

Occlusion of Insulin Delivery Due to Bubble Formation in Infusion Pump Therapy

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ABSTRACT

Various models of insulin pumps were used in this in-vitro experimental study to investigate the delivery performance when operating at various pre-set basal flow rates. The effect of insulin type on the measured delivery performance was also investigated by using three different types of insulin derivatives, namely: Humalog (“lispro”), Novolog (“aspart”), and Apidra (“glulisine”). Experiments were performed in a controlled laboratory environment in which data were collected using an automated computerized data acquisition setup, with temperature control to simulate body contact, and agitation to simulate typical activity levels. Each experiment ran for up to 5 days. Statistical analysis was performed on the data collected to determine significant differences and deviations in insulin delivery rates that might be due to factors such as: pump type, the set basal flow rate, insulin type, vibration, and possible insulin occlusion due to air bubble formation within the infusion line. Results of the study showed that insulin occlusion due to bubble formation occurred in about 7% of experimental runs and could last for 8 to 10 hours, depending on the flow rate and other conditions.

Introduction

Advances in the development of insulin pumps and their ability to deliver controlled, continuous and accurate doses of insulin have significantly improved the quality of life for diabetic patients. Thanks to these advances, patients with type 1 diabetes have the option of a reliable insulin pump therapy, via continuous subcutaneous insulin infusion (CSII), as an alternative to having multiple daily injections.

In recent studies, insulin pumps have worked successfully in all but a handful of cases. Upon review of various literatures there seems to be some debate on the exact cause of pumped insulin delivery failure. Cases and studies presented by Wolpert *et al.* (2002), Poulsen *et al.* (2005), and Becker (2002), suggest that delivery failure may be caused by precipitation build-up of insulin within the infusion set. The studies further suggest that insulin type (i.e. insulin aspart and insulin lispro) may have a significant effect on the frequency of catheter occlusions. Wolpert *et al.* (2002) cite two cases both involving female patients 42 and 31 years of age who switched from buffered regular insulin to lispro insulin. Both of these patients experienced unexpected blood glucose level fluctuations and upon further analysis linked this occurrence to catheter occlusion. Poulsen *et al.* (2005) reported similar isolated incidents of catheter occlusion. They

suggested ‘isoelectric precipitation’ could be the cause of insulin occlusion. Results concluded that the quantity of precipitated insulin depended strongly on the pH level of the sample. Also noted in this study was that when a certain pH level was reached a steep increase in precipitated insulin was observed. Ultimately it was determined that aspart insulin had the greatest resistance to isoelectric precipitation followed by buffered regular insulin and finally with the least resistance, lispro insulin. The study also concluded that increased turbidity and reductions in pH were caused by diffusion-driven CO₂ absorption.

As a final note, Poulsen et al. (2005) mention that infection at the infusion site or some other physiological reason may negatively affect insulin absorption and occlusion frequencies. Becker (2002) cites a 12-year old patient who was initially treated with a mixed-split regimen of NPH (Neutral Protamine Hagedorn) insulin and insulin lispro in multiple daily injection therapy. The patient was then switched to insulin pump therapy using insulin lispro only. During treatment the patients blood glucose levels became more difficult to control and insulin requirements progressively increased. A pattern was noticed which was related to infusion site duration. At the end of the three-day period the infusion site showed signs of irritation and swelling requiring a new infusion site. The patient was eventually switched to insulin aspart and was then able to keep the same infusion site up to five days.

Accounts given by patients and doctors suggest that pumping insulin at low flow rates (i.e. pediatric use) may also adversely affect the accuracy of insulin delivery by increasing the frequency of occlusions in relation to the actual insulin pumping frequency, meaning that at the lower basal dosage settings, occlusion of insulin is much more significant than at higher settings. To date, the cause of this phenomenon is not exactly known and is still the subject of much debate. Speculation exists that the flow of insulin through the infusion set may be reduced or inhibited by air bubbles that are entrained into the flow. This suggests that flow rate is a significant factor at the lower rates necessary for pediatric use that may effect insulin occlusion and ultimately insulin delivery.

Although this controlled in-vitro laboratory study does not use real test subjects and thus will not answer the effects of possible insulin occlusion due to physiological interactions between insulin/infusion set and a patient, nor will it address isoelectric precipitation due to changes in pH at the infusion site, the study will however investigate other key and possibly more basic factors that might contribute to insulin occlusion such as: the set insulin basal flow rate, pump type, insulin derivative type, vibration effects and possible insulin occlusion due to air bubble formation within the infusion line.

