

# The hearts of large mammals generate higher pressures, are less efficient and use more energy than those of small mammals

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## ABSTRACT

A prevailing assumption in the cardiovascular field is that the metabolic rate of the heart is a constant proportion of a mammal's whole-body aerobic metabolic rate. In this Commentary, we assemble previously published cardiovascular, metabolic and body mass data from matched terrestrial mammalian species, at rest and during heavy exercise, and reveal scaling relationships that challenge this assumption. Our analyses indicate that the fractional metabolic cost of systemic perfusion compared with whole-body metabolic rate increases significantly with body size among resting mammals, from ~2.5% in a mouse to ~10% in an elephant. We propose that two significant body size-dependent effects contribute to this conclusion; namely, that larger species generate higher mean systemic arterial blood pressure and that their myocardium operates with lower external mechanical efficiencies compared with those of smaller species. We discuss potential physiological and mechanical explanations, including the additional energy needed to support the arterial blood column above the heart in larger species, especially those with long necks, as well as the possible sources of greater internal energy losses from the heart of larger species. Thus, we present an updated view of how increasing blood pressure and decreasing efficiency of the myocardium result in an increasing fractional metabolic cost of perfusion as body size increases among resting mammals.

**KEY WORDS:** Body size, Cardiac efficiency, Left ventricle, Mechanical work, Metabolic energy, Scaling

## Introduction

A long-standing assumption in the cardiovascular field is that the metabolic rate of the heart is proportional to the aerobic metabolic rate of the whole body. The prevailing argument makes use of cardiovascular variation among mammals of different body size, and is set to scaling 'rules' that still are widely accepted; namely, that (i) mean systemic arterial blood pressure is independent of body mass, (ii) stroke volume and heart mass are directly proportional to body mass, and (iii) the mechanical efficiency of the myocardium is independent of body mass. In a landmark study, Loiselle and Gibbs (1979) questioned the accuracy of some of these assumptions and challenged the idea that the heart consumes a fixed percentage of whole-body metabolic rate among mammals. Their *in vitro* study of the energetics of papillary muscle from rat, guinea pig and cat

hearts, and further data from the literature on rabbit, dog and human hearts, indicated that the smaller species had more efficient myocardia than larger species. Thus, the fractional metabolic cost of systemic perfusion compared with whole-body metabolic rate appeared to increase with increasing body size from approximately 4% in the smaller species to about 10% in the larger ones. Since their study (Loiselle and Gibbs, 1979), there have been more investigations of the scaling of cardiovascular variables in mammals over a wide body size range that show that mean systemic arterial blood pressure increases in larger species (Seymour and Blaylock, 2000; White and Seymour, 2014) and that myocardial efficiency decreases in larger hearts (Horrell et al., 2022). Further, *in vivo* treadmill studies involving relevant cardiovascular data now allow us to explore heart energetics at resting and maximal aerobic rates in mammals ranging from rats to horses (Gleeson et al., 1983; Jones et al., 1989; Kuczumski et al., 2018; Taylor et al., 1987).

The energetics of the heart involve conversion of chemical energy in metabolic substrates to mechanical energy of pressurised blood flow, where energy is lost as heat at several levels of the cascade (Fig. 1). Ultimately, all energy put into the heart is lost as heat from inefficiencies of the heart itself and from frictional heat throughout the circulatory system. The ratio of energy conservation to energy input at each step is known generally as efficiency, and the specific terminology depends on which steps are involved (Knaapen et al., 2007; Schipke, 1994; Westerhof, 2000). Some energy is lost by friction in the coronary circulation as it supplies metabolic substrates and removes waste. Subsequently, energy in substrates is lost during substrate-level and oxidative phosphorylation to produce ATP. Energy in ATP is lost while maintaining basal cardiac metabolism and during contractile crossbridge and calcium cycling (Fig. 1). Some of the muscle mechanical energy is lost to friction within the heart wall (internal work), while the remaining energy in every beat of the heart is put into external work, which is usually referenced as stroke work, defined here as the sum of pressure energy (the area within the left ventricle's pressure–volume loop) and kinetic energy (the velocity and volume of the blood entering the aorta during ejection). The left ventricular external mechanical work rate,  $\dot{E}_{LV,ext}$ , is the product of stroke work and heart rate (Fig. 1). The left ventricular metabolic rate,  $\dot{E}_{LV,met}$ , includes  $\dot{E}_{LV,ext}$  and the sum of all previous heat loss rates. The ratio of the two,  $\dot{E}_{LV,ext}/\dot{E}_{LV,met}$ , represents the left ventricular external mechanical efficiency. Further,  $\dot{E}_{LV,met}$  in relation to whole-body metabolic rate,  $\dot{E}_B$ , can be termed the relative cost of perfusion,  $\dot{E}_{LV,met}/\dot{E}_B$ . The main aim of our analysis concerns these ratios. See List of symbols and abbreviations for a definition of those used herein.

We are concerned with the left ventricle only, primarily because not enough comparative data are available for the right ventricle. The external mechanical energy of the right ventricle is only ~14% of the whole heart among mammals (Snelling et al., 2015a), so any error resulting from its exclusion should be minor. We also focus on

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### List of symbols and abbreviations

$\dot{E}_B$	whole-body metabolic rate ( $W=J\ s^{-1}$ )
$\dot{E}_{B,max}$	whole-body metabolic rate at $\dot{V}_{O_2,max}$ ( $W$ )
$\dot{E}_{B,rest}$	whole-body metabolic rate at $\dot{V}_{O_2,rest}$ ( $W$ )
$\dot{E}_{LV,ext}$	left ventricular external mechanical work rate ( $W$ )
$\dot{E}_{LV,ext}/\dot{E}_B$	fractional mechanical cost of systemic perfusion
$\dot{E}_{LV,ext}/\dot{E}_{LV,met}$	left ventricular external mechanical efficiency
$\dot{E}_{LV,ext}/M_{LV}$	left ventricular external mechanical work rate relative to mass of myocardium ( $W\ g^{-1}$ )
$\dot{E}_{LV,met}$	left ventricular metabolic rate ( $W$ )
$\dot{E}_{LV,met}/\dot{E}_B$	fractional metabolic cost of systemic perfusion
$\dot{E}_{LV,met}/M_{LV}$	left ventricular metabolic rate relative to mass of myocardium ( $W\ g^{-1}$ )
$f_H$	heart rate (beats $s^{-1}$ )
$M_B$	body mass (kg)
$M_H$	heart mass (g)
$M_{LV}$	left ventricular mass (g)
$P_g$	component of $P_{sys}$ due to gravity ( $kPa=J\ l^{-1}\approx 7.5\ mmHg$ )
$P_r$	component of $P_{sys}$ due to vascular resistance (kPa)
$P_{sys}$	mean systemic arterial blood pressure (kPa)
$\dot{V}_{BL}$	systemic blood flow rate (cardiac output; $l\ s^{-1}$ )
$\dot{V}_{O_2,max}$	whole-body maximum $O_2$ consumption rate ( $ml\ O_2\ min^{-1}$ )
$\dot{V}_{O_2,rest}$	whole-body resting $O_2$ consumption rate ( $ml\ O_2\ min^{-1}$ )
$V_S$	stroke volume (l)

pressure energy, which is the major form of energy put into the blood ejected from the left ventricle. However, because the blood has velocity, there is also a small kinetic energy component that is generally negligible and ignored in resting mammals (Blick and Stein, 1977). Nonetheless, the relative contribution by kinetic energy to total blood energy might increase during heavy exercise (Burton, 1965; Folkow and Neil, 1971) and possibly as a function of increasing body size (Calder, 1996).

