig. 2- the tendon is marked with +).

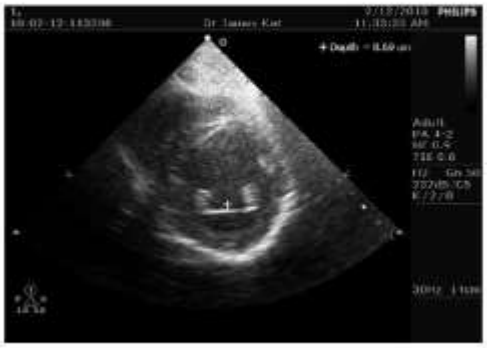

Figure 1. Parasternal, short-axis view during diastole.
Note: This is the parasternal, short-axis view during ventricular diastole. The ventricle is filled, thus pulling the tendon taut between the two papillary muscles. Note the appearance of the papillary muscle-tendon complex, resembling a musical note. The tendon is marked with +.

Supplementary Figure 1 is a movie clip which clearly demonstrates the continuous and rhythmic cycle of the tendon being pulled taut and relaxing during ventricular diastole and systole respectively. Supplementary Figure 2 is a movie clip which clearly demonstrates a structurally normal mitral valve.

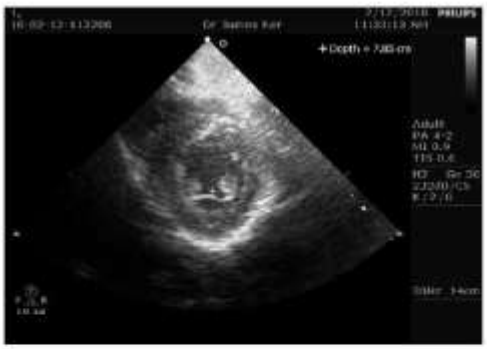

Figure 2. Parasternal, short-axis view during systole.
Note: This is the parasternal, short-axis view during ventricular systole. The ventricle is contracted, thus reducing the internal diameter and reducing the tension on the tendon as a result. During ventricular filling, the tendon will suddenly be pulled taut and consequently a ping will be audible.

Discussion

In this case report a peculiar echocardiographical entity is described—the "violin heart". This picture is the result of a false tendon extending between the two heads of the papillary muscles.

The differential diagnosis of ventricular false tendons include the following:[1] isolated, left ventricular non-compaction, hypertrophic cardiomyopathy and levo-transposition of the great arteries.

The production of sound[4,5] is not the only physiological action of tendons: Bhatt et al[6] have demonstrated that patients with cardiomyopathy who have false tendons present in the left ventricular cavity have less severe mitral regurgitation. The mechanism for this reduction in functional mitral regurgitation is thought to be less severe mitral valve deformation when a false tendon is present.[6] Long false tendons are also at risk for rupture and can then act as a nidus for infection or thrombus formation.[1,7]

The embryologic basis of left ventricular false tendons is unknown, but may be due to the extension of the cardiac conduction system into the left ventricular cavity.[1,8] False tendons can be associated with ventricular septal defects, a bicuspid aortic valve and coarctation of the aorta.[1,9]

A substudy of the Framingham Heart Study[5] have shown that these tendons are not associated with an increased mortality if no associated pathology is present and thus, the patient in this case report has a good prognosis.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.

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Clinical Medicine Insights: Cardiology

CASE REPORT

The Liver and Right Atrium—Hepatic Cyst as a Cause of Arrhythmia

James Ker

Department of Physiology, University of Pretoria, Gesina, Pretoria, South Africa.
Corresponding author email: jker@wol.co.za

Abstract: Simple hepatic cysts are a relatively common radiological finding. These cysts may be classified as parasitic and non-parasitic. They are usually asymptomatic, but may cause symptoms due to local compression. These compressive complications include: portal hypertension, edema due to caval compression, extrinsic gastric compression and duodenal compression with obstruction.
However, no reports in the literature exist describing atrial compression by hepatic cysts.
In this case report a simple hepatic cyst causing slight right atrial compression is described. This slight compression is the cause of atrial premature beats.
It is proposed that simple hepatic cysts may be the cause of atrial premature beats.

Keywords: hepatic cyst, atrium, atrial premature beats

Clinical Medicine Insights: Cardiology 2010:4 63–67

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Introduction

Simple hepatic cysts is a frequent finding and occur in approximately 2.5% of the population.[1] They are usually benign, asymptomatic and require no treatment.[2]

Although usually asymptomatic they may cause symptoms due to local compression, such as: abdominal discomfort or pain, dyspnoea, early satiety, swelling of the lower limbs due to caval compression, portal hypertension or jaundice.[1]

This report describes the occurrence of atrial arrhythmia due to right atrial compression by a simple hepatic cyst in a 71-year old man.

Case Report

A case report is presented where it is postulated that a simple hepatic cyst, located just beneath the right atrium is responsible for symptomatic palpitations due to frequent atrial premature beats, induced by slight right atrial compression.

A 71-year old, Caucasian male presented with the clinical problem of symptomatic palpitations for a period of two years. He was not using any medication, never smoked, and never had any previous surgery. The clinical examination did not reveal any abnormalities. The electrocardiogram was normal, however Holter monitoring revealed frequent atrial premature beats (see Fig. 1 and 2).

The transthoracic echocardiogram did not reveal any pathological findings, however the subcostal view demonstrated a large, simple hepatic cyst, measuring 4.49 cm in diameter with occasional slight compression of the right atrium (see Fig. 3, 4 and 5).

All electrolytes and the thyroid function tests were within normal limits. The patient did not have any obstructive respiratory disease, a common cause of atrial premature beats.

Discussion

True hepatic cysts can be classified as parasitic or non-parasitic.[3] The former is almost exclusively the result of hydatidosis[3], caused by the cestode Echinococcus[4]. Echinococcus is classified into two species: E. granulosis, the most common which causes chronic disease and E. multilocularis, which causes a more progressive and multifocal infection.[4] The liver is the main site of infection with the right lobe most frequently affected.[4] Non-parasitic cysts are the result of congenital anomalies which affect the intra-and extrahepatic biliary ducts, leading to varying degrees of cystic dilatations.[3] These may be solitary or polycystic.[1] According to Henson et al[1] non-parasitic and non-congenital cysts may be classified as neoplastic, inflammatory and traumatic cysts.

Although usually asymptomatic, hepatic cysts may cause clinical symptoms due to local compression, such as abdominal discomfort or pain, dyspnoea, early satiety, swelling of the lower limbs due to caval compression, portal hypertension or jaundice.[1] Liver function enzymes will only be abnormal if biliary compression is present[3] and cyst infection may occur if a communication is present between the biliary tree and the cyst.[3,5] These cysts may also cause extrinsic gastric compression and mimic the symptoms and endoscopic findings of gastric submucosal tumors.[6,7] A case of extrinsic duodenal compression with obstruction due to a hepatic cyst have also been described.[8]

In this case report a subcapsular, simple hepatic cyst is shown in the left lobe of the liver. Other case reports have shown cysts such as this to lead to gastric compression, mimicking the endoscopical appearance of submucosal tumors and duodenal compression, leading to intestinal obstruction. Figures 3, 4 and 5 clearly show that the cyst is causing slight right atrial compression.

Thus, a new complication of simple hepatic cysts is proposed—atrial premature beats due to right atrial compression.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

Written consent was obtained from the patient for publication of this study.

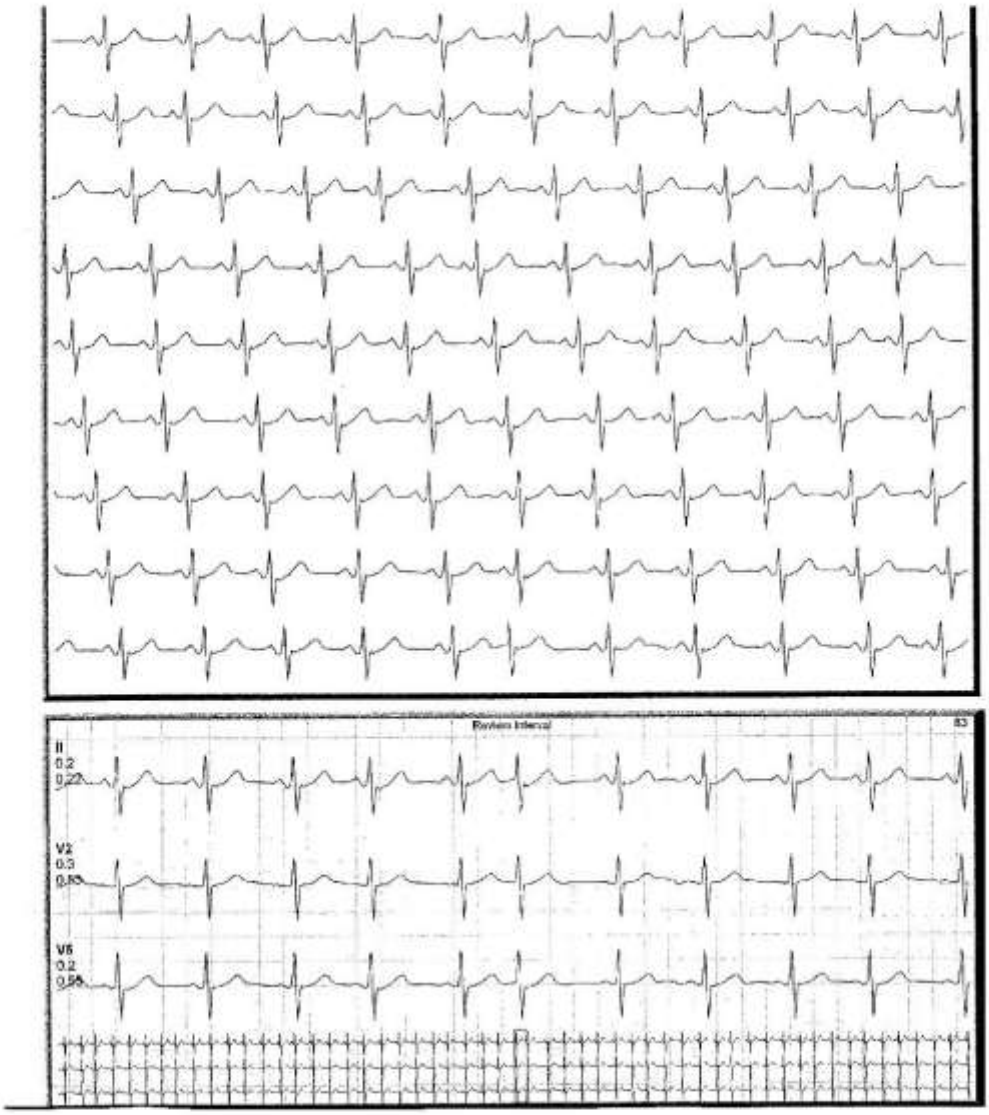

Figure 1. Electrocardiogram.
Note: Electrocardiographic image, demonstrating atrial premature beats.

