An Experimental Study of Pulsed Micro-Flows Driven by an Insulin Pump

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In recent years, there is a surge in the popularity of using insulin pump or continuous subcutaneous insulin infusion (CSII) therapy, as opposed to multiple daily injections (MDI) by insulin syringe or an insulin pen. Some case studies have suggested that insulin delivery failure may be caused by the precipitation of insulin within the infusion set. Speculation also exists that the flow of insulin through an insulin infusion set may be reduced or inhibited by air bubbles entrained into the micro-sized capillary tubing system since there are chances that air be introduced into the insulin reservoir during the filling process. In the present study, an experimental study was conducted to investigate the pulsed microflow inside the micro-sized infusion tubing system driven by an insulin pump. A microscopic Particle Image Velocimetry (micro-PIV) system was used to conduct detailed flow velocity field measurements to characterize the transient behavior of the pulsed micro-flows inside the micro-sized tubing system of an insulin infusion set with an insulin pump operating in basal mode (i.e., pulsed insulin pumping). The effects of the air bubbles entrained into the micro-sized capillary tubing system on the insulin delivery process were also assessed based on the micro-PIV measurements.

I. Introduction

Type 1 diabetes affects about 1 in 400 children under the age of 18 years. In recent years, there has been a surge in the use of continuous subcutaneous insulin infusion (CSII), also known as insulin pump therapy, as opposed to the more traditional use of multiple daily injection (MDI) therapy to treat Type 1 diabetes (Shalitin et al. 2008). CSII delivers insulin to the person with diabetes continuously, simulating the natural internal secretion of insulin from the pancreas (Rossetti et al. 2008). Major advantages of CSII over MDI include: more precise amounts of insulin can be delivered as needed than by use of a syringe; better control over background or 'basal' insulin dosage can be gained to meet all the body’s non-food related insulin needs; insulin pump software automatically determines the 'bolus' infusion dosages based on expected carbohydrate intake and current blood sugar level.

During CSII, insulin must travel from the insulin pump’s reservoir, through various lengths of micron-sized capillary tubing, infusion set, and finally via a catheter to the patient’s subcutaneous space, without occlusion. This must occur accurately, regardless of ambient temperature, the activity level of the patient, or low basal infusion rates. Young children require very small amounts of insulin to manage their diabetes. This results in a very slow rate

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of continuous insulin infusion, often one the order of 0.001 mL (or 0.1 units of insulin) per hour. As a consequence of this slow infusion rate, occlusion to insulin flow can, and often does, occur. There is anecdotal evidence, supported by results of a national survey (Gyuricsko et al. 2009), that the actual insulin delivery dosage might fall short of the pre-programmed value at relatively low flowrates, leading to reduced glycemic control. Occlusion of insulin delivery, if not detected and immediately treated, may result in severe, sustained hyperglycemia or diabetic ketoacidosis (DKA). Frequent occlusive episodes may result in sub-optimal glycemic control, elevated hemoglobin A1C values, and an increased risk of long-term complications of diabetes. Cases and studies presented by Poulsen et al. (2005) and Wolpert et al. (2002) suggest that delivery failure may be caused by precipitation of insulin within the infusion set. There is also speculation that the flow of insulin through the infusion set may be reduced or impeded by air bubble formation in the micron-sized capillary-tubing of the infusion set, during the typical three- to five-day operation between refills. To date, this is still a subject of much debate.

Currently, most solutions to insulin occlusion related problems are based on clinical trials. It is of great value to elucidate underlying physics of insulin infusion process, from the pump action to the catheter delivery, and from a fluid dynamics perspective, in order to provide a better guidance for troubleshooting. In this regard, Demuren & Doane (2007) carried out a pioneer study on the accuracy of insulin delivery by a Medtronic Paradigm 511 insulin pump over a wide range of flow rates from 0.1 to 2.0 units per hour (U/H). They found that the operation of the Paradigm 511 insulin pump was anything but continuous. The insulin pump uses a stepper motor which operates for only about 0.25 seconds each time. The screw pump to which it is attached delivered 0.1 unit (0.001mL) during that time. The consequence is that for an infant with a prescribed basal dosage of 0.1 U/H, the pump only operates once per hour, and if the flow was occluded in any way, would have to wait another hour for the next delivery opportunity. On the other hand, an adult, with a typical basal dosage of 1.0 U/H only had to wait for 6 minutes for the next delivery opportunity. Thus, dangers from occlusive events are much more severe in infants and young children than in adults. More recently, Demuren et al. (2009) measured insulin flow rates for a wider range of pump types (Paradigm 511/512/712, Animas, and Omnipod). They found that insulin delivery in CSII therapy is a highly unsteady process which is much more interesting than the creeping flow that the nominal average flow rates would suggest. Instantaneous flow rate was found to be as high as 1000 times the average flow rate, and shear rates are correspondingly higher. It should be noted that flow rate pulses and shear rates are the same for any insulin pumping pulses irrespective of nominal basal dosage; they merely occur more frequently at higher programmed dosages. Demuren et al. (2009) also observed air bubble formation and injection in infusion sets during experiments, but were unable to characterize the extent and overall impact of air bubbles on insulin delivery in CSII therapy.