In this Commentary, we have used published data to derive scaling relationships for basic cardiovascular variables and for whole-body metabolic rate in resting and exercising terrestrial mammals. Our findings challenge long-held assumptions by indicating that in resting mammals, the left ventricle consumes disproportionately more of the body's metabolic energy as body size increases, mostly because the pressure load increases and the myocardium becomes less efficient. The results have implications for medical and evolutionary cardiovascular research. They are relevant to studies on heart disease, cardiac failure and cardiovascular pathology, especially where experimental animals are used to model the human condition without hitherto appreciating the significant differences in cardiac function and energetics. The results are of further importance within an evolutionary context, because they suggest that body size might represent a constraint on cardiovascular function and whole-body metabolic rate that could inform on the limits of body size among past and present species.

### How scaling reveals the effect of body size on the cardiovascular system

The effects of body size are studied usually with scaling (allometry) analyses (Calder, 1996), which when applied to the cardiovascular system can reveal important structural and functional changes across development (Snelling et al., 2015a,b; Snelling et al., 2019) and across different species of mammals (White and Seymour, 2014; Horrell et al., 2022). The effects of body size are studied usually with scaling (allometry) analyses (Calder, 1996). In this Commentary, we use this approach to relate cardiovascular (or

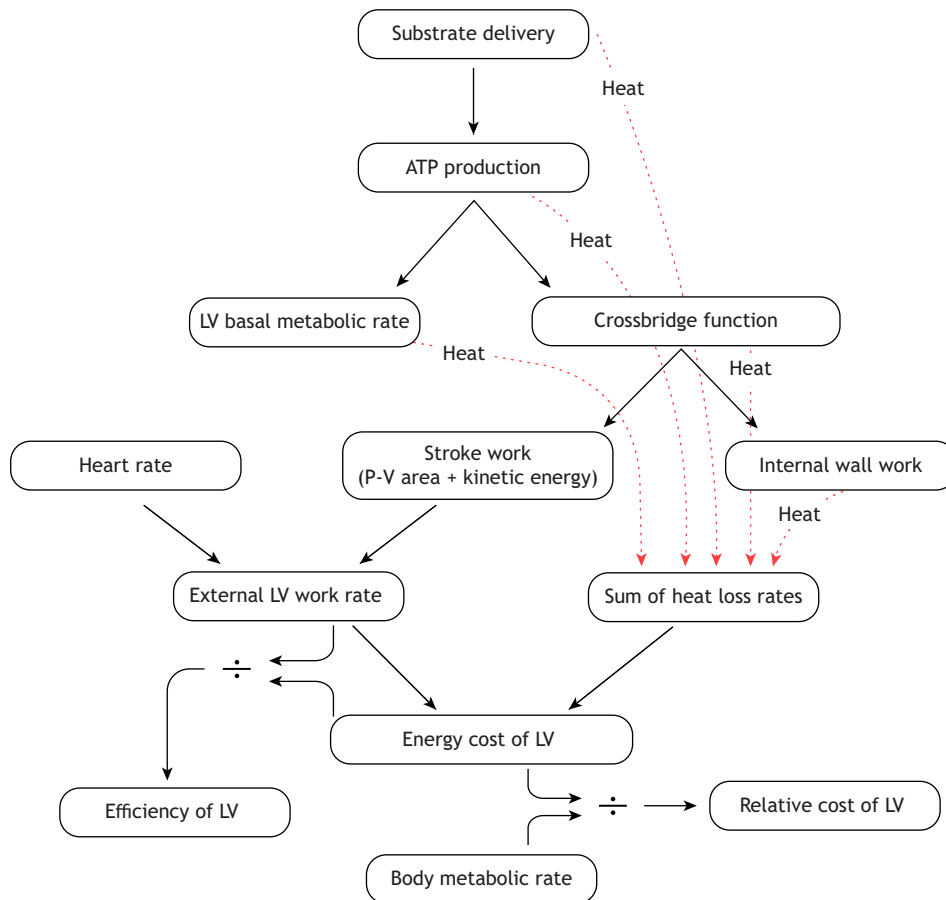
metabolic) variables ( $Y$ ) to body mass ( $M_B$ ), according to the standard two-parameter power equation,  $Y=aM_B^b$ , where parameter  $a$  (the coefficient) defines the elevation of the curvilinear line and parameter  $b$  (the exponent) describes its shape. When  $b=1$ ,  $Y$  is directly proportional to  $M_B$ ; when  $b=0$ ,  $Y$  is independent of  $M_B$ ; when  $1>b>0$ ,  $Y$  increases with a curve that has a decreasing slope against  $M_B$ ; when  $b>1$ ,  $Y$  increases with a curve with an increasing slope against  $M_B$ ; and when  $0>b>-1$ ,  $Y$  decreases with a curve that has a decreasing slope against  $M_B$ . Although the variable is plotted on the ordinate ( $y$ -axis) and body mass on the abscissa ( $x$ -axis), the results here are correlations, without inferences of dependency. The variables are usually influenced by immediate factors, only distantly related to body mass.

Conventional scaling of cardiovascular variables yields exponents suggesting that heart rate, stroke volume and mean systemic arterial blood pressure conspire to match the exponent of whole-body metabolic rate. However, this conclusion has been reached by rounding exponents to ideal values, and dismissing deviations from the ideal as annoying errors in the datasets. That approach is dangerous because the adult body mass range of terrestrial mammals is a millionfold (3 g shrew–3000 kg elephant), and so even a very shallow exponent, or a minor deviation from the ideal exponent, when expanded across such a broad range, can have profound changes for the cardiac variable under examination. For example, if the exponent is 1.0, then an arbitrary variable with a value of 1 for a 1 kg rabbit predicts a value of 3000 for a 3000 kg elephant. If the exponent is 1.05, the predicted value for the elephant becomes 4477, which is 49% higher. Likewise, if the exponent is 0.05, the calculated value will be 49% higher than if the exponent is assumed to be 0.0. Therefore, we should avoid the temptation to round exponents to convenient ideals, especially when shown to be statistically different. In this Commentary, for those relationships derived from the datasets presented herein, we assign an asterisk to low exponents that are nevertheless significantly different from zero at an  $\alpha$ -level of 0.05.