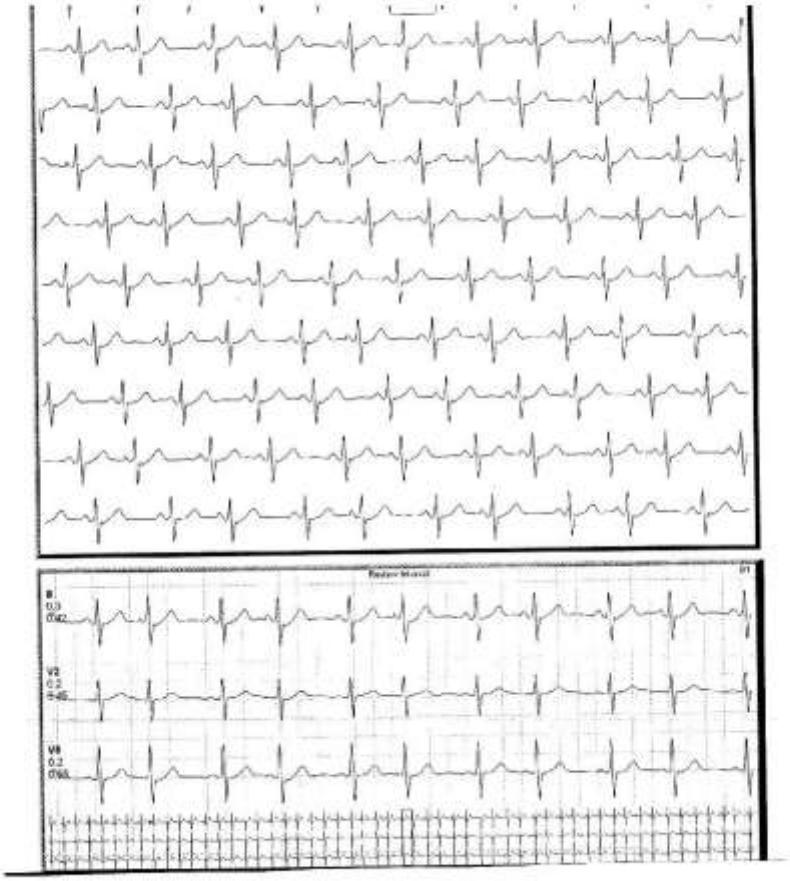

Figure 2. Electrocardiogram.
Note: Another electrocardiographic image, demonstrating atrial premature beats.

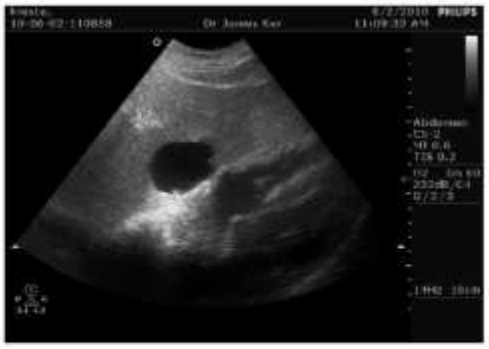

Figure 3. Subcostal echocardiographic image to demonstrate the hepatic cyst touching the right atrium.
Note: Subcostal echocardiographic image to demonstrate the hepatic cyst touching the right atrium.

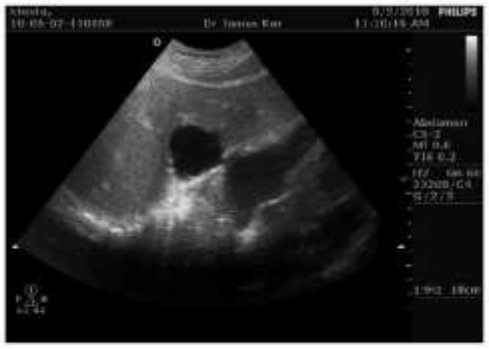

Figure 4. Subcostal echocardiographic image to demonstrate the hepatic cyst touching the right atrium.
Note: Subcostal echocardiographic image to demonstrate the hepatic cyst touching the right atrium.

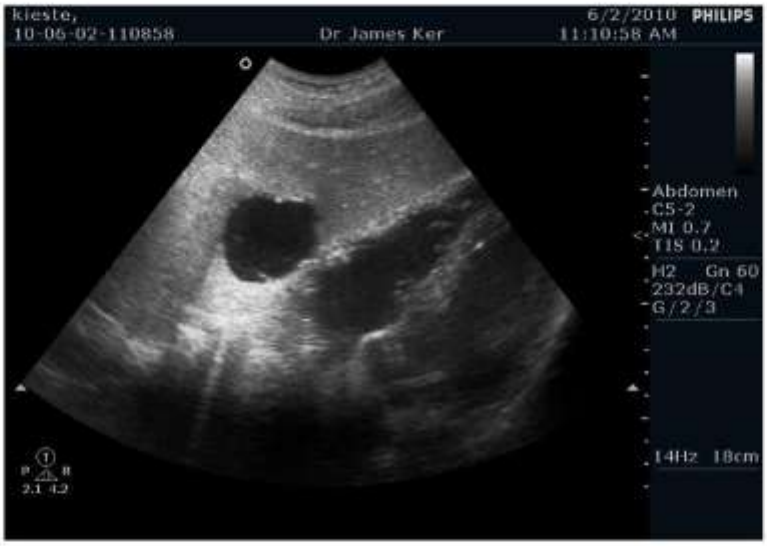

Figure 5. Subcostal image.
Note: Echocardiographic image, demonstrating slight right atrial compression by a simple hepatic cyst.

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CARDIOVASCULAR ULTRASOUND

CASE REPORT Open Access

The serpentine mitral valve and cerebral embolism

James Ker

Abstract

Valvular strands, well-delineated filiform masses, attached to cardiac valve edges are associated with cerebral embolism and stroke. Strokes, caused by emboli from valvular strands, tend to occur among younger persons. In this case report a valvular strand, giving a peculiar serpentine appearance to the mitral valve is described. This mitral valvular strand was the only explanation for an episode of cerebral embolism, presenting with a transient right sided hemiparesis.

It is proposed that a randomized study involving combined treatment with aspirin and clopidogrel is warranted in young patients with valvular strands, presenting with a first episode of cerebral embolism.

Introduction

Valvular strands have been described as small, well-delineated masses with a predilection for the valvular endocardium [1]. Clinically these strands present as filiform material attached to cardiac valve edges and is detected by transesophageal echocardiography [2].

These strands, as visualized by transesophageal echocardiography are associated with systemic embolization, especially stroke and notably these strokes tend to occur among younger persons [3,4].

Case report

A 32 year old man presented with an acute onset of right sided hemiparesis. This occurred within the matter of minutes without any preceding warning symptoms. He had no known illnesses or allergies. He was a non smoker who never had any previous surgery and did not use illicit drugs. He works in the pharmaceutical industry and never experienced any similar symptoms before.

The right sided hemiparesis resolved spontaneously over the next three hours and at the time of clinical examination no objective neurological signs were present. An MRI and MRA scan of the brain and cerebral vasculature were normal. His electrocardiogram and biochemical analysis, including electrolytes, glucose, thyroid function and full blood count were within normal limits. Carotid-IMT and Doppler studies of both carotid arteries were normal. Holter electrocardiography excluded the occurrence of intermittent arrhythmias as a possible cause for embolism. Paradoxical embolism was excluded by the absence of both a patent foramen ovale and deep venous thrombosis. Infective endocarditis was excluded by the absence of positive blood cultures and vegetations.

Transthoracic, two-dimensional echocardiography revealed a peculiar serpentine strand attached to the coapting edge of the mitral valve (see additional files 1, 2 and 3).

He was diagnosed with a valvular strand attached to the mitral valve as the cause for a cerebral embolism to the left mid-cerebral artery. He was treated with a combination of aspirin (100 mg daily) and clopidogrel (75 mg every second day). This maintained his platelet ADP function below 50%. Follow up during the following three years was without any further incidents.

Discussion

Vilem Dusan Lambl, a Bohemian physician (1824-1895) were the first to describe the occurrence of small, filiform processes he observed on the aortic valve in 1856 [5]. Today, these Lambl's excrescences are also referred to as valvular strands and have been observed on all native and prosthetic valves [5]. These strands may occur as single strands, in rows or even in clusters [5]. They can vary in length from 1 mm to 10 mm and are usually less than 1 mm in thickness [5].

Correspondence: jker@worl.co.za
Department of Physiology, University of Pretoria, Pretoria, South Africa, PO Box 24318, Gesina, Pretoria, 0031 South Africa

Valvular strands are composed of a fibroelastic, avascular core, covered by a layer of endothelial cells [5,6].

The exact pathogenesis of formation of these structures are still unclear, however current opinion is that the initiating factor is that of an endocardial lesion in areas of trauma and/or high shear stress [5,6]. These denuded areas are then covered by fibrin with subsequent covering by an endothelial layer [5,6]. The prevalence of valvular strands has been estimated as 5.5% in a general population referred for transesophageal echocardiography and 40% in patients with stroke of unknown cause [1,2].

The differential diagnosis for valvular strands includes the following [5]: a myxoma, thrombi, valvular vegetations, nonbacterial thrombotic (marantic) endocarditis, cardiac metastases, a fibroelastoma and other primary cardiac neoplasms.

Of all of the above, the most difficult distinction is that between a valvular strand and a fibroelastoma [5,7]. Histologically, these two entities are very similar with both containing a central core of elastic connective tissue, covered by endothelium. However, valvular strands are covered by a single layer of endothelial cells, but fibroelastomas contain regions of multiple layers of endothelial cells [5,7].

Echocardiographically, fibroelastomas are more bulky, with stalks or pedestals sometimes present and multiple, fingerlike projections on their surface [5]. As fibroelastomas are usually found on the mechanically less strained parts of valves and endocardium they tend to be larger than valvular strands [5]. Valvular strands (Lambl's excrescences) are always found on the affected valve's line of closure and this limits their growth [5].

Several published case reports have shown that valvular strands are associated with emboli to the coronary, pulmonary, spinal, retinal and cerebral circulation [1].

Specifically regarding stroke, numerous reports have demonstrated an association with valvular strands, particularly in young patients [3,4,8,9]. The mechanism for embolic events is either that of thrombi forming on the strands which then embolize or it is possible that the valvular strand itself can embolize [2]. Direct visualization of thrombus on a valvular strand have indeed been described before [10].

In conclusion, a case of a valvular strand, attached to the coapting edge of the mitral valve is presented, giving a serpentine appearance to the mitral valve. This valvular strand was the cause for a cerebral embolism which presented with a transient right sided hemiparesis. This is the only current case in the literature, where the combination of aspirin and clopidogrel is used for the prevention of further episodes of cerebral embolism. In the only randomized treatment study to date, no difference in relation to efficacy of warfarin compared to aspirin was found in patients with valvular strands and previous embolic episodes [2]. For this reason a combination of antiplatelet therapy was initiated as a therapeutic trial.

It is proposed that a randomized controlled study involving the combination of aspirin and clopidogrel is warranted in patients with valvular strands presenting with a first episode of cerebral embolism.

Additional material

Additional file 1: Serpentine mitral valve. Transthoracic echocardiographic image. Note the mitral valvular strand, marked with +.