Experimental Setup

The experiments are designed to reproduce typical operating conditions for CSII. Figure 1 shows a schematic of the experimental setup. Insulin pumps are attached to a temperature controlled hot water jacket to simulate body temperature and are placed on a vibrating table, which can be programmed to simulate physical activity of the patients with diabetes. Insulin pump reservoirs are filled with desired insulin and primed to eliminate all bubbles from the infusion set. The desired basal rate is set and the experiment run for up to 5-day duration as commonly used in CSII therapy. Volume flow rates of insulin through the CSII infusion sets are measured with Sensirion SLG1430-480 flow-meters and recorded on a computer every 0.64 second, along with pump temperatures and total mass of insulin deposited in bottles placed on an analytical balances (Sartorius TE-64) with sensitivity of 0.0001g. The experiments are controlled and the data recorded with a LABVIEW program running on the computer. The flow-meters register presence of air/vapor bubbles through gaps in reading.

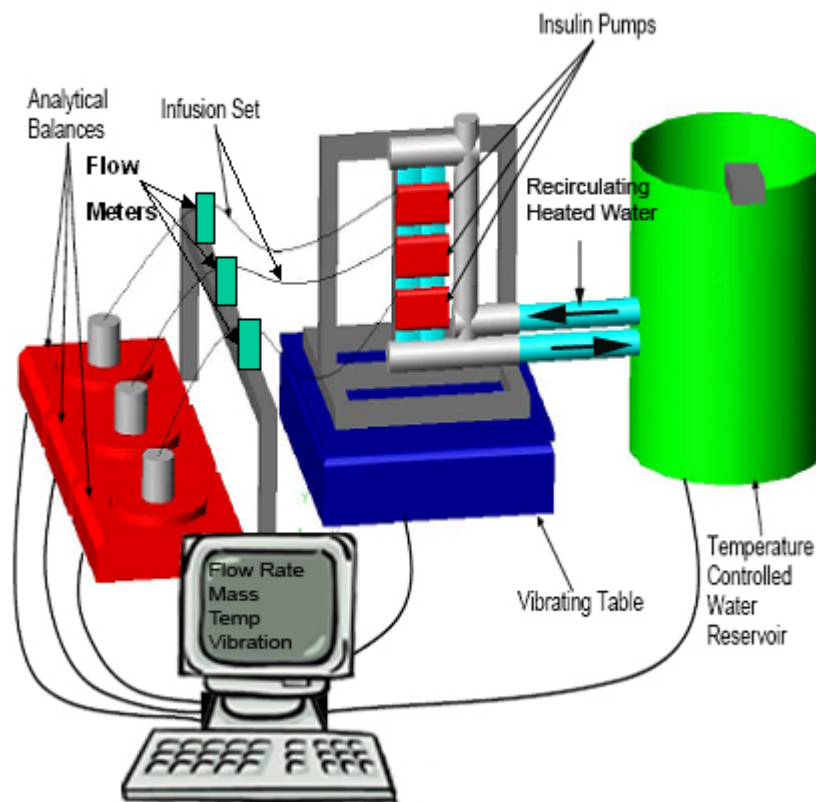


Figure 1: Sketch of Experimental Setup

It was observed by Demuren and Doane (2007) that, contrary to expectations, insulin pumps operated intermittently, rather than continuously. Many use stepper motors to move screw-type pumps. Each unit (U) of insulin represents a volume of 0.01 mL or 10 micro-liters. With one widely used pump type, each unit operation lasted for 0.4 seconds, and 1 micro-liter (or 0.1U) of insulin was delivered in the process. Therefore, to deliver a programmed dosage of 10 micro-liters-per-hour (or 1U/hr.) to an adult it would operate for 0.4s every 6 minutes, delivering 1 micro-liter, each time. On the other hand, for an infant with a basal dosage of 1 micro-liter-per-hour, (or 0.1U/hr.) it will only operate for 0.4s, once in the hour. Three different models of insulin pumps investigated, namely, the Paradigm M511, Paradigm M712, and Animas IR-1200. All pumps operate intermittently at a frequency, which depended on the set basal rate. For example, the Paradigm M511 delivers 0.1U per actuation in basal dosage mode. At a basal rate of 0.1U/hr. the pump would be actuated once per hour, at 0.3U/hr. three times per hour, at 1.0U/hr. ten times per hour and so on. The pumps are connected to the flow meters and bottles on the analytical balances with two types of infusion sets, namely, the Sof-Set and Quick Set. The three types of insulin used in this study: Apidra (glulisine), Humalog (lispro) and Novolog (aspart). All three types are rapid acting insulin analogs in common use. In various studies, Plank et al. (2002), Hedman et al. (2001), and von Mach et al. (2002) found that there was little statistical difference in pharmacokinetics between Humalog and Novolog. However, Apidra appeared to be faster acting in some patients.

The Sensirion flow-meter can measure a maximum flow rate of 40,000nl/min (240U/hr) with a resolution of 7nl/min (0.042U/hr) and a repeatability of 0.6% of the measured value. The flow-meter is very sensitive to environmental conditions and must

be recalibrated frequently. For this purpose, the Harvard PHD 2000 Programmable calibration apparatus was utilized.