### The external work of the left ventricle in resting mammals

The external mechanical work rate of the left ventricle ( $\dot{E}_{LV,ext}$ ), expressed in watts, can be calculated from data for heart rate ( $f_H$ ), stroke volume ( $V_S$ ) and mean systemic arterial blood pressure ( $P_{sys}$ ). We set out to calculate  $\dot{E}_{LV,ext}$  using published data collected from resting mammals, as well as their estimated whole-body metabolic rate at  $\dot{V}_{O_2,rest}$  ( $\dot{E}_{B,rest}$ ), relative to body mass ( $M_B$ ). The scaling equations of each of these variables could have been based on different sets of species, but they would have not been matched. Consequently, we assembled all variables for the same set of 23 species from mouse to elephant but have excluded the giraffe from regression fitting to avoid bias (Table S1).

Our analysis shows that  $\dot{E}_{LV,ext}$  increases with  $M_B$  raised to an exponent of 0.85 and  $\dot{E}_{B,rest}$  increases with an exponent of 0.79 (Fig. 2A). Their ratio,  $\dot{E}_{LV,ext}/\dot{E}_{B,rest}$ , termed the fractional mechanical cost of perfusion (%), scales with  $M_B$  raised to an exponent of 0.06\* (\* $P<0.05$ ). As the myocardium is not 100% efficient, the left ventricular metabolic rate,  $\dot{E}_{LV,met}$ , is by definition greater than  $\dot{E}_{LV,ext}$ . If the efficiency of the myocardium does not vary systematically with  $M_B$  (say 25% in all species regardless of body size), then the exponent for  $\dot{E}_{LV,met}/\dot{E}_{B,rest}$ , termed the fractional metabolic cost of perfusion (%), is unchanged at 0.06\* (Fig. 2B). However, a steeper exponent for  $\dot{E}_{LV,met}/\dot{E}_{B,rest}$  would arise if efficiency declines in larger species. In either case, the relationships show that the relative metabolic cost of perfusion increases with body size among resting mammals.



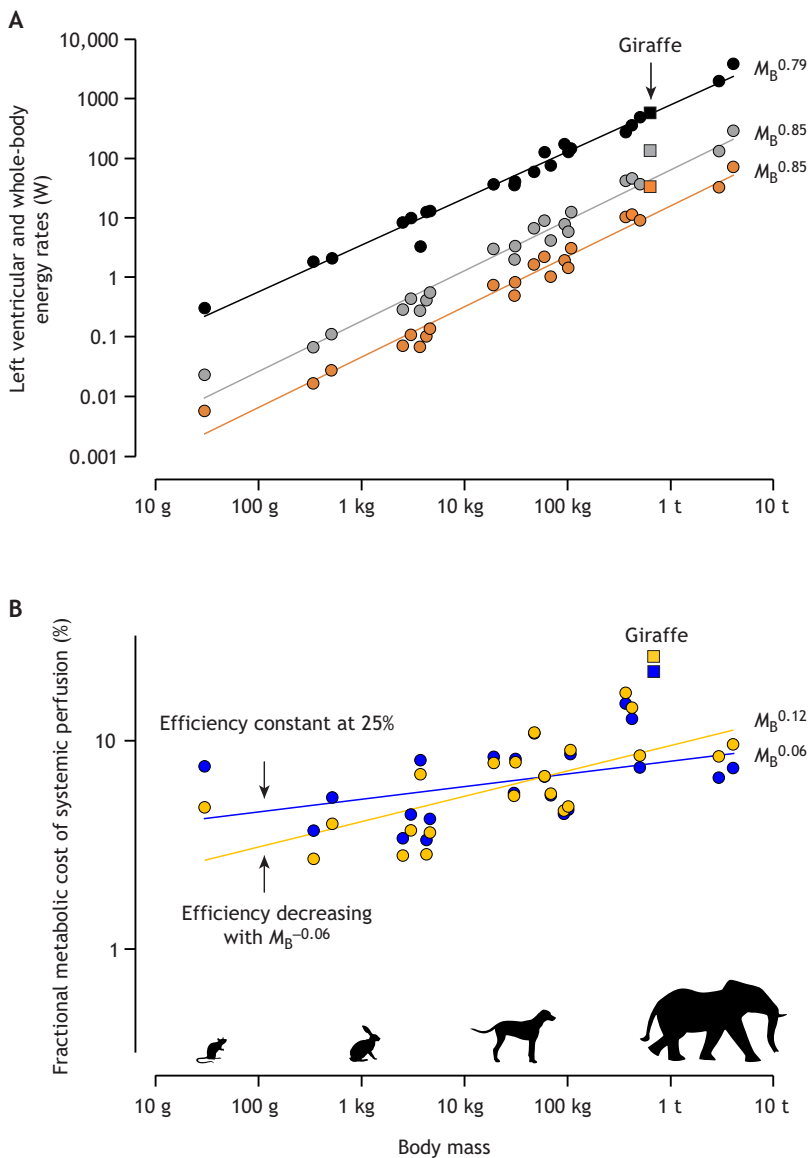
**Fig. 1. Energy cascade of the left ventricle (LV).** The diagram shows the steps where energy is transferred to the next level and where some energy is lost as heat. Energy is initially lost as friction in the coronary circulation responsible for substrate delivery. Inefficiencies are present in substrate-level and oxidative phosphorylation involved in ATP production. ATP powers maintenance functions of the myocardium as LV basal metabolic rate, as well as contractile crossbridge and calcium cycling. Crossbridge function puts energy into stroke work, measured as pressure energy and stroke volume ( $P$ - $V$  loop area) plus the kinetic energy of the blood entering the aorta, and internal wall work, which deforms the heart and stores energy in the visco-elastic wall elements, ultimately lost as heat. The heart rate multiplied by stroke work defines the external LV work rate (LV external mechanical work rate;  $\dot{E}_{LV,ext}$ ). The total energy cost of the LV (LV metabolic rate;  $\dot{E}_{LV,met}$ ) is the sum of the external LV work rate and heat loss rates from all steps. The ratio of external LV work rate and energy cost of the LV is the efficiency of the LV myocardium ( $\dot{E}_{LV,ext}/\dot{E}_{LV,met}$ ), and in turn the relative cost of the LV is the ratio of the energy cost of the LV and whole-body metabolic rate ( $\dot{E}_{LV,met}/\dot{E}_B$ ).