Additional file 2: Serpentine mitral valve. This is another transthoracic echocardiographic image of the same mitral valvular strand, marked with +. Note the difference in endoventricular position, compared with additional file 1, clearly demonstrating the mobile nature of the strand.

Additional file 3: Serpentine mitral valve. This is a movie clip, demonstrating the mobile nature of the mitral valvular strand, giving a peculiar serpentine appearance to the mitral valve.

Competing interests
The author declares that they have no competing interests.

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CASE REPORT Open Access

Thyroxine and cardiac electrophysiology—a forgotten physiological duo?

James Ker*

Abstract

Thyroid hormone exerts numerous effects on the cardiovascular system. Hypothyroidism can lead to various electrocardiographic and mechanical changes in the heart and blood vessels.
The potential risk for sudden cardiac death in patients with hypothyroidism have never been properly explored. However, numerous reports of various electrocardiographic changes indicative of such a risk has been published. In this case report the occurrence of ventricular late potentials in a case of overt hypothyroidism is described and furthermore, the disappearance of these potentials with T4 treatment alone is shown.
It is concluded that the concept that undiagnosed and/or untreated hypothyroidism poses a risk for sudden cardiac death is worth exploring.

Keywords: Hypothyroidism, Late potentials, Sudden cardiac death

Introduction

Thyroid hormone has important physiological effects on the cardiovascular system [1]. Cardiovascular effects of hypothyroidism can include electrocardiographic changes, such as bradycardia, right bundle branch block, flattened or inverted T waves, QRS prolongation and even torsades de pointes ventricular arrhythmia [2].

Mechanical cardiovascular effects of hypothyroidism include a remarkable increase in peripheral vascular resistance [3], an increase in arterial stiffness [4], an impairment in left ventricular diastolic function as characterized by a slowing of myocardial relaxation and impaired early ventricular filling [5] and pericardial effusion [6].

Currently, there is an interesting electrocardiographic contrast between thyrotoxicosis and hypothyroidism [2]: In thyrotoxicosis atrial tachyarrhythmias are common and ventricular arrhythmias are rare. However, in hypothyroidism QT interval prolongation and ever QT dispersion can occur and lead to ventricular arrhythmias, such as torsade de pointes ventricular tachycardia which can be resolved with T4 treatment alone [2,7].

In this case report it is shown that severe, primary hypothyroidism can present with an abnormal signal averaged electrocardiogram and that this can be corrected with T4 treatment alone. To date this is the only report of primary hypothyroidism presenting with an abnormal signal-averaged electrocardiogram corrected with T4 treatment alone.

Case report

A 66 year old Caucasian woman was referred for a cardiovascular examination due to an abnormal electrocardiogram, taken by her primary care physician after complaining of tiredness. The 12 lead, surface electrocardiogram revealed the presence of low QRS voltages and flattened and inverted T waves, all findings suggestive of and compatible with hypothyroidism (Figure 1).

At no stage did the patient experience any symptoms suggestive of hypothyroidism or any other disease.

The serum TSH (thyroid stimulating hormone) measured 76.11 mIU/L and was indicative of severe, primary hypothyroidism (normal range 0.27 – 4.20 mIU/L).

No other pathology was found. Specifically no secondary hyperlipidemia was present and the serum glucose level was normal. No classical signs of hypothyroidism were present. Thyroid ultrasonography revealed a small and hypoechogenic thyroid gland with the typical appearance of advanced Hashimoto thyroiditis with no nodules present.

A signal-averaged electrocardiogram (SAECG) was done and this was clearly abnormal (Figure 2) with the root-mean square voltage of the terminal 40 ms (RMS 40)

* Correspondence: jker@wcd.co.za
Department of Physiology, University of Pretoria, PO Box 24318, Gezina, Pretoria 0031, South Africa

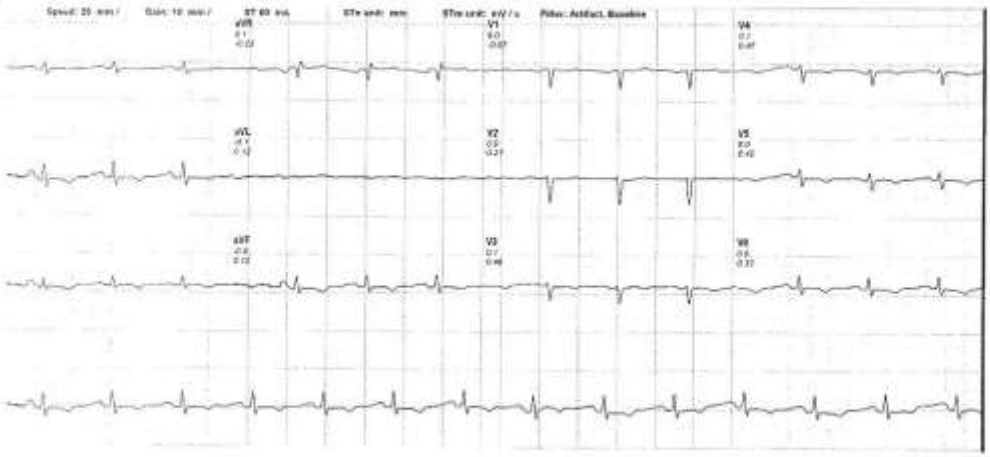

Figure 1 12lead surface electrocardiogram.

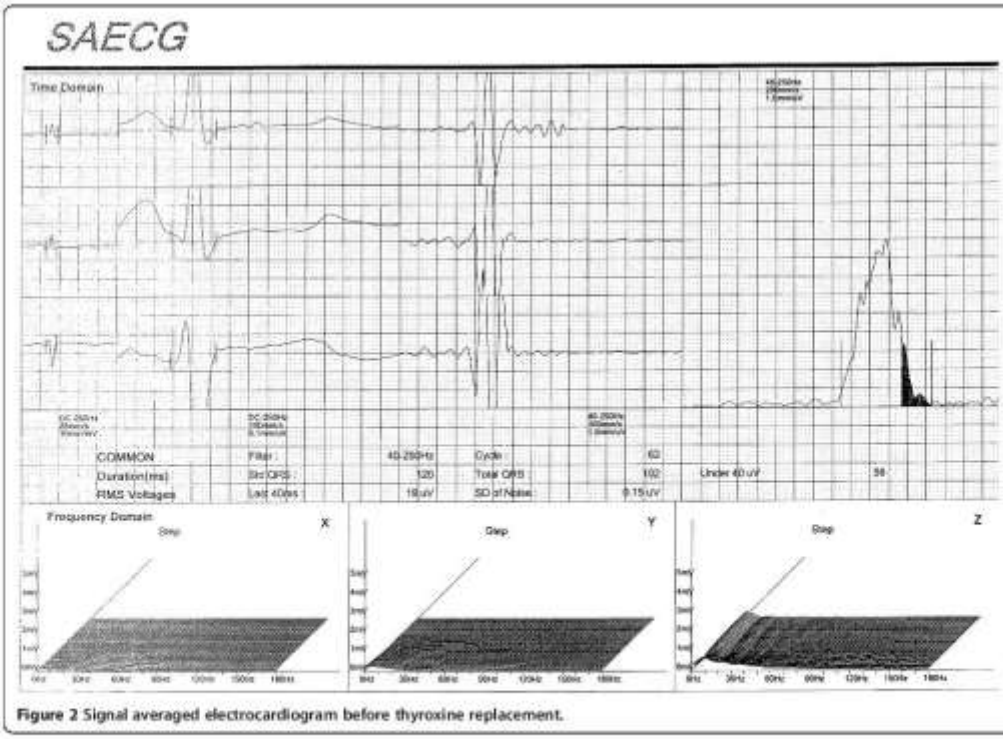

Figure 2 Signal averaged electrocardiogram before thyroxine replacement.

measuring 19uV and the duration of low-amplitude signal < 40uV (LASd) measuring 56 ms.

The patient was treated with 100 ug of T4 daily and the TSH level after two months of therapy measured 2.34 mIU/L and the signal-averaged electrocardiogram was repeated (Figure 3). The RMS 40 now measured 40 uV and the LASd measured 40 ms. The measured parameters of the SAECG thus changed from clearly abnormal into the normal range (see Figure 2 and Figure 3). During the first two weeks of therapy the dose of T4 was started at 50 ug daily and this was increased to 100 ug daily thereafter.

The patient remains well with a normal signal-averaged electrocardiogram after one year of clinical follow-up.

Discussion

Three aspects of this case merit discussion. Firstly, this is the first case report in the literature which describes the presence of ventricular late potentials in the myocardium of a patient with overt hypothyroidism. The signal-averaged electrocardiogram is a technique used to detect the presence of ventricular late potentials [8]. Ventricular late potentials correspond to areas in the ventricular myocardium where there is slowed conduction velocity and these cause delayed ventricular activation [8]. These ventricular late potentials indicate an increased risk for the occurrence of ventricular arrhythmias [8]. These observed ventricular late potentials disappeared in this patient after T4 treatment alone.

Secondly, other parameters indicating an increased ventricular arrhythmic risk has been described in hypothyroidism [9-11]. An increase in the QTc interval have been described in hypothyroidism and that this increase is directly related to the severity of hypothyroidism [9]. TSH levels have also been shown to be directly related to QT prolongation and QT dispersion [10]. QT dispersion is the interlead variability of the QT interval on the surface ECG that reflects regional variations in myocardial repolarization and an increased QT dispersion has been found to be strongly associated with an increase in ventricular arrhythmias and sudden cardiac death [2]. Lastly, an improvement in heart rate variability have also been documented in treated hypothyroidism [2].

Thirdly, hypothyroidism can affect cardiac structure [11-13]. These structural effects manifests clinically in hypothyroidism as an increase in myocardial echoreflectivity [13,14], perhaps an explanation for the observed

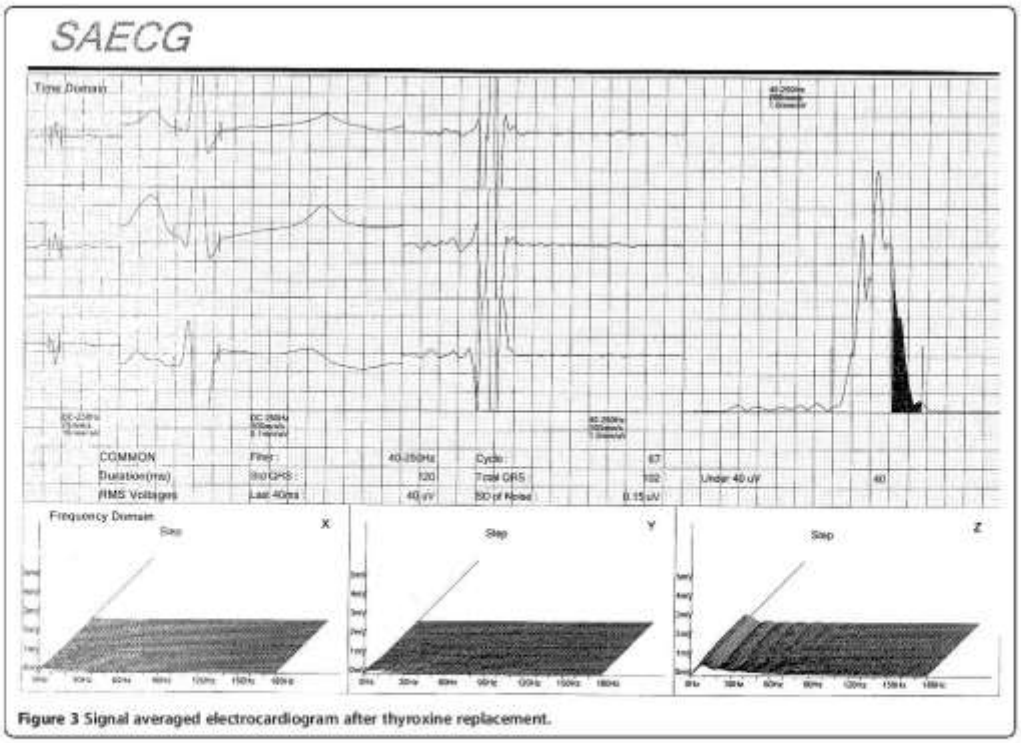

Figure 3 Signal averaged electrocardiogram after thyroxine replacement.

electrocardiographic abnormalities observed in hypothyroidism?