It should be noted that the work of Demuren & Doane (2007) and Demuren et al. (2009) was conducted based on bulk flow rate measurements, it is quite difficult, if not impossible, to extract detailed information at the microscopic levels (i.e., temporal-and-spatially-resolved flow field measurement results) to quantify the transient behavior of the highly unsteady flow inside the micro-sized tubing system of insulin infusion sets from the bulk flow rate measurements. In the present study, a microscopic Particle Image Velocimetry (micro-PIV) system is used to conduct detailed flow velocity field measurements to characterize the transient behavior of the highly unsteady micro-flows inside a micro-sized capillary infusion tubing system commonly used in CSII therapy. The effects of the air bubbles entrained into the micro-sized tubing system on the insulin delivery process are also assessed based on the detailed micro-PIV measurements. The objective of the study is to elucidate underlying physics for a better understanding of the microphysical process associated with the insulin delivery in CSII therapy in order to provide a better guidance for troubleshooting of insulin occlusion in CSII therapy.

II. Experimental Setup and Micro-PIV Measurements

In the present study, a microscopic Particle Image Velocimetry (Micro-PIV) system was be used to conduct detailed flow velocity field measurements to characterize the transient behavior of the micro-flows inside the micro-sized capillary infusion tubing system in CSII therapy. Micro-PIV, which is the most commonly used tool for in-situ imaging of micro-flows to derive flow velocity vectors by observing the motions of tracer particles seeded in the flow (Santiago et al 1998; Meinhart et al. 1999; Olsen & Bourdon 2003). It should be noted that, while microchannel flows driven by either pressure force (Santiago et al. 1998, Li & Olsen 2006), capillary effects (Prins et al. 2001, Gallardo et al. 1999), electric fields (Kim MJ., 2002), magnetic field (Bau et al. 2001) or centrifugal forces (Johnson et al. 2001) have been investigated extensively in recent years, majority of the previous studies were
conducted with the microchannel flows in steady state and driven by steady (time-invariant) compelling forces. The present study will deal with transient micro-flows inside micro-sized capillaries driven by pulsed pressure gradients, which have not been explored in details before.

Figure 1 shows the schematic of the experimental setup used in the present study. A Medtronic MiniMed Paradigm 512 insulin pump was used to drive the flow passing through a standard Paradigm Quick-Set infusion set. The inner diameter (I. D.) of the infusion tubing of the Paradigm Quick-Set infusion set is 356µm. The insulin pump uses a program-controlled proprietary stepper motor turning a captive lead screw that pushes the plunger on the reservoir, and delivers insulin in discrete 0.1 unit increments (1.0µL) per pulse cycle. In the present study, the pump operates in basal mode. The volume basal flow rate was varied in the range of 1.0~20 µL/H. As shown in Fig. 1, a 300×300µm(W×H) straight microchannel (Translume Corp.) was used to act as a part of the tubing system for the micro-PIV measurements.

For simplicity, distilled water, instead of insulin, was used as the working fluid in the present study. Nile red fluorescent FluoSpheres® beads (535/575nm, ~ 1µm in diameter) were premixed in the reservoir as the tracers for micro-PIV measurements. Illumination was provided by a double-pulsed Nd:YAG laser (NewWave) adjusted on the second harmonic and emitting two pulses of ~2 mJ at the wavelength of 532 nm with a repetition rate of 10 Hz. Upon the pulsed excitations of the green laser beam at 532nm, the tracer particles seeded in the microchannel will emit fluorescent light of broad bandwidth with emission peak at 575nm. The fluorescent from the exited trac particles, which passes through a 10X objective lens (NA=0.4), a long pass optic filter (610nm long pass filter) and the optical path inside an inverted microscope (Leica DM-IL), was recorded by a 12-bit high resolution (1376 x 1040 pixel) CCD camera (SensiCam-QE, Cooke Corp.). The CCD camera and the double-pulsed Nd:YAG laser were connected to a workstation (host computer) via a Digital Delay Generator (Berkeley Nucleonics, Model 565), which controlled the timing of the laser illumination and image acquisition.