An important influence on the metabolic cost of perfusion is the increased  $\bar{P}_{sys}$  in larger species. Previous literature on scaling gives the impression that  $\bar{P}_{sys}$  is independent of body size in mammals, probably because the exponents from the standard two-parameter power equations are close to zero; for example, 0.03 (Günther, 1975), 0.026 (Calder, 1996) and 0.05 (Seymour and Blaylock, 2000). A survey of  $\bar{P}_{sys}$  (kPa) and  $M_B$ , set to a two-parameter power equation and weighted for phylogenetic relatedness among 44 species, shows the relationship is statistically significant, where  $\bar{P}_{sys}=13.2M_B^{0.04}$  (White and Seymour, 2014). The measurements of  $\bar{P}_{sys}$  were taken from all available studies of mammals including conscious, anaesthetised, free-ranging and restrained individuals. There were no apparent differences between the whole dataset and studies of only unrestrained and un-anaesthetised individuals (Poulsen et al., 2018), and a sensitivity analysis indicated that the dataset were robust to these influences during measurement (White and Seymour, 2014). Moreover, it is recognised that the vertical distance between the heart and the top of the arterial tree influences  $\bar{P}_{sys}$  (Poulsen et al., 2018; Sandal et al., 2019). It is now known that the two-parameter equation is not appropriate for blood pressure, because it forces  $\bar{P}_{sys}$  toward zero in very small mammals, underestimates values from both small and large species, and overestimates values in the mid-range of  $M_B$ . The two-parameter equation fails to recognise the two components of  $\bar{P}_{sys}$ : pressure needed to overcome the resistance of the peripheral vascular system ( $P_r$ ) and pressure necessary to raise the blood against gravity ( $P_g$ ), calculated as  $\rho gh$  [product of blood density ( $\rho$ ), acceleration due to gravity ( $g$ ) and vertical distance ( $h$ ) of the arterial tree above the heart].  $P_r$  can be called the perfusion pressure and  $P_g$

the gravitational (or hydrostatic) pressure, and they are theoretically additive ( $\bar{P}_{sys}=P_r+P_g$ ). A three-parameter equation based on the same data ( $\bar{P}_{sys}=12+1.3M_B^{0.23}$ ) mirrors this relationship (White and Seymour, 2014). The first term is a constant, reflecting that  $\bar{P}_{sys}$  plateaus at around 12 kPa (90 mmHg) in a wide range of small mammals. The exponent of 0.23 in the second term represents most of the increasing vertical distance between the heart and the top of the arterial tree (theoretically 0.33 in similarly shaped animals). The equation predicts that  $\bar{P}_{sys}=12.5$  kPa (94 mmHg) in a 20 g mammal and 20.1 kPa (151 mmHg) in a 3000 kg one. In the giraffe, its long neck makes  $P_g$  much higher, and so measured  $\bar{P}_{sys}=28.5$  kPa or 214 mmHg (Table S1; Seymour and Blaylock, 2000).

### The external work of the left ventricle in exercising mammals

The analyses so far consider the left ventricle when the animal is resting, but we can obtain an independent set of values for  $\dot{V}_{BL}$ ,  $\bar{P}_{sys}$  and whole-body metabolic rate at rest and during heavy exercise on a treadmill from five species of lab or domestic mammals (39 *Rattus norvegicus*, three *Canis familiaris*, three *Capra hircus*, six *Equus caballus* and six *Bos taurus*), which range in  $M_B$  from 0.28 to 453 kg (Gleeson et al., 1983; Jones et al., 1989; Kuczmariski et al., 2018; Taylor et al., 1987). The cardiovascular and whole-body metabolic measurements were taken when the animals were either resting (standing quietly) or undertaking heavy exercise (running at their highest aerobic speed). The measurements were recorded concurrently in the same individuals, and averaged for each group (dog, goat, pony, calf, horse and steer), except for rats, where  $\dot{V}_{BL}$



**Fig. 2. Effect of body size on left ventricular metabolic rate, whole-body metabolic rate and the fractional metabolic cost of perfusion in 23 species of resting mammals.**