Conclusions

In conclusion, a case is presented showing the presence of cardiac late potentials in a patient with overt hypothyroidism. Disappearance of these late potentials with only T4 treatment is shown. It is proposed that undiagnosed and/or untreated hypothyroidism poses a threat of sudden cardiac death and that this concept is worthwhile to be studied in a proper randomized trial.

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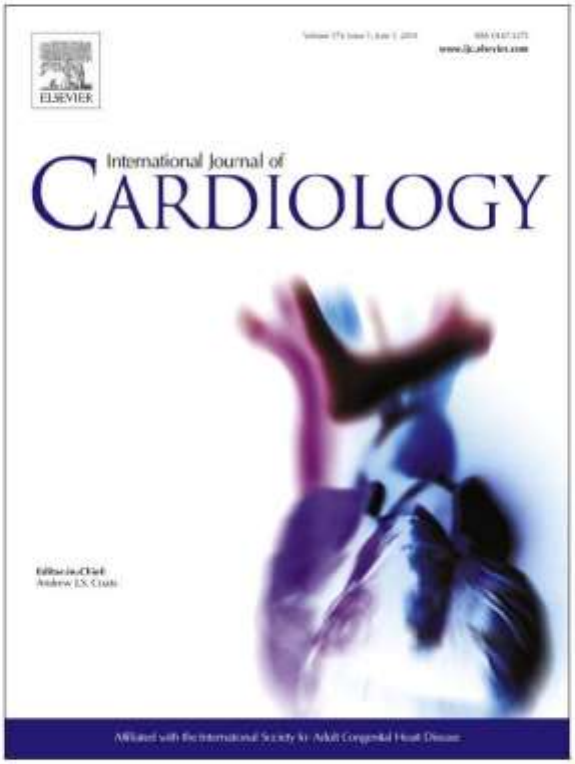

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Bicuspid aortic valve disease and lipoprotein(a)—A concept worth exploring?

James Ker *

Department of Internal Medicine, University of Pretoria, Pretoria, South Africa

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Bicuspid aortic valve (BAV) disease is the most common form of congenital heart disease with a prevalence of 1–2% in the population [1,2]. For the clinician BAV is the most important congenital cardiac lesion, because this results in more morbidity than all other congenital cardiac lesions combined [1,3,4]. This can be a sporadic or familial affliction with a male to female ratio of 3–4:1 [1,2].

A bicuspid aortic valve is the end result of a complex developmental abnormality and is not simply the result of the fusion of two normal cusps [1]. This is a diverse and complex condition with a significant morphological variability [1,5,6]. The following phenotypes of BAV can be seen ₅. The two groups of BAV are: i) those with a raphe and ii) those without a raphe.

The group with a raphe has the following possibilities and thus phenotypes: i) fusion of the right- and left-coronary cusps, ii) fusion of the right coronary and non-coronary cusps, and iii) fusion of the left coronary and non-coronary cusps. The group without a raphe is classified according to the orientation of the free edge of the cusps. This can be either anterior–posterior (BAV-AP) or lateral (BAV-LA) [7].

The major clinical significance of this common condition is the fact that only 20% of such patients will maintain a functioning valve throughout their lifetime [1,8]. The complication includes aortic dissection, infective endocarditis, aortic regurgitation and aortic stenosis [1,9].

The creasing of the BAV and resultant turbulent flow is currently thought to contribute to the calcification of such valves [2,10].

Recently a genomewide association study by Thanassoulis et al. [11] identified a SNP in the LPA locus that is significantly associated with aortic valve calcification in cases of normal aortic valves. Specifically, that study implicates genetic variants at the LPA locus with elevated plasma lipoprotein(a) levels as a cause for aortic valve calcification in the general population with normal aortic valves [11]. This leads to the clinical question of whether lipoprotein(a) may be an important role player in calcification of the bicuspid aortic valve?

The purpose of this observational study was thus to correlate the plasma lipoprotein(a) level with the presence or absence of calcification of bicuspid aortic valves.

This is an observational study looking at 10 cases of BAV disease—all discovered incidentally. These 10 cases were chosen as no other diseases were present, no medication was used by any of the patients and they were all asymptomatic.

The absence or presence of calcification of the bicuspid aortic valve was documented in each case and the plasma lipoprotein(a) level was measured in each case.

The echocardiographic images of the 10 cases of BAV disease are displayed as Figs. 1–10.

Of these 10 cases, 4 clearly demonstrates calcification (Figs 2, 4, 5 and 10).

All of the cases without calcification has normal plasma lipoprotein(a) levels.

3 of the 4 cases with calcification has elevated plasma lipoprotein(a) levels.

In this case series a male predominance is seen which correlates with the current literature [1,2]. The youngest patient with calcification is 38 years old and the oldest patient without calcification is 55 years old.

Sex	Age	Calcification	Lipoprotein(a)
1. M	27 years	No	Normal
2. M	38 years	Yes	Elevated
3. M	50 years	No	Normal
4. M	47 years	Yes	Elevated
5. F	54 years	Yes	Elevated
6. M	41 years	No	Normal
7. M	24 years	No	Normal
8. M	55 years	No	Normal
9. M	28 years	No	Normal
10. M	45 years	Yes	Normal

* Tel.: +27 128092810.
E-mail address: jker@wol.co.za.

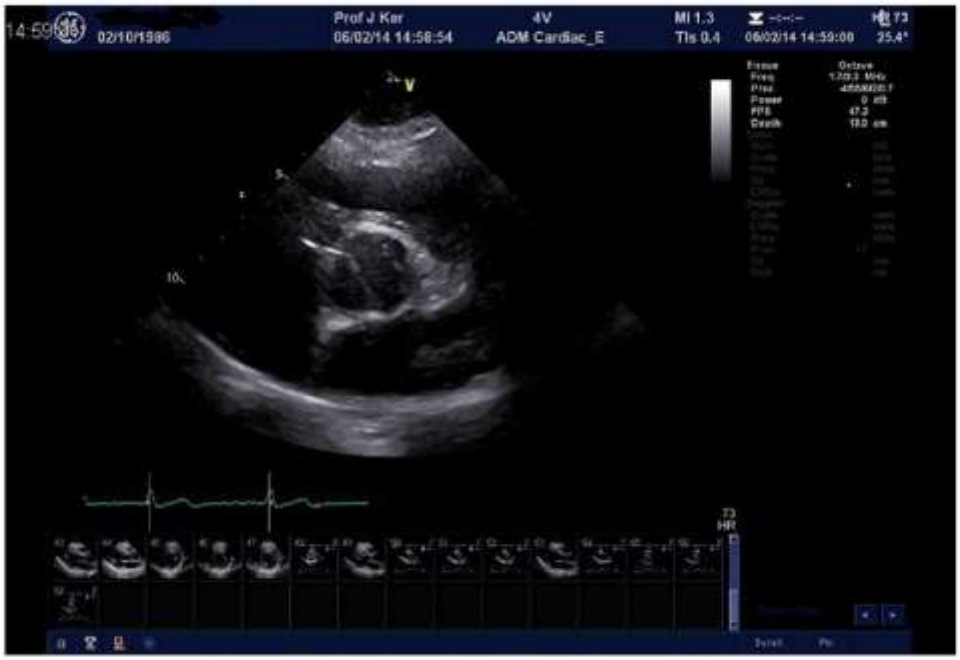

Fig. 1. No calcification. Normal plasma lipoprotein(a).

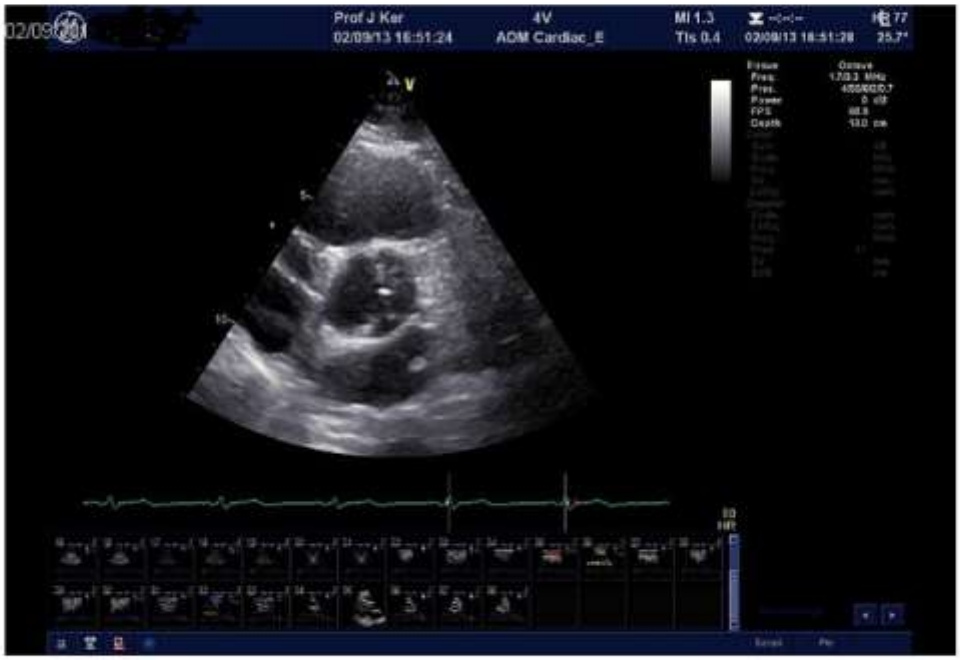

Fig. 2. Calcification. Elevated plasma lipoprotein(a).