Results and Analysis:

Subject to an analysis of variance (ANOVA) using the software Design-Expert, Montgomery (2005), experimental conditions are designed as a randomized mixture of tested variables. Table 1 summarizes the experimental configuration undertaken for the following pumps: the Animas IR1200, the three Paradigm M511 models and one Paradigm M712 pump. Each set includes three flow configurations, Flow1, Flow2 and Flow3, which correspond to each measurement line, with the flowrate, Insulin Type, Pump Type and vibration settings varied as input parameters for the statistical analysis.

		Flow1	Flow2	Flow3
Set1	Flowrate	0.1U/hr	0.3U/hr	1.0U/hr
	2Runs			
	Insulin	Humalog	Apidra	Apidra
	Pump	M511-#1	M511-#2	Animas
	Vibration	Vib1 (0)	Vib1 (0)	Vib1 (0)
Set2	Flowrate	0.1U/hr	0.3U/hr	1.0U/hr
	2Runs			
	Insulin	Novolog	Apidra	Novolog
	Pump	Animas	M511-#1	M511-#3
	Vibration	Vib2 (100RPM)	Vib2 (100RPM)	Vib2 (100RPM)
Set3	Flowrate	0.3U/hr	0.3U/hr	1.0U/hr
	2Runs			
	Insulin	Humalog	Humalog	Novolog
	Pump	M511-#3	Animas	M511-#1
	Vibration	Vib3 (200RPM)	Vib3 (200RPM)	Vib3 (200RPM)
Set4	Flowrate	0.3U/hr	0.1U/hr	0.3U/hr
	2Runs			
	Insulin	Apidra	Apidra	Novolog
	Pump	M511-#2	M511-#3	M712
	Vibration	Vib1 (0)	Vib1 (0)	Vib1 (0)
Set5	Flowrate	0.1U/hr	0.3U/hr	1.0U/hr
	2Runs*			
	Insulin	Apidra	Novolog	Humalog
	Pump	M712	M511-#3	M712
	Vibration	Vib3 (200RPM)	Vib2 (100RPM)	Vib2 (100RPM)

*1Run Flow1

Table 1: Experimental configuration

Experimental Data:

Typical experimental data collected for one of the runs are shown in figure 2. The mass data monitored and measured by scale#1 and flow rate data measured by the Sensirion flow-meter#1 for the Paradigm M511#1 pump set to deliver 0.1U/hr. of Humalog insulin for experimental configuration Set1 Flow1 Run1. Fig 2(a) shows the flow rate versus time as measured by the Sensirion flow-meter#1 at a frequency of 1.5625 Hz or every 0.64 seconds. Based on the flow rate data the cumulative volume was calculated by taking the integral of the measured flow rate with respect to time. The cumulative volume based on the scale's measurement of total mass of insulin delivered is also calculated from the total mass of insulin recorded approximately every 2 seconds divided by the density of insulin. These two cumulative volume estimates, along with

corresponding linear regression fits, are compared with the ‘theoretical’ or ideal delivery volumes based on the nominal pump basal dose rate. Over the 115 hours (~ 5 days) of data collection, there is a good correlation between measured and expected volume flow rates. There is also no evidence of bubble formation. Hence, in the case, the pump operated as expected, delivering the set basal rate over the whole 5-day period.

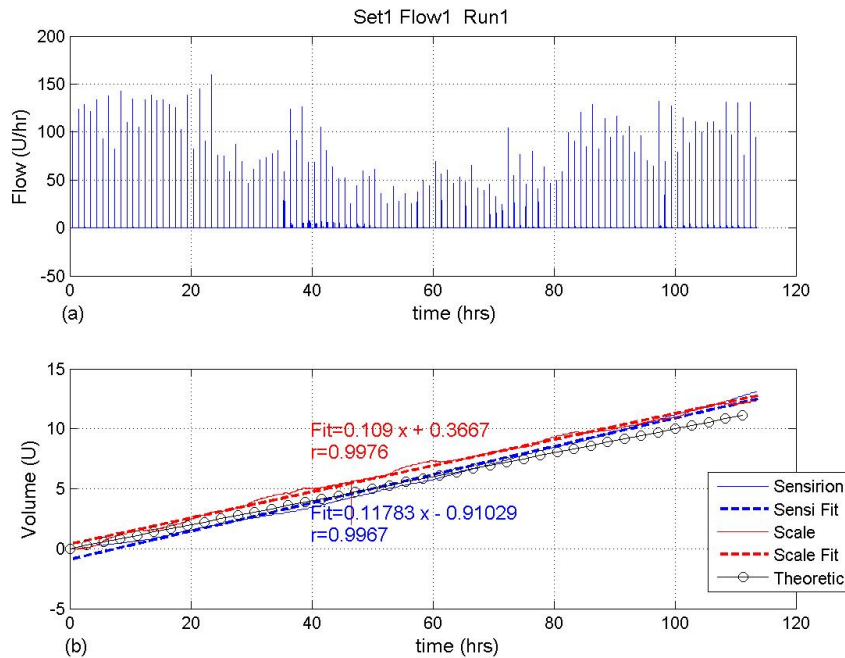


Figure 2: Set1 Flow1 Run1: 0.1U/hr, M511#1, Humalog, 0-RPM (a) Flow rate, (b)Volume