In the present study, the micro-PIV measurements were conducted in the mid-plane of the microchannel for all the discussed cases. The scaling factor of the micro-PIV images is 0.97µm/pixel. After micro-PIV images were acquired, instantaneous PIV velocity vectors were obtained by a frame to frame cross-correlation technique involving successive frames of patterns of particle images in an interrogation window 32×32 pixels. An effective overlap of 50% of the interrogation windows was employed in PIV image processing. The measurement uncertainty level for the velocity vectors was estimated to be within 2.0%.

III. Experimental Results and Discussions

Figure 2 shows an example of the acquired micro-PIV images and a typical instantaneous velocity distribution derived from the micro-PIV images when the insulin pump was set to operate in the basal mode with the flow rate of 2.0 U/H. Based on time sequences of the micro-PIV measurements, the transient behavior of the pulsed micro-flows inside the infusion tubing system was revealed in great detail. Figure 3 shows the histogram of the flow velocity variation at the center of the micro channel derived from the micro-PIV measurements. It can be seen clearly that the
micro-flow inside the infusion capillary tubing system was quite unsteady with the flow velocity changing significantly as a function of the time. The period of the pulsed operation cycle of the insulin pump was found to be 180s when the insulin pump was set at 2.0 U/H basal rate. The flow velocity inside the infusion tubing system was found to be very small for most of the time in the insulin pump operation cycle, except within the short time period when the insulin pump operates. The time-averaged flow velocity in an insulin pumping cycle was also given in the figure as the red dash line for comparison. It can be seen clearly that, while the time-averaged flow velocity was only about 0.10 mm/s (corresponding Reynolds number of the micro flow, ReD = 0.0356), the maximum flow velocity inside the infusion capillary tubing system at the end of the insulin pumping pulse was found to be about 20.0 mm/s, which is 200 times higher than the time-averaged flow velocity.

Fig. 2. A typical micro-PIV measurements.

Fig. 3: Histogram of the flow velocity at the centerline of the microchannel at 2.0 U/H basal rate.

Fig. 4 reveals more details about the dynamic response of the micro-flows inside the infusion tubing system before and after the operation pulse of the insulin pump. It can be seen clearly that, the flow velocity inside the infusion tubing system was very small, i.e., almost zero, before the pulse of the insulin pump action. The flow velocity inside the infusion tubing system was found to increase astronomically as the insulin pump operation pulse started. Within the period of the insulin pump operation cycle of 180s at the basal rate of 2.0 U/H, the insulin pump operates only within a short duration of about 0.25s. Since a large pressure gradient was built up inside the infusion tubing system due to the pulsed action of the insulin pump, the centerline flow velocity inside the infusion tubing system was found to reach as high as 20.0mm/s at the end of the insulin pump operation pulse. After the insulin pump operation pulse, no additional pressure heads would be generated inside the infusion tubing system any more. As a result, the flow velocity inside the infusion tubing system was found to experience a rapid decay process. As shown clearly in the Fig. 4, the decay process of the centerline flow velocity inside the infusion tubing system was found to be represented by an exponential curve well with the characteristic decay time, \( \tau = 0.16s \).
Fig. 4: Flow velocity decay process after an insulin pump operation pulse

Fig. 5: Instantaneous velocity distributions inside the microchannel at 2.0 U/H basal rate.

The significant variations of the flow velocity within the infusion tubing system in the decay process were revealed more clearly and quantitatively from the instantaneous velocity distributions shown in Fig. 5 with the insulin pumping pulse ending at time $t = t_0$. It can be seen clearly that the flow velocity within the infusion tubing system would decrease very rapidly. The flow velocity within the infusion tubing system was found to be almost zero at about 5.0 seconds after the operation pulse of the insulin pump. Based on the instantaneous velocity distributions as those given in Fig. 5, the streamwise-averaged velocity profiles across the microchannel can be
obtained, which are given in Figure 6. Surprisingly, although the magnitude of the flow velocity inside the infusion tubing system was found to decrease rapidly after the operation pulse of the insulin pump, the normalized velocity profiles during the decay process were found to almost self-similar, which can be fitted reasonably well by using a parabolic curve. It should be noted that, according to Purday (1949), the velocity profile inside a square channel will be parabolic for a fully-developed, pressure-driven laminar flow. The micro-PIV measurements confirmed that the flow velocity distribution inside the square microchannel would also be parabolic even though the microflow was in a transient state in the decay process after the insulin pump operation pulse.