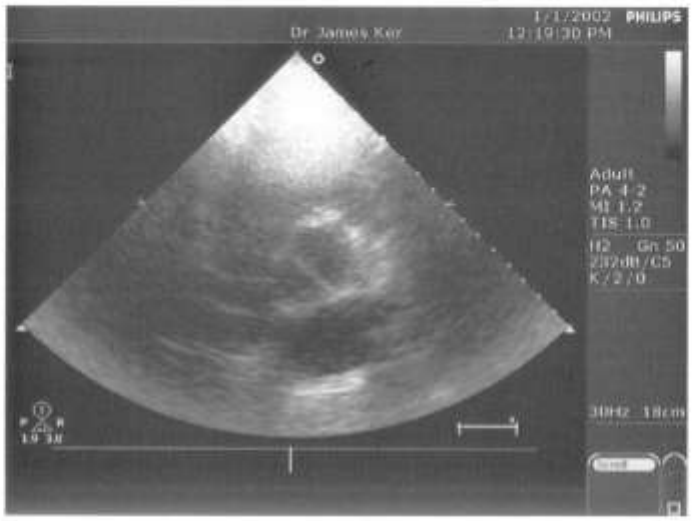

Fig. 3. No calcification. Normal plasma lipoprotein(a).

Of note, the youngest with calcification had an elevated plasma lipoprotein(a) level and the eldest without calcification had a normal plasma level of lipoprotein(a). This means that the calcification of the bicuspid aortic valve may not merely be a consequence of time.

A clear association between plasma lipoprotein(a) level and the presence or absence of calcification of the bicuspid aortic valve is seen in this case series.

It is therefore postulated that the concept that the plasma lipoprotein(a) level is a major role player of the calcification process of the bicuspid aortic valve is worth exploring in a randomized controlled trial looking at the long term effect of reducing the plasma lipoprotein(a) level in patients with bicuspid aortic valve disease.

This is a small case series merely exploring a concept. This observation needs to be repeated with a larger sample volume.

The long term clinical effects of reducing the plasma lipoprotein(a) level in patients with bicuspid aortic valve disease needs to be studied in a randomized controlled trial.

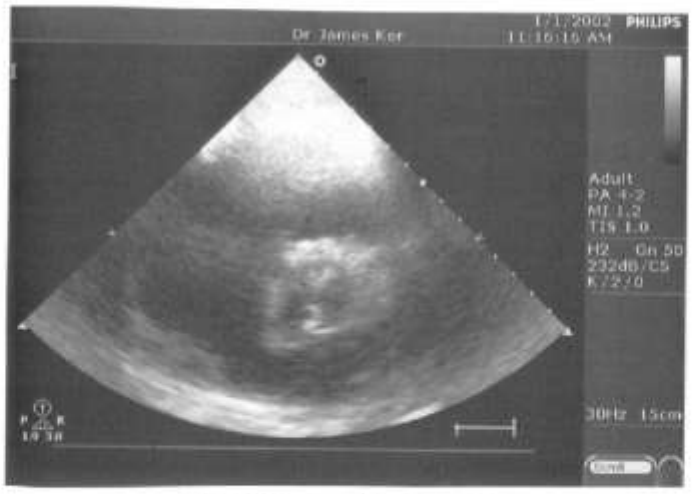

Fig. 4. Calcification. Elevated plasma lipoprotein(a).

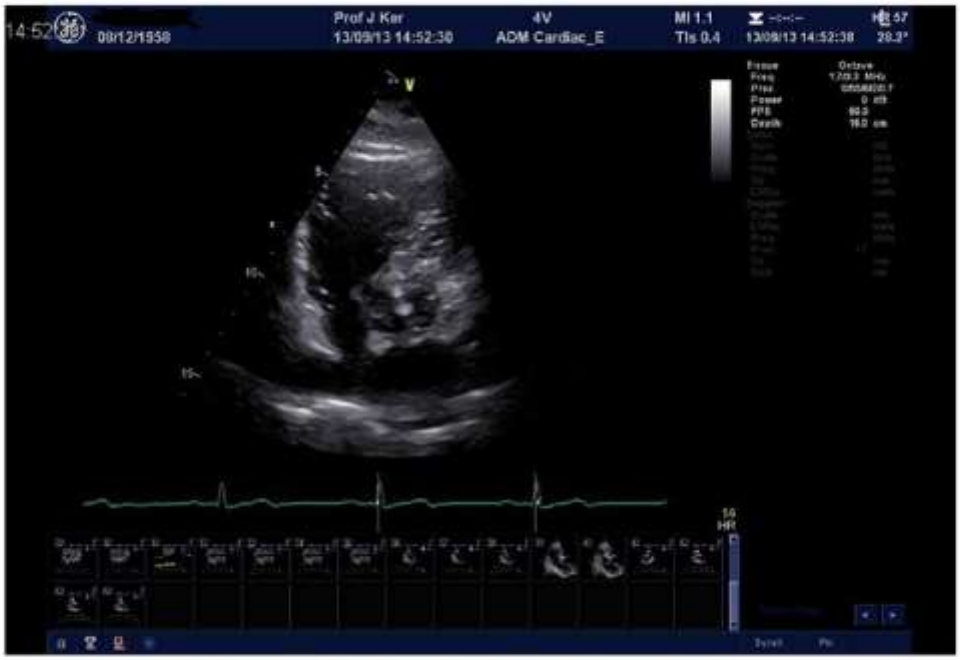

Fig. 5. Calcification. Elevated plasma lipoprotein(a).

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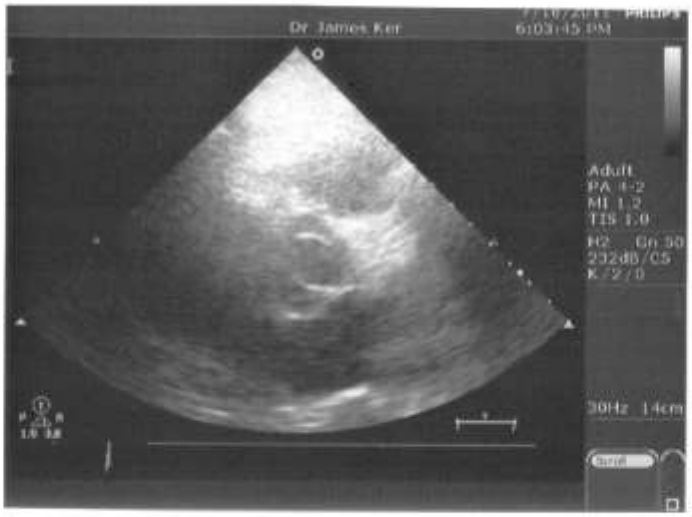

Fig. 6. No calcification. Normal plasma lipoprotein(a).

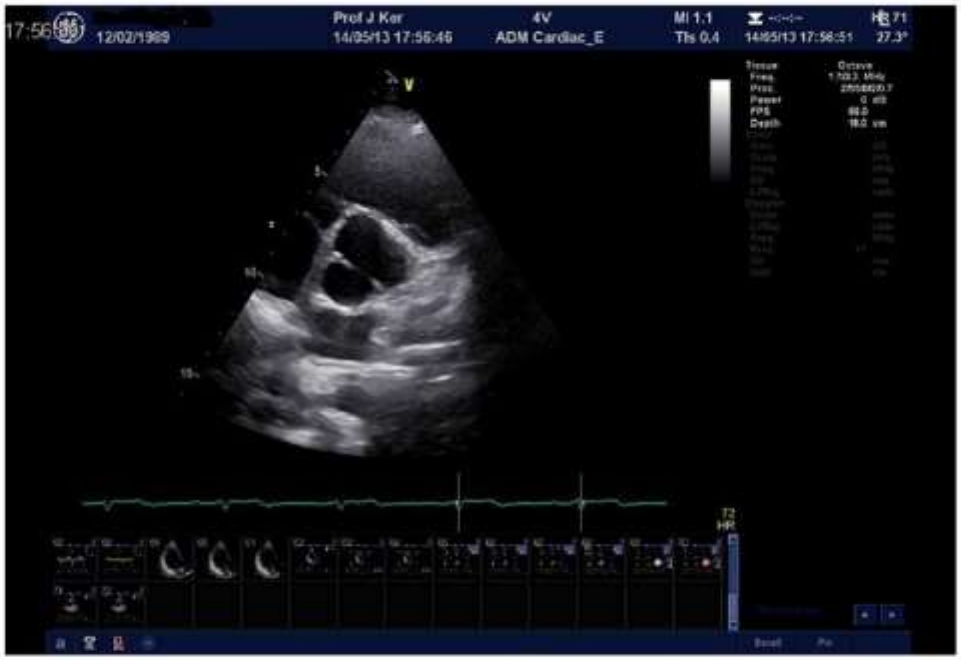

Fig. 7. No calcification. Normal plasma lipoprotein(a).

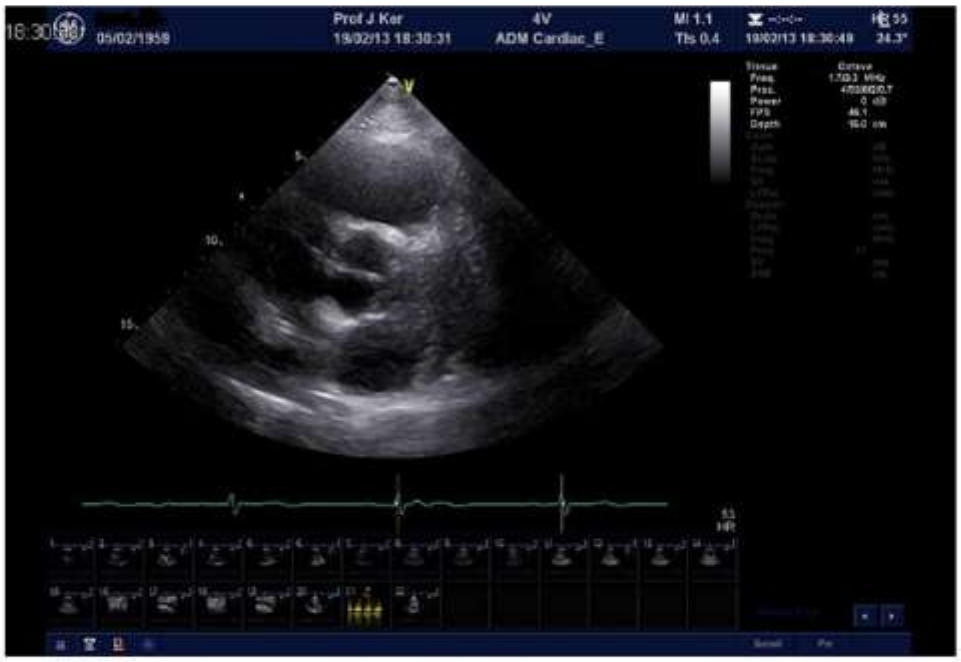

Fig. 8. No calcification. Normal plasma lipoprotein(a).

Fig. 9. No calcification. Normal plasma lipoprotein(a).