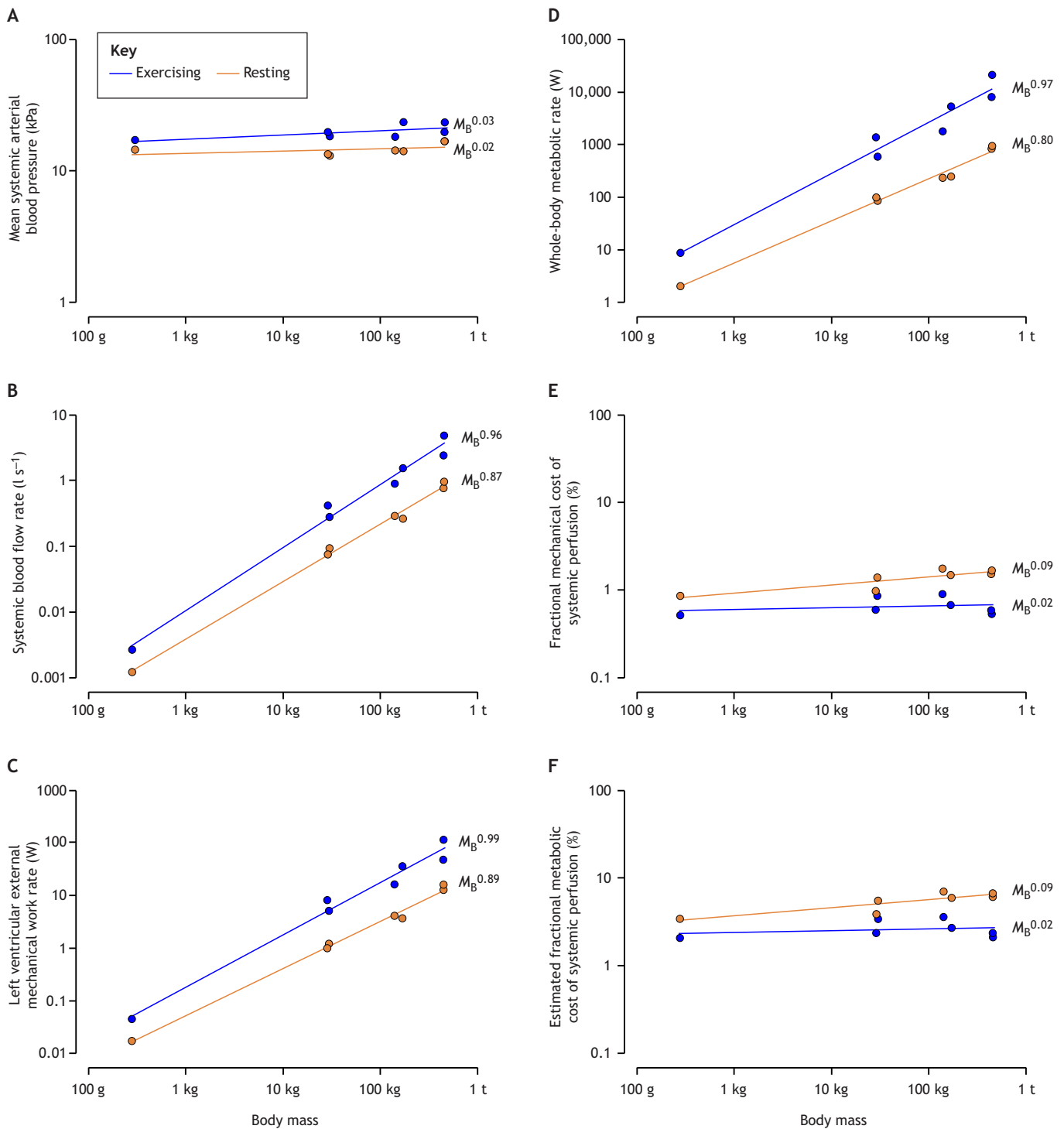
(A) Shown is the scaling of left ventricular external mechanical work rate as orange circles ( $\dot{E}_{LV,ext}=0.045M_B^{0.85\pm0.06}$ , mean $\pm$ 95% CI), estimated left ventricular metabolic rate as grey circles ( $\dot{E}_{LV,met}=0.18M_B^{0.85\pm0.06}$ , calculated assuming an arbitrary left ventricular external mechanical efficiency of 25% across all species) and whole-body metabolic rate at  $\dot{V}_{O_2,rest}$  as black circles ( $\dot{E}_{B,rest}=3.47M_B^{0.79\pm0.05}$ ). (B) Also shown, in the same group of mammals, is the scaling of estimated fractional metabolic cost of perfusion as a percentage of whole-body metabolic rate. Blue circles depict the cost when  $\dot{E}_{LV,met}$  is calculated from raw  $\dot{E}_{LV,ext}$  data assuming an arbitrary external mechanical efficiency of 25% across all species ( $\dot{E}_{LV,met}/\dot{E}_{B,rest}=5.24M_B^{0.06\pm0.06}$ ). Yellow circles depict the same relationship, except  $\dot{E}_{LV,met}$  is calculated assuming an efficiency of 25% at 60 kg  $M_B$  (estimated for running humans; Krasnow et al., 1964), but otherwise varying in proportion to  $M_B^{-0.06}$  ( $\dot{E}_{LV,met}/\dot{E}_{B,rest}=4.08M_B^{0.12\pm0.06}$ ). See text and Fig. 4 for justification of varying efficiency. The two lines intersect where the efficiencies used in the  $\dot{E}_{LV,met}$  calculations are matched. Data were taken from 23 species of mammal and plotted in relation to body mass ( $M_B$ ; kg) on logarithmic axes. But, to avoid bias, giraffe are depicted (squares) only to show the effect of high  $\dot{P}_{sys}$  and are not included in any of the regressions or equations.  $M_B$  in equations is always in kg. See Table S1 for species list, data and derived values.

and whole-body metabolic data (Gleeson et al., 1983) were combined with  $\dot{P}_{sys}$  (Kuczmarowski et al., 2018) from separate treadmill studies. These datasets allow us to compare the mechanical and metabolic energy requirements of the left ventricle with whole-body metabolic rate at rest and during maximal performance elicited through heavy exercise and provide an independent verification of the conclusions drawn in the previous section that utilises a broader selection of mammals.

In our analysis, the scaling of  $\dot{P}_{sys}$  with  $M_B$  produces exponents of 0.02 at rest and 0.03 during heavy exercise, although neither is statistically different from zero in this small sample (Fig. 3A; Table S2). The scaling of  $\dot{V}_{BL}$  produces exponents of 0.87 and 0.96 at rest and during heavy exercise, respectively (Fig. 3B), while the scaling of heart mass is also quite steep (1.09; Table S2).  $\dot{E}_{LV,ext}$  increases with  $M_B$  with predictably steep exponents of 0.89 at rest and 0.99 during heavy exercise (Fig. 3C). These exponents are not statistically different from each other and the average increase in  $\dot{E}_{LV,ext}$  is 5.6-fold from rest to heavy exercise. Whole-body metabolic rate increases greatly from rest ( $\dot{E}_{B,rest}$ ) to heavy exercise ( $\dot{E}_{B,max}$ ), with exponents of 0.80 and 0.97, respectively

(Fig. 3D). These exponents are once again not statistically different from each other with an average factorial metabolic scope of 12.1-fold.

The consequence of the different scaling patterns for  $\dot{E}_{LV,ext}$  and  $\dot{E}_B$  at rest and during heavy exercise in these results is a different pattern for the fractional mechanical cost of perfusion ( $\dot{E}_{LV,ext}/\dot{E}_B$ ) and the estimated fractional metabolic cost of perfusion ( $\dot{E}_{LV,met}/\dot{E}_B$ ; calculated assuming a nominal external mechanical efficiency of 25% across all species) (Fig. 3E,F). In resting animals, both  $\dot{E}_{LV,ext}/\dot{E}_B$  and  $\dot{E}_{LV,met}/\dot{E}_B$  scale with an exponent of 0.09\*, not significantly different from the exponent (0.06\*) in the analysis on the broader selection of mammals in the previous section. However, the exponent during heavy exercise, 0.02, is not significantly different from zero, meaning that when systems reach maximum capacity under such energy-demanding conditions, the fractional cost of perfusion is statistically unrelated to body size. It is further evident that the fractional mechanical and metabolic costs of perfusion are higher at rest than they are during heavy exercise (Fig. 3E,F). Of course, the heart is not resting when the body is resting, because it is still generating



**Fig. 3. Effect of body size on cardiovascular variables and whole-body metabolic rate in seven groups of five species of resting (standing quietly) and exercising mammals (running at highest aerobic speed).** Shown is the scaling of (A) mean systemic arterial blood pressure ( $P_{sys}$ ), (B) systemic blood flow rate (cardiac output;  $\dot{V}_{BL}$ ), (C) left ventricular external mechanical work rate ( $\dot{E}_{LV,ext}$ ), (D) whole-body metabolic rate at  $\dot{V}_{O_2,rest}$  ( $\dot{E}_{B,rest}$ ) and  $\dot{V}_{O_2,max}$  ( $\dot{E}_{B,max}$ ), (E) the fractional mechanical cost of perfusion as a percentage of whole-body metabolic rate ( $\dot{E}_{LV,ext}/\dot{E}_B$ ) and (F) the estimated fractional metabolic cost of perfusion as a percentage of whole-body metabolic rate ( $\dot{E}_{LV,met}/\dot{E}_B$ ), calculated assuming an arbitrary left ventricular external mechanical efficiency of 25% across all species. Data were taken from seven groups of lab or domestic mammals, comprising rat, dog, goat, pony, calf, horse and steer (Gleeson et al., 1983; Jones et al., 1989; Kuczumski et al., 2018; Taylor et al., 1987), and plotted in relation to body mass ( $M_B$ ; kg) on logarithmic axes. See Table S2 for full equations.