As aforementioned, it has been suggested that air bubbles entrained into the micro-sized capillary tubing system may reduce or inhibit insulin delivery in CSII therapy. In the present study, an experimental study was also conducted to assess the effects of air bubbles entrained into the micro-sized infusion tubing system on the insulin delivery process based on the detailed micro-PIV measurements. Fig. 7 shows typical micro-PIV measurements of the flow velocity vector fields surrounding a small air bubble entrained inside the microchannel. As shown in the figure, the tip-to-tip length of the air bubble inside the microchannel is about 450µm. For the micro-PIV measurements results shown in Fig. 7, the micro-flow is in the low speed range of the decay process (~ 2.0 s after the operation pulse of the insulin pump). It is well known that air bubbles traveling in a micro-channel usually have relatively sharp advancing edges and relatively blunt receding edges. While the bullet-like body shape was hard to distinguish from the acquired raw images shown in Fig. 7, the measured flow velocity vectors around the air bubble, with higher flow velocities near the rear end and relatively lower flow speed near the front end, actually indicate such feature clearly. It can also be seen clearly that the fluid flow diverges along the interfaces near the rear end, and converges towards the centerline near the front end. By using the air bubble as the frame of reference, the advancing tip would be a converging stagnation point, whereas the receding tip would be a diverging stagnation point.

Fig. 8 shows the micro-PIV measurement results surrounding a relatively long air bubble entrained inside the infusion tubing system. The tip-to-tip length of the air bubble was about 2.0mm. Again, similar flow patterns can be observed around the long air bubble. It suggests that the flow velocity field change due to the existence of air bubbles inside the infusion tubing system is mainly influenced by the interface shapes between the fluid flow and air bubble, which is almost independent of the length of the air bubble.

Based on the micro-PIV measurement result as shown in Fig. 8, the flow velocity profiles across the microchannel at the front and rear ends of the migrating air bubble were extracted, which were given in Fig. 9. It can be seen clearly that, flow velocity profiles in the regions near two ends of the air bubble was found to change gradually due to the existence of the air bubble. Outside the influential area (i.e. about 0.15mm away from the front and rear ends of the air bubble), the flow velocity profiles were found to be parabolic described above. As the fluid flow approaching the rear end of the air bubble, the flow velocity near the center line of the microchannel was found to decrease rapidly, and the transverse velocity profiles were found to become more flat. Further towards the interface between the air bubble and fluid flow, the flow velocity profile was found to have an apparent deficit in the middle and two peaks at two corner regions, i.e., the flow velocity profiles was found to become bimodal. Such measurement results were found to agree with those reported by Miessner et al. (2008) and Yamaguchi et al. (2009).
Fig. 7: Micro-PIV measurements around a small migrating air bubble inside the microchannel at 2.0 U/H basal rate.

(a). $t = t_0$

(b). $t = t_0 + 1.4s$

Fig. 8: Micro-PIV measurements around a long migrating air bubble inside the microchannel at 2.0 U/H basal rate.

(a). at the front of the long migrating air bubble

(b). at the rear end of the long migrating air bubble
Fig. 9: Measured flow velocity profiles near the front and rear ends of the migrating air bubbles

Fig. 9 shows the effects of the air bubble entrained inside the infusion tubing system on the flow decay process after the operation pulse of the insulin pump at 2.0 U/H basal rates. It can be seen clearly that, when no air bubbles were entrained in the infusion tubing system, the centerline velocity decay curve was found to be much smoother. For the case with the air bubbles entrained inside the infusion tubing system, the flow velocity decay curve were found to become much “noisier” with several “bumps” riding on the decay curve. This may be explained by that the air bubbles in the infusion tubing system would be compressed when the wave front of the pressure gradient generated by the pulsed operation of the insulin pump approaching the rear end of the air bubble. As the wave front of the pressure gradient travelling further downstream, the compressed air bubble would stretch/expend to adjust the pressure difference across the air bubble. As a result, the propagation process of the pressure wave would be modified due to the deformation of the air bubble entrained inside the infusion tubing system. From the comparison of the initial decay curves of the flow velocity inside infusion tubing system shown in Fig. 10, it can be seen clearly that the flow velocity decay process would be slow down due to the existence of the air bubble inside the infusion tubing system. The decay characteristic time, \( \tau \), was found to increase from \