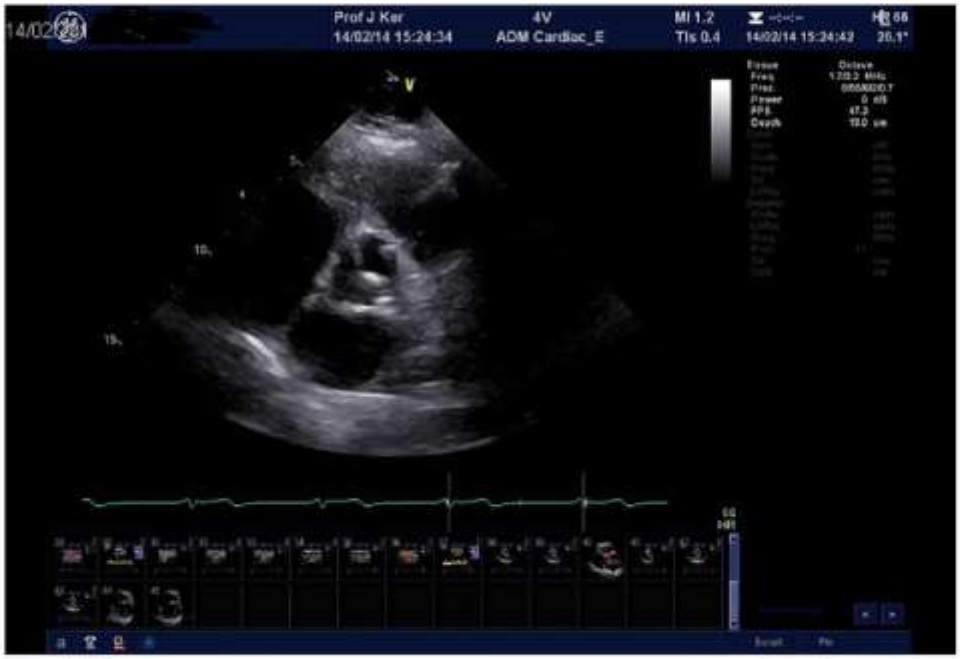

Fig. 10. Calcification. Normal plasma lipoprotein(a).

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Increased serum level of CTRP1 is associated with low coronary collateralization in stable angina patients with chronic total occlusion

Ying Shen [a], Lin Lu [a], Zhu Hui Liu [b], Feng Wu [c], Jin Zhou Zhu [b], Zhen Sun [a], Rui Yan Zhang [a], Qi Zhang [a], Jian Hu [a], Qiu Jing Chen [b], Zong Gui Wu [c,*], Wei Feng Shen [a,b,**]

[a] Department of Cardiology, Shanghai Rui Jin Hospital, Shanghai, People's Republic of China
[b] Institute of Cardiovascular Diseases, School of Medicine, Shanghai Jiaotong University, Shanghai, People's Republic of China
[c] Department of Cardiology, Second Hospital Affiliated to Second Military Medical University, Shanghai, People's Republic of China

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Development of collateral vessels is a physiological adaption to severe coronary artery narrowing and/or occlusion for myocardium to circumvent ischemia [1,2], and contributes to better outcomes after acute myocardial infarction [3,4]. However, patients with similar degrees of coronary artery obstruction may exhibit significant variability of collaterals. The reasons for this heterogeneity remain largely unknown. C1q TNF related protein (CTRP) has been shown to have diverse biological influences on cardiovascular system [5–8]. It remains unclear whether CTRP1 and CTRP3 affect coronary collateral growth. In this study, we analyzed serum levels of CTRP1 and CTRP3 in patients with stable angina and angiographic chronic total occlusion with high or low coronary collateralization, categorized according to Rentrop score [9]. Since endothelial progenitor cells (EPCs) are responsible for endothelial recovery after injury and angiogenesis in ischemia [10], we also assessed the effect of significant CTRP on angiogenic property of EPCs from patients with multi-vessel coronary disease on matrigel. Moreover, the expression of vascular endothelial growth factor (VEGF) and its receptors (VEGFR1 and VEGFR2) were examined in these CTRP-treated EPCs because they were crucially involved in angiogenesis [11,12].

* Correspondence to: Z.G. Wu, Department of Cardiology, Second Hospital Affiliated to the Second Military Medical University, 415 Fengyang Road, Shanghai 200003, People's Republic of China. Fax: +86 21 63520020.
** Correspondence to: W.F. Shen, Department of Cardiology, Rui Jin Hospital, 197 Rui Jin Road II, Shanghai 200025, People's Republic of China. Fax: +86 21 64457177.
E-mail addresses: zgwu@medmail.com.cn (Z.G. Wu), rjshenweifeng@gmail.com (W.F. Shen).

A total of 357 consecutive patients who had stable angina and at least one lesion with 100% occlusion between January 2010 and September 2012 were screened. For the purpose of research, patients with type 1 diabetes, chronic heart failure, pulmonary heart disease, malignant tumor or immune system disorders and those who had a history of coronary artery bypass grafting or received percutaneous coronary intervention within prior 3 months were excluded. We also excluded patients with intermittent claudication to avoid the influence of peripheral collateral circulation. The remaining 264 eligible patients with stable angina and chronic total coronary occlusion (>3 months) were selected for analysis. The study protocol was approved by the Hospital Ethics Committee and written informed consent was obtained from all patients. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Coronary angiography was performed through femoral or radial approach [13]. All angiograms were reviewed by two experienced cardiologists blinded to study protocol and biochemical measurements, and the presence/absence and extent of collaterals were determined with Rentrop score [14–16].

Blood samples were collected on the day of angiography after overnight fasting. Serum glucose, glycosylated hemoglobin (HbA1c), creatinine, uric acid, and lipid profile were measured with standard laboratory techniques [17,18]. Serum levels of CTRP1, CTRP3 and high-sensitivity C-reactive protein (hsCRP) were assayed using ELISA kits.

Peripheral blood mononuclear cells from 26 patients with multi-vessel disease were isolated by density gradient centrifugation and plated on culture dishes at 37 °C in a 5% CO_2 humidified atmosphere. Colonies of EPCs usually appeared between 10 and 20 days [19]. Based upon serum CTRP1 level detected in participants, EPCs were treated with increasing concentrations of recombinant human CTRP1 protein (0, 10, 100, 1000 ng/mL) for 72 h (Aviscerabioscience, Santa Clara, CA, USA). These cells were then harvested and placed on a 96-well glass slide pre-coated with matrigel (BD Bioscience, San Jose, CA, USA) and stimulated with CTRP1. Afterwards, plated EPCs were grown in normal condition for 12 h. The angiogenic capacity of EPCs was graded by the length of the cordlike structure and the branch point number in randomly selected fields located within 5 mm of the center of the wells using NIH image program [20]. Two investigators who were blinded to the protocol randomly examined the selected fields. EPCs were harvested after CTRP induction, and

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Correspondence

Rare congenital anomaly of the inferior vena cava

Congenital anomaly of the inferior vena cava (IVC) is a well described phenomenon [1,2]. These anomalies include complete absence, partial absence or duplication of the IVC [3]. Such anomalies of the IVC are seen more frequently in those with other congenital cardiac anomalies (0.6%–2%) [4].

This congenital condition can be discovered incidentally, or due to symptoms of associated congenital heart disease, asplenia, polysplenia, congenital kidney anomalies or deep venous thrombosis [1,2,3].

Figs. 1 and 2 are the CT angiography images of the venous system of the lower extremities and inferior vena cava of a 44 year old Caucasian male who presented with a long history of intermittent edema of both lower extremities. His clinical examination was perfectly normal. CT angiography of the lower extremities and IVC demonstrated patent popliteal, femoral and iliac veins with a completely absent IVC. Massively dilated collateral vessels were visible with large, dilated azygos and hemi-azygos veins. The azygos vein drained into the superior vena cava. In addition the lumbar veins were dilated with multiple collaterals present in the pelvis and abdomen. He tested heterozygous for the factor V Leiden mutation (R506Q).

Although congenital anomaly of the IVC is a well known clinical entity, combined absence of the suprarenal and infrarenal IVC (as demon-

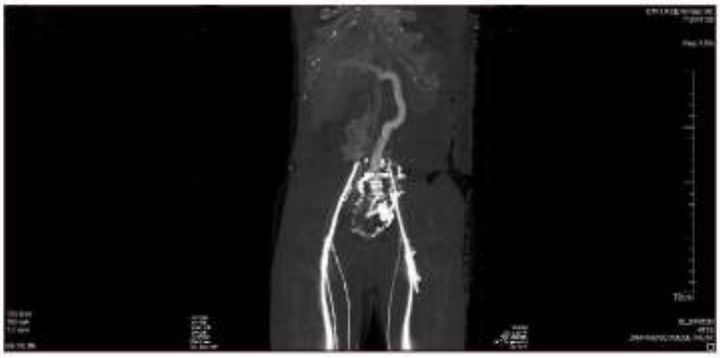

Fig. 1. CT angiography image demonstrating absence of the infra- and suprarenal portions of the inferior vena cava with numerous collateral vessels.

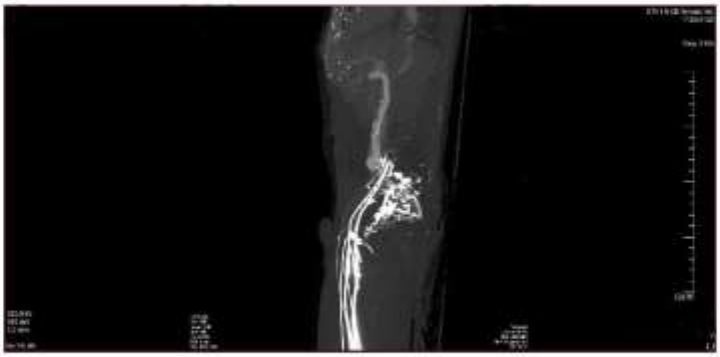

Fig. 2. CT angiography image demonstrating absence of the infra- and suprarenal portions of the inferior vena cava with numerous collateral vessels from a lateral view.

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strated in this particular case) has been reported in only eight cases [1]. Furthermore, whether the absence of all or only a segment of the IVC is an embryonic anomaly or the result of perinatal thrombosis with regression and subsequent disappearance of the affected segment is currently a controversial topic [5].

The clinical implications of this interesting congenital anomaly include the following: 1) it can lead to an erroneous diagnosis of deep venous thrombosis [6], 2) the azygous continuation may mimic a right paravertebral or tracheobronchial tumour [6] and an accessory hemiazygos vein may mimic an enlarged aortic knuckle [6], 3) a fatal outcome after ligation of the azygos vein in an undiagnosed patient with an absent IVC during surgery has been reported [7], and 4) congenital absence of the IVC has been described to create difficulties for catheter ablation of arrhythmias via the femoral vein approach [8]. It has been recommended that all patients with an IVC anomaly be screened for a thrombophilic disorder; as in a series by Gayer et al. [2] 7 out of 9 patients with an IVC anomaly and deep venous thrombosis (DVT) had a positive thrombophilic screen [2]. Ruggeri et al. [9] also found that congenital absence of the IVC may be a potential independent risk factor for DVT in the young [9].

In light of this the patient was started on Rivaroxaban (Xarelto®) 10 mg daily.

Isolated absence of the IVC rarely occurs in isolation and is usually associated with other cardiac and/or visceral anomalies, such as dextrocardia, polysplenia or malrotation of abdominal viscera [6].

In summary, this particular case of congenital absence of IVC is unique due to the fact that no other cardiac and/or abdominal visceral anomalies are present. Furthermore, a combined absence of the supra- and infrarenal portions of the IVC is present and as stated only eight cases are found in the literature.