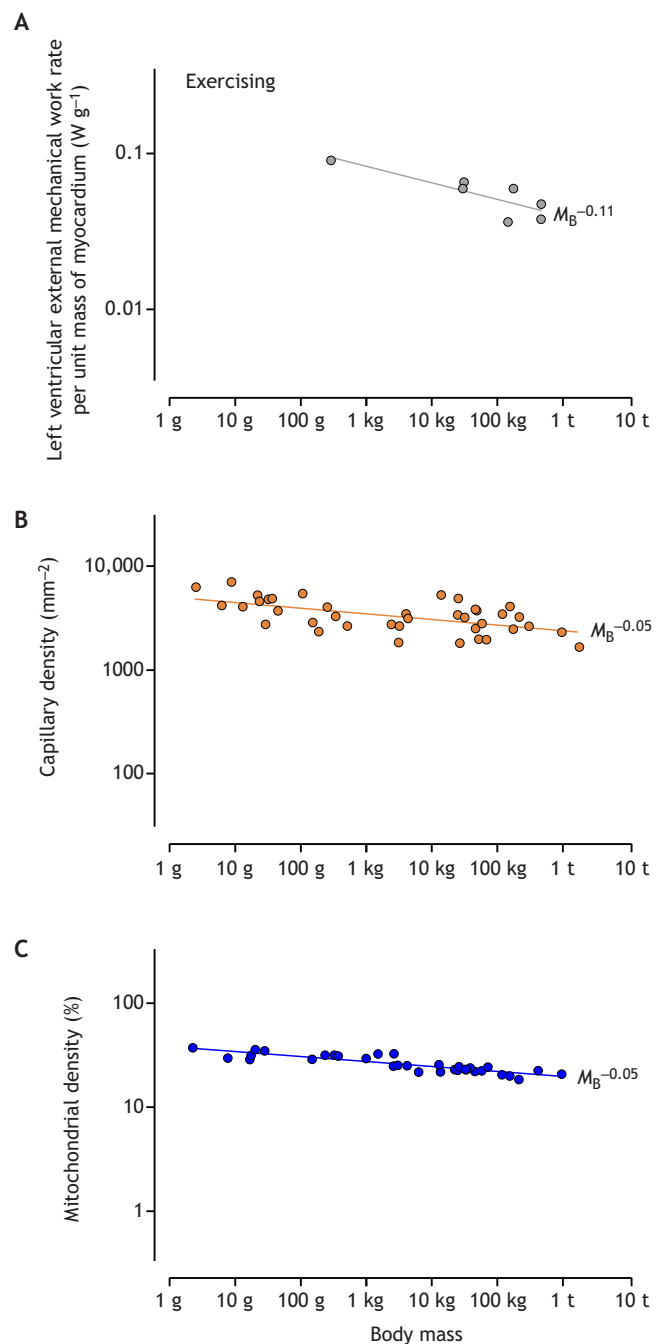
mechanical energy of pressurised blood flow, and so under these conditions, the heart uses up a greater fraction of whole-body metabolic rate.

**The efficiency of the left ventricle in exercising mammals**  
 Left ventricular external mechanical efficiency describes the chamber's ability to take chemical energy in metabolic substrates

and convert it to mechanical energy of pressurised blood flow ( $\dot{E}_{LV,ext}/\dot{E}_{LV,met}$ ; Fig. 1). Of the few measurements that exist,  $\dot{E}_{LV,ext}/\dot{E}_{LV,met}$  is typically in the range of 15–30% (Knaapen et al., 2007; Schipke, 1994; Westerhof, 2000). This means that, of the total metabolic energy passing through the heart, 70–85% is heat generated in the myocardium and largely lost to the blood passing through the heart, and 15–30% of the energy exits the left ventricle as pressurised blood flow, which loses its energy as frictional heat throughout the circulatory system. Until recently, the effect of body size on left ventricular efficiency was unclear, but we can now use scaling principles to make an estimate, at least under maximal conditions elicited during heavy exercise (Horrell et al., 2022). We established already that the scaling of  $\dot{E}_{LV,ext}$  during heavy exercise is proportional to body mass raised to an exponent of 0.99 among five species of lab or domestic mammals (Fig. 3C; Table S2). As heart mass in this small selection of mammals scales with a steep exponent (1.09), it is necessary to correct for this by dividing  $\dot{E}_{LV,ext}$  by the mass of the myocardium performing that external work ( $M_{LV}$ ; assumed to equal two-thirds heart mass,  $\frac{2}{3}M_H$ ). This variable is the maximum left ventricular external mechanical work rate per unit mass of myocardium,  $\dot{E}_{LV,ext}/M_{LV}$  ( $W g^{-1}$ ), and it is related to body mass raised to an exponent of  $-0.11^*$  (Fig. 4A; Table S3).

Now that we have an estimate of the scaling of maximum  $\dot{E}_{LV,ext}/M_{LV}$ , we need an estimate of the scaling of the maximum left ventricular metabolic rate per unit mass of myocardium,  $\dot{E}_{LV,met}/M_{LV}$  ( $W g^{-1}$ ). A recent meta-analysis used capillary numerical density and mitochondrial volume density as proxies for the maximum metabolic intensity of the myocardium in more than 30 species of mammal (Horrell et al., 2022). The reasoning behind this approach is that capillary numerical density and mitochondrial volume density reflect maximum local oxygen supply and consumption rates of the myocardium, respectively (Hoppeler and Kayar, 1988), especially in tissues that utilise predominantly aerobic metabolic power (Snelling et al., 2016; Stanley et al., 2005). The use of capillary density as a proxy for metabolic intensity nonetheless requires some additional caution because it is likely influenced by additional variables, such as fibre cross-sectional area (summarised in Snelling et al., 2018).