In contrast, figure 3 show results with insulin occlusion due to bubble formation from approximately the 8-16 hours. Fig 3(a) shows the gap in the Sensiron flow-meter reading, which indicates the presence of the bubble in the infusion set. The reading resumes at the 16 hr. mark. Fig 3(b) shows the integrated flow over the total 112-hour period. The slope of the correlation fit is 0.3 U/hr., which agrees with the pre-set basal flow rate. This suggests that, in spite of insulin occlusion, total volume delivery over 5 days is as expected. The main problem is the 8-hour period in the patient is potentially deprived of insulin. On the other hand, the scale records slightly lower mass of insulin deposited into the weighing container. That may be explained by environmental conditions or a slight evaporation over the period.

Occlusion due to bubble formation was observed in one other experimental run. Therefore, in 2 out of a total of experimental runs, occlusion was observed, indicating an incidence rate of about 7%.

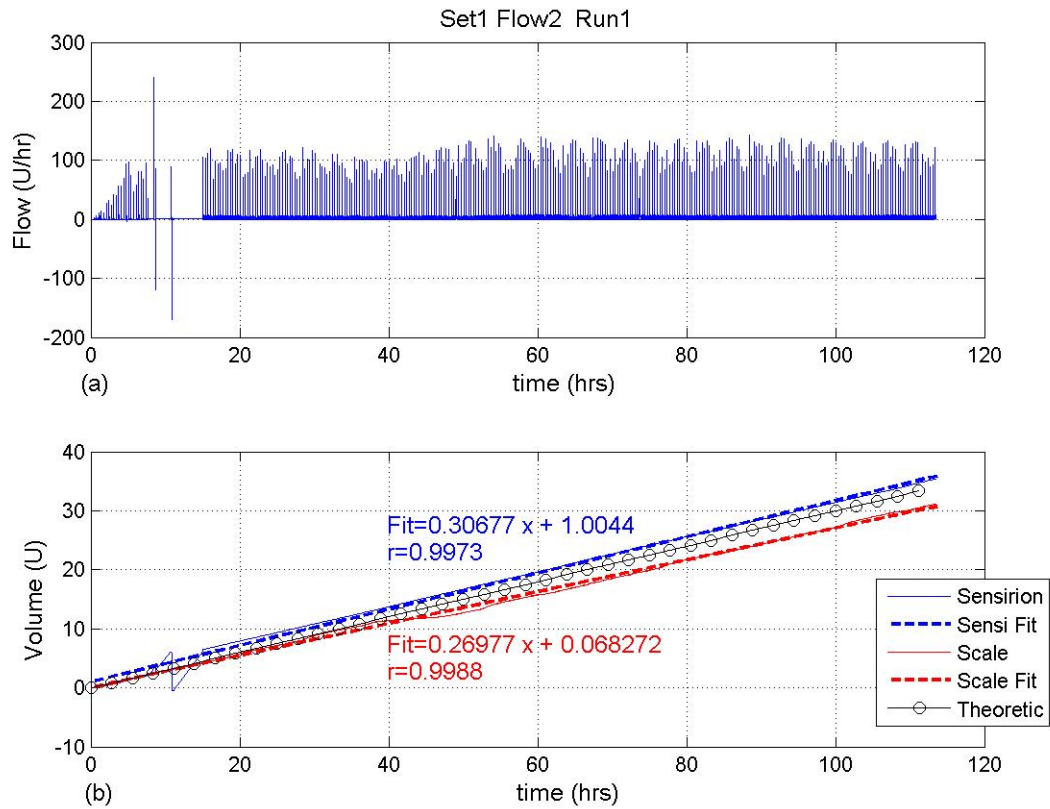


Figure 3: Set1 Flow2 Run1: 0.3U/hr, M511#2, Apidra, 0-RPM (a) Flow rate, (b) Volume.

Conclusion:

The present study showed that insulin occlusion due to bubble formation could last for 8 to 10 hours, depending on the flow rate and other conditions. However, more study is required to determine exact mechanisms for bubble formation and how to mitigate it. It was not possible at this stage to determine if certain insulin or pump types had a greater tendency for bubble formation. Insulin occlusion was observed in about 7% of the cases.

References

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