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James Ker
Department of Internal Medicine and Genetics, University of Pretoria, Pretoria, South Africa
E-mail address: jker@wol.co.za

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Editorial

Aortic diverticulae and transient cerebral ischemic attacks—Another reason for aortic imaging in unexplained TIA?

James Ker

Department of Internal Medicine and Genetics, University of Pretoria, Pretoria, South Africa

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Traditionally a transient ischemic attack (TIA) was defined as a brief episode of a neurologic deficit due to focal cerebral or retinal ischemia which lasts less than 24 h [1]. However, Albers et al. [2] delivered a compelling argument for a redefinition of a TIA as "a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 h, and without evidence of acute infarction."

It is imperative to exclude cardiac sources of emboli in the assessment of the patient with a TIA [3–6]. Such cardiac causes include: atrial fibrillation, the presence of prosthetic valves, native valve disease (rheumatic and non-rheumatic), complicated mitral valve prolapse, interatrial septal aneurysms, lipomatous atrial septal hypertrophy, patent foramen ovale, mitral valvular strands, left atrial bands, mitral annular calcification, dilated cardiomyopathy and akinetic/dyskinetic left ventricular segments with intraventricular clot formation, atrial myxoma, papillary fibroelastoma of the aortic valve and aortic plaques [3–6].

Figs. 1 and 2 are CT aortograms of a 38-year old Caucasian woman who presented with an episode of aphasia which resolved spontaneously within 30 min. The current transient episode of neurologic dysfunction was the third one experienced during the past two years. The clinical examination was unremarkable with no abnormalities found. The echocardiogram was perfectly normal and ultrasound examination of both carotid arteries was perfectly normal. All biochemical analyses were normal with normal blood glucose and cholesterol levels. Hypothyroidism was excluded. The CT aortogram was then done to exclude possible atheromatous plaques in the aortic arch. Instead an aortic diverticula was found at the end of the arch (see arrow in Figs. 1 and 2). Clopidogrel at a dose of 75 mg once daily was prescribed and after 24 months of follow up no further TIA episodes have occurred.

Diverticular outpouchings of the aortic arch are important to both radiologists and clinicians as they may be confused with aneurysms and mediastinal masses [7]. Three types of aortic diverticula can be found [6]: 1) An aortic diverticulum in a left sided aortic arch with an aberrant right subclavian artery. This anomaly presents as an outpouching at the origin of the aberrant right subclavian artery and this is the classical "diverticulum of Kommerell" described in 1936 [7,8]. 2) An aortic diverticulum in a right sided aortic arch with an aberrant left subclavian artery. This is sometimes incorrectly labeled as diverticulum of Kommerell—a term which applies to a diverticulum at an aberrant right subclavian artery in a left sided aortic arch [9]. 3) An aortic diverticulum at the aortoductal junction. This diverticulum presents as a bulge along the inner aspect of the aortic isthmus distal to the subclavian artery [7]. This particular diverticulum represents a remnant of the infundibular part of the ductus arteriosus [7]. This is the diverticulum in this particular case (Figs. 1 and 2).

In this particular case of recurrent TIAs in a young woman with no other cause found, it is postulated that the source of cerebral emboli

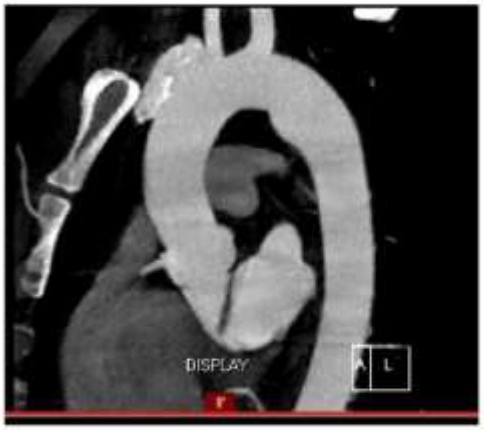

Fig. 1. CT aortogram demonstrating aortic diverticulum distal to the left subclavian artery.

E-mail address: jker@wol.co.za.

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Fig. 2. 3D CT aortogram demonstrating the aortic diverticulum (arrow).

was a diverticular outpouching of the aortic arch (the third type of aortic diverticula discussed) and that a daily dose of 75 mg of clopidogrel was sufficient to prevent further episodes after 24 months of clinical follow up.

It is suggested that an undiagnosed aortic diverticulum be added to the list of causes for unexplained episodes of transient cerebral ischemic attacks.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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HLA-B27-associated J-wave — A new variant of HLA-B27-associated cardiac disease?

James Ker *

Department of Physiology, University of Pretoria, PO Box 24338, Gezina, Pretoria 0031, South Africa

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In 1973 the strong association between the immunogenetic marker HLA-B27 and ankylosing spondylitis was described [1]. The strength of this association was unprecedented — HLA-B27 incurred a relative risk of more than 100 for ankylosing spondylitis [2].

In 1997 Bergfeldt [2] noted the presence of a cardiac syndrome, consisting of severe conduction system abnormalities plus aortic regurgitation, associated with HLA-B27 — present in 67% to 88% of patients with both these cardiac findings. The strength of this association led him to replace the concept of "cardiac complications of HLA-B27" with the term "HLA-B27-associated cardiac disease" [2]. An increased incidence of arrhythmias was also noted.

In this study it was hypothesized that a high incidence of electrocardiographic abnormalities will be present in patients with the immunogenetic marker HLA-B27. In this retrospective analysis a total of 62 patients with the immunogenetic marker HLA-B27 were identified out of a total of 1500 patient files from a cardiac clinic.

Electrocardiographic abnormalities were present in 69% of these patients. Of interest is that the most common electrocardiographic abnormality in this group of patients was J-waves in the inferior electrocardiographic leads, present in 44% of these patients (see Fig. 1).

Tikkanen et al. [3] noted that an early repolarization pattern (J-wave) in the inferior leads of the electrocardiogram is associated with an increased risk of death from cardiac causes in middle aged subjects.

Kazmierczak et al. [4] recently published their study on the incidence of cardiac arrhythmias in 31 patients with ankylosing spondylitis and they found a high incidence (55%) of ventricular extrasystoles.

Number of patients with HLA-B27:	**62**
Men:	**36**
Women:	**26**
Average age (years):	**52**
Normal electrocardiogram:	**19**
Abnormal electrocardiogram:	**43**
Left bundle branch block:	**1**
Right bundle branch block:	**3**
Premature ventricularcomplexes:	**7**
Delta-waves:	**3**
Inferior J-waves:	**27**
AV-reentry:	**1**
Inferior ST-depression:	**1**

Fig. 1. Patient characteristics.

This is the first observation of a high incidence of inferior J-waves – an entity with a proven risk for cardiac death – in patients with the immunogenetic marker HLA-B27.

It is postulated that the same obliterative endarteritis and fibrosis which are present in the tissues adjacent to afflicted joints [2] in these patients, are also present in the myocardium and are responsible for the inferior J-waves.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [5].

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* Tel.: +27 12 3430078; fax: +27 12 3430079.
E-mail address: jker@worl.co.za.

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Research Article Open Access

HLA-B27 and an Electrocardiographic Peculiarity

James Ker

Department of Physiology, University of Pretoria, South Africa

Abstract

Introduction: An increased cardiovascular mortality has been described in patients with spondyloarthropathies due to HLA-B27. Numerous cardiovascular afflictions are currently known to be associated with HLA-B27. These include aortic root dilation, aortic regurgitation, mitral regurgitation, myocarditis, heart failure, pericarditis, pericardial effusion, atrioventricular conduction block and more recently, the presence of J-waves.

Materials and methods: 48 HLA-B27 positive patients (23 men and 25 women) were included in this observational study. A 12-lead electrocardiogram and a signal-averaged electrocardiogram was recorded in every patient in order to detect any possible J-waves and ventricular late potentials respectively.

Results: 27 out of these 48 patients demonstrated a visible J-wave in the inferolateral leads. It was revealed that there is a likelihood ratio of 11.386 (p=0.00074) to demonstrate a visible J-wave if the duration of low-amplitude signals is less than 30 ms.

Conclusion: HLA-B27 positive patients has a high incidence of inferolateral cardiac J-waves. There is a high probability of demonstrating such a J-wave on the 12-lead electrocardiogram if the duration of ventricular late potentials is less than 30 ms. The possible mechanisms of this electrocardiographic paradox is discussed.

Keywords: HLA-B27; Ventricular; Late potentials; J-wave

Introduction

In 1973 the strong association between the immunogenetic marker HLA-B27 and ankylosing spondylitis was described [1,2]. More than 11 subtypes or polymorphisms of HLA-B27 have been described since, each one varying in frequency in different ethnic groups, with HLA-B*2705 the so-called "parent" allele, common in all racial groups [3].

It was subsequently realized that HLA-B27 is common to the entire spectrum of seronegative spondyloarthropathies, such as ankylosing spondylitis, Reiter's syndrome, psoriatic spondylitis, spondylitis in association with inflammatory bowel disease, juvenile spondyloarthropathy, undifferentiated spondyloarthropathy and acute anterior uveitis [2,3]. This spectrum can range from the majority of individuals who have no disease at all to isolated skin, eye or joint involvement to full-blown ankylosing spondylitis [3].

It has been reported that there is an increased cardiovascular mortality in patients with spondyloarthropathies [4]. In fact the first reported case of cardiac involvement in spondyloarthropathy already appeared in 1936 [5,6]. Aortic root involvement is echocardiographically detectable in 61 % of patients with ankylosing spondylitis [4,7,8] presenting echocardiograpically as thickening of the posterior aortic wall with occasional aortic root dilation [4,7,8]. Aortic regurgitation is a known complication of HLA-B27 spondyloarthropathy as a result of cusp thickening and aortic root dilation [4,9]. A study by Roldan et al 10 found mitral regurgitation in 30 % of 44 patients. The predominant reason being basal thickening of the anterior mitral leaflet [4,10]. Another classic echocardiographic feature is the so-called "subaortic bump"-hyperechoic thickening of the aortic-mitral junction [4,8,11]. Myocardial and pericardial involvement in spondyloarthropathy is a well described entity with myocarditis, heart failure, symptomatic pericarditis and pericardial effusion known sequelae [2,4,12,13]. More interesting and much more common is involvement of the cardiac conduction system in HLA-B27 positive patients [2,4]. Atrioventricular conduction blocks have been reported since the 1940's as a complication of ankylosing spondylitis and is regarded as the most common cardiac complication [2,14]. It has been suggested that as many as 20 % of male patients with permanent pacemakers may have an HLA-B27 related disease as the underlying cause for the pacemaker [2,15,16].

An important feature of atrioventricular block in HLA-B27 positive patients is that there is a tendency for these blocks to occur intermittently and it has been stated that this feature supports the notion that a reversible inflammatory process, rather than fibrosis is the cause of the conduction blocks in these patients [2,17-19].

Ker [20] detected a high incidence of inferior J-waves on the electrocardiograms of asymptomatic HLA-B27-positive patients. Might this be evidence that HLA-B27 positivity may be a risk factor for sudden cardiac death as it has been reported that J-waves in the inferior electrocardiographic leads is associated with an increased risk of death [21].