Cardiac capillary numerical density decreases with  $M_B$  with an exponent of  $-0.05^*$  (capillaries per  $mm^2$  of fibre area; Fig. 4B), and mitochondrial volume density similarly decreases with an exponent of  $-0.05^*$  (% of fibre volume; Fig. 4C, Table S3). Phylogenetically informed analysis of the data return similar exponents of  $-0.07^*$  and  $-0.04^*$ , respectively (Horrell et al., 2022), reflecting a gradual decline in the maximum metabolic intensity of the myocardium as body mass increases among mammals. However, this decline in metabolic intensity of the myocardium,  $\dot{E}_{LV,met}/M_{LV}$ , as a function of increasing body size (exponents of  $-0.05^*$ ) is not as steep as that calculated above for the maximum left ventricular external mechanical work rate per unit mass of myocardium,  $\dot{E}_{LV,ext}/M_{LV}$  (exponent of  $-0.11^*$ ). The exponents are statistically different when  $\dot{E}_{LV,ext}/M_{LV}$  is compared with the mitochondrial volume density (ANCOVA,  $P < 0.05$ ), but not when compared with the capillary numerical density ( $P = 0.28$ ), probably because the mitochondria–body mass relationship is much tighter. As external mechanical efficiency is defined as  $\dot{E}_{LV,ext}/\dot{E}_{LV,met}$  or  $(\dot{E}_{LV,ext}/M_{LV})/(\dot{E}_{LV,met}/M_{LV})$  when correcting for myocardial mass in different groups of animals, we can calculate the efficiency of the left ventricular myocardium when systems reach maximum capacity during heavy exercise. Here, efficiency declines with  $M_B$  with an



**Fig. 4. Effect of body size on maximum cardiac work rate in seven groups of five species of exercising mammals (running at highest aerobic speed) and cardiac capillary and mitochondrial densities in more than 30 species of mammals.** (A) Shown is the scaling of maximum left ventricular external mechanical work rate, corrected for mass of the myocardium ( $\dot{E}_{LV,ext}/M_{LV} = 0.08M_B^{-0.11 \pm 0.08}$ , mean  $\pm$  95% CI). These data were derived from exercising mammals running at their highest aerobic speed on a treadmill and are the same group as in Fig. 3. (B) Also shown is the scaling of cardiac capillary numerical density ( $N_{A, cap, fib} = 3464M_B^{-0.05 \pm 0.03}$ ; capillaries per  $mm^2$  of fibre area) and (C) mitochondrial volume density ( $V_{V, mito, fib} = 27.3M_B^{-0.05 \pm 0.01}$ ; percentage of fibre volume occupied by mitochondria), which we have used as proxies for the maximum left ventricular metabolic rate per unit mass of myocardium. These data were taken from a meta-analysis of 69 published studies that provided capillary values in 39 species and mitochondrial values in 33 species over five orders of magnitude in body size (Horrell et al., 2022). The mismatch of scaling exponents indicates a left ventricular external mechanical efficiency ( $\dot{E}_{LV,ext}/\dot{E}_{LV,met}$ ) that declines with  $M_B^{-0.06}$  [ $(-0.11) - (-0.05)$ ].  $M_B$  in equations is always in kg. See Table S3 for full equations.

exponent of  $-0.06$  [ $(-0.11^*)$ – $(-0.05^*)$ ], a value that we cannot test statistically because it is derived by the allometric cancellation of relationships taken from different sets of animals.

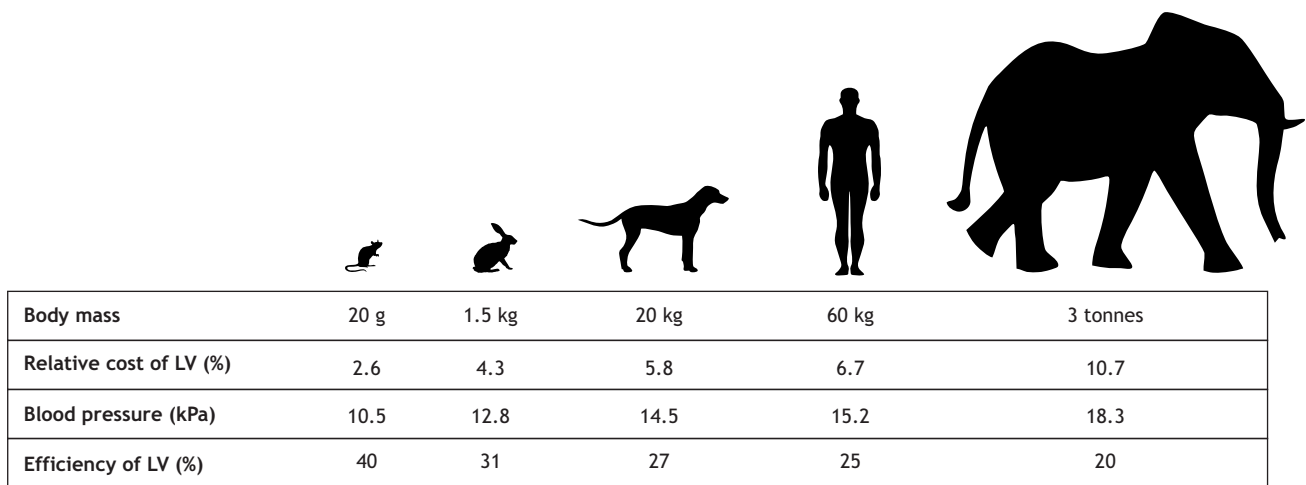
The fact that left ventricular external mechanical efficiency decreases with  $M_B$  suggests that larger mammals are putting disproportionately more energy into the heart in the form of metabolic substrates, but getting relatively less energy out of it in the form of mechanical energy of pressurised blood flow. The idea means that it is the rapidly beating smaller hearts that are, in fact, more efficient than the slowly beating larger ones. If the external mechanical efficiency is 25% in 60 kg exercising humans (Krasnow et al., 1964), then we can use this point to define the elevation of the relationship, and our first attempt at setting a full scaling equation becomes  $\dot{E}_{LV,ext}/\dot{E}_{LV,met}=32M_B^{-0.06}$  (%). The scaling equation translates to a predicted efficiency of approximately 40% in a mouse, declining to 20% in an elephant. The apparent decrease in left ventricular efficiency in larger mammals could be explained, at least in part, if the kinetic energy component of total blood energy, which is typically ignored for its trivial contribution, becomes more significant in larger mammals, especially during heavy exercise. Otherwise, it appears that disproportionately more energy is lost internally as heat in larger mammals, which could occur anywhere along the multi-step pathway summarised in Fig. 1.

#### Size-related factors affecting energy losses in the left ventricle

The contraction of the heart deforms the myocardial tissues and stores some energy in visco-elastic elements at several levels within the walls. The energy-storage elements include collagen and elastin between muscle fascicles (Rushmer, 1956; Rushmer et al., 1953) and cardiac myocytes (Robinson et al., 1986), as well as elastic elements within the sarcomeres, notably large titin proteins (Helmes et al., 1996) and microtubules (Caporizzo et al., 2019). The sarcomere of a relaxed cardiomyocyte shows a so-called ‘equilibrium length’, and the contracted length is shorter. Thus, the relaxing left ventricle produces a suction force that reduces ventricular pressure (without necessarily becoming negative) and augments ventricular filling (Bell et al., 2000; Notomi et al., 2008).

The energy involved in left ventricular wall deformation is called internal wall work (Fig. 1). Because all stored energy in the left ventricular wall is released during diastole as friction in the wall and in the blood behind the closed aortic valve, no wall energy can be transferred to the systemic circuit. It seems reasonable that the amount of energy lost as internal wall work should be greater in thicker-walled hearts than in thinner ones of the same ventricular blood volume if the energy stored in a unit volume of myocardium were constant. However, there is molecular evidence that individual cardiac myocytes are more compliant (less stiff) in larger species (Cazorla et al., 2000). Implicated here are the large titin proteins, which extend from the Z-disc to the M-band of sarcomeres and play a role in passive tension and mechanical restoring force. Titin is expressed in cardiac myocytes in two isoforms, N2B and N2BA. The N2B isoform is stiffer than the N2BA isoform. Hearts of small mammals (mice and rats) express nearly 100% of the stiffer N2B, while larger mammals (rabbits, dogs, humans, pigs and cows) express progressively more of the less stiff N2BA in a mix with N2B (Cazorla et al., 2000). The functional significance of the reduction in myocyte stiffness in larger hearts may be a compensation for disproportionate thickening of ventricular walls in larger species. The extent of compensation is unknown, but it is unlikely to be complete if driven by natural selection for reduction in wall work in larger species.

Much is known about the causes and effects of wall thickening in human hearts. Aside from genetic predisposition, left ventricular hypertrophy can be produced in two ways: chronic volume overload and chronic pressure overload (Mihl et al., 2008). Volume overload is the requirement to increase stroke volume and cardiac output and it results in enlargement of the ventricular walls by adding sarcomeres in series, and thus primarily increasing myocyte length, termed eccentric hypertrophy. Pressure overload is the requirement to maintain cardiac output against increased  $\bar{P}_{sys}$  by adding sarcomeres in parallel, termed concentric hypertrophy. These conditions can occur together. Whatever the cause, we may ask how hypertrophy affects the efficiency of the heart apart from the obvious increase in work rate. Left ventricular external mechanical efficiency is calculated as the ratio of external



**Fig. 5. Left ventricular energy costs, calculated for different body sizes, in resting mammals.** The scaling analyses presented in this Commentary show that as body size increases among resting mammals, the left ventricle (i) uses up more of the body’s aerobic metabolic energy ( $\dot{E}_{LV,met}/\dot{E}_B$ ; incorporating the effect of efficiency decreasing as  $M_B^{-0.06}$ ), (ii) generates higher mean arterial blood pressure ( $\bar{P}_{sys}$ ) and (iii) becomes less efficient at converting chemical energy in metabolic substrates into mechanical energy of pressurised blood flow ( $\dot{E}_{LV,ext}/\dot{E}_{LV,met}$ ). Mean values are calculated (not measured) for each body mass according to the scaling relationships derived from the same broad selection of resting mammals as depicted in Fig. 2 and presented in Table S1.

mechanical work rate and the metabolic rate of the myocardium (Fig. 1). The external work rate is approximated as the product of  $\dot{V}_{BL}$  and  $\bar{P}_{sys}$ . Oxygen uptake rate by the myocardium can be measured invasively in experimental work and recently non-invasively in humans by  $^{11}\text{C}$ -acetate uptake. A recent review put efficiency of normal human hearts between 16% and 42%, with the best estimate around 25% (Sørensen et al., 2020). This review indicated that efficiency declines with pressure overload (due to hypertension or hypertrophic cardiomyopathy), but not in volume overload (due to endurance training). Experimental left ventricular volume overloading in dogs produces hypertrophy and increased passive stiffness, but efficiency was not measured (Ashikaga et al., 2005). It is unlikely that the effects of human endurance training will reveal differences in efficiency because endurance training produces only 8% thicker walls, but strength training, which elevates  $\bar{P}_{sys}$ , produces 22% thicker walls (Pluim et al., 1999). Overall, the effects of hypertrophy on ventricular efficiency in human hearts are somewhat equivocal, variable and possibly influenced by disease.

The scaling of efficiency in healthy mammals is clearly necessary, but difficult to measure. Natural pressure overloading occurs across species because  $\bar{P}_{sys}$  increases with body size (White and Seymour, 2014). Pressure overloading also occurs in some species independent of their body size, which is particularly evident in the giraffe, whose long neck is responsible for extreme systemic hypertension (Smerup et al., 2016). Data from our previous study (Seymour and Blaylock, 2000) compared the giraffe with 23 other mammal species, showing an approximate doubling of  $\bar{P}_{sys}$  (means of 214 versus 111 mmHg, respectively). Although the total heart mass of giraffes is similar to predictions from other species given its body mass (Mitchell and Skinner, 2009), the left ventricle wall thickness is twice the prediction (5.6 versus 2.8 cm, respectively). Overall stiffness of the giraffe ventricle is expected to be high, resulting in greater loss of restoration energy and reduced external mechanical efficiency.

### Conclusions and implications

The heart works in circulating blood to supply the animal's whole-body aerobic metabolic rate. The scaling relationships presented in this Commentary question the prevailing assumption that the fractional metabolic cost of perfusion, which is simply the ratio between left ventricular and whole-body metabolic rates, is a constant among mammals. We show that in resting mammals of increasing body size, the left ventricle generates higher blood pressures and thus puts relatively more energy into the ejected blood, and it does so despite a decreasing efficiency of the myocardium. The result is a fractional metabolic cost of perfusion that increases with body size – larger hearts of larger mammals generally use more of the body's metabolic rate to circulate blood around the body, to service the body's metabolic rate (Fig. 5). Such relationships cannot continue *ad infinitum* without imposing cardiovascular and metabolic challenges on the largest and tallest terrestrial species, either past or present, and so our findings will resonate with evolutionary researchers searching for answers on the constraints of body size. In addition, our description of the changes in cardiac function and energetics will be an important consideration for medical researchers acquiring cardiovascular data from model animals that can differ greatly from humans in their body size, cardiac energetics, whole-body metabolic rate and susceptibility to heart disease.

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### Competing interests

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### Special Issue

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