Materials and Methods

48 HLA-B27-positive patients (23 men and 25 women) were included in this study. All of these patients were chosen in a retrospective manner from a cardiology practice. Only patients where no comorbities were present were chosen for the study. They all had a normal echocardiographic study. This was done to exclude the possibility that any concomitant disease could affect the electrocardiogram. A 12-lead electrocardiogram was then recorded in

Corresponding author: Professor James Ker, MRCP, PhD, FESC, FACC, Department of Physiology, University of Pretoria, South Africa, Tel: +2712-3430078; Fax: +2712-3430079; E-mail: jker@wol.co.za

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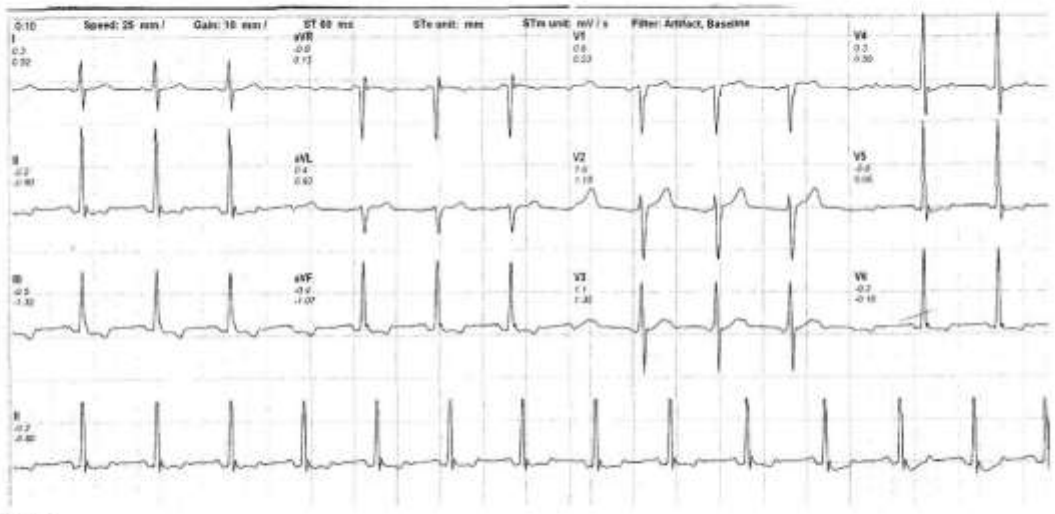

Figure 1:

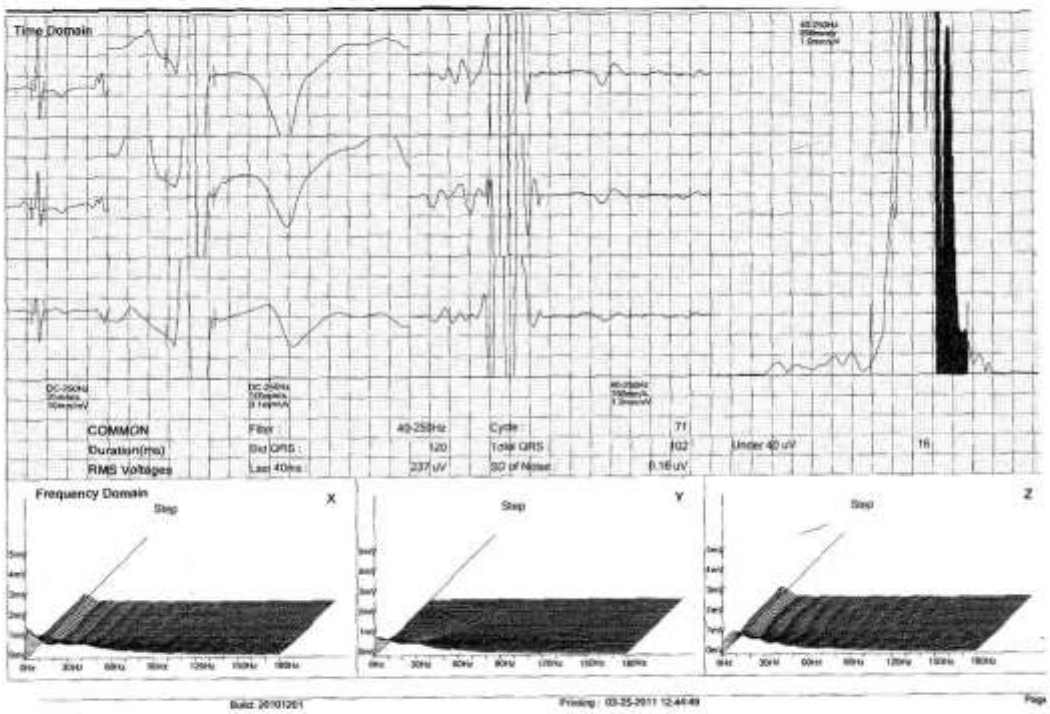

Figure 2:

LAS duration < 30 ms with J-wave present: 18	LAS duration > 30 ms with J-wave present: 9
LAS duration < 30 ms with J-wave absent: 4	LAS duration > 30 ms with J-wave absent: 17

Likelihood ratio=11.386 (p=0.00074)
LAS denotes low amplitude signal

Table 1: Electrocardiographic characteristics.

every patient and the presence of any J-waves noted. Subsequently a signal-averaged electrocardiogram was recorded in every patient.

The aim of this observational study was to describe the signal-averaged electrocardiographic features in HLA-B27 positive patients and to detect any possible differences between the group of HLA-B27 positive patients with and without J-waves on the 12-lead electrocardiogram. It has been shown before that a high prevalence of inferolateral J-waves exist in HLA-B27 positive patients, but no there is currently no data on the possibility of cardiac late potentials in this patient population.

The author of this manuscript certify that he complied with the principles of ethical publishing in the International Journal of Cardiology.

Results

Out of these 48 patients a total of 27 demonstrated a visible J-wave on the 12-lead electrocardiogram. All observed J-waves was seen in the inferolateral leads (leads II, III, aVF and V3-V6) (Figure 1).

All of the signal-averaged electrocardiograms were within normal limits according to current published criteria. However, when scrutinizing both the 12-lead surface electrocardiograms and the signal-averaged electrocardiograms it was seen that almost all observed J-waves occurred in the SAECG's of patients where the low-amplitude signal (LAS) duration was less than 30 ms.

A two-by-two table was then used to calculate the likelihood ratio to observe J-waves in cases where the LAS duration is less that 30 ms.

The two-by-two table (Table 1) revealed a likelihood ratio of 11.386 (p=0.00074) to demonstrate a visible J-wave on the 12-lead electrocardiogram if the low-amplitude signal (LAS) duration is less that 30 ms on the signal-averaged electrocardiogram (SAECG).

Discussion

The J-point marks the end of the QRS complex and the J-wave is a low frequency deflection at the end of the QRS complex [22]. Currently,it is not clear whether the J-wave represents ventricular depolarization or early repolarization [22]. However, for the clinician it may become one of the most important electrocardiographic risk markers for cardiovascular death: Haissaguerre [23] found a J-wave in 31 % of survivors from idiopathic ventricular fibrillation versus only 5 % in control subjects [22,23]. Tikkanen [24] found a strong association between an inferior J-wave and risk for cardiac death among 630 middle aged subjects. Recently, Sinner [25] published a prospective study of 2063 subjects between the age of 35 and 74 years. It was found that the prevalence of a J-wave was 18.5 % and this was associated with an increase in cardiovascular mortality [22,25].

Thus, according to available data the J-wave is associated with a dispersion of repolarization within the ventricular myocardium with a subsequent risk for cardiac arrhythmia [26]. A recent classification scheme for cardiac J-waves divides the electrocardiographic pattern into four possible types [26,27]: Type 1 demonstrates J-waves in the lateral precordial leads. This pattern has a low level of risk for arrhythmic events and is prevalent among healthy male athletes. Type 2 demonstrates J-waves in the inferior or inferolateral leads and is associated with a moderate level of risk. Type 3 demonstrates J-waves globally in the inferior, lateral and right precordial leads and can be associated with electrical storms. The fourth type represents Brugada syndrome with J-waves limited to the right precordial leads.

The observed J-waves in this population of HLA-B27 positive patients thus fits the criteria for type 2 (Figure 1). The incidence and electrocardiographic pattern of observed J-waves in this study corresponds to that of a previous study in HLA-B27 positive patients [20]. But, what might the underlying physiological reason be for these type 2 J-waves in HLA-B27 positive patients? Cardiomyopathy was reported in patients with ankylosing spondylitis 31 years ago already [28]. In a series of studies in such patients with cardiomyopathy, but without aortic regurgitation or conduction abnormalities-other known sequelae of HLA-B27-–early diastolic dysfunction was found [29,30] with histological examination showing a mild and diffuse increase in interstitial connective tissue [29]. It was shown that the myocardium can develop histopathological abnormalities in the small arteries-an obliterative intimal proliferation-this obliterative arteritis is also found in the tissues adjacent to affected joints, the sinus node artery, the atrioventricular nodal artery and the vasa vasora of the proximal aorta [2]. It is thus suggested that the high incidence of J-waves in this population is related to such histopathological abnormalities in the myocardium of afflicted patients.

Signal averaged electrocardiography is designed to detect low amplitude signals in the terminal part of the QRS complex and early ST segment by the elimination of noice which contaminates the surface electrocardiogram [31]. The principal clinical indication for this method is for the detection of ventricular late potentials [31]. Ventricular late potentials are microvolt signals that are part of the terminal QRS complex and persist into the ST segment [31]. These late potentials correspond to areas of delayed ventricular activation due to slowed conduction velocity [31]. On such a signal averaged electrocardiogram (SAECG) the so-called root-mean-square voltage of the terminal at 40 ms (RMS40) represents the relative amplitude of the late potential component and the low amplitude signal (LAS) is the duration of the signal whose initial value is less than 40 uV [32].

(Figure 2) is the signal averaged electrocardiogram of the patient with the prominent inferolateral J-waves as seen in (Figure 1). On the SAECG in this case (Figure 2) the duration of the low amplitude signal is 16 ms. As shown by the two-by-two table the likelihood of demonstrating J-waves on the 12-lead ECG is 11.386 (p=0.00074) if the low amplitude signal duration is less than 30 ms.

Current opinion favours the concept that the J-wave is a marker of early repolarization [26] and that low amplitude signals (or ventricular late potentials) correspond to areas of delayed ventricular activation (depolarization) [31]. It is therefore physiologically plausible that in cases where low amplitude signals has a low duration, that earlier repolarization is possible and thus the higher probability of observing a J-wave on the 12-lead ECG.

However, as both these entities (J-waves and late potentials) have been shown to be electrocardiographic risk markers for arrhythmia, this study raises the possibility that HLA-B27 positive patients displays a double risk for arrhythmia-either early repolarization or late potentials.

It is proposed that this question merits an observational study of

adequate size and duration to answer the specific question of whether the presence of HLA-B27 0is a risk factor for death to due cardiac arrhythmia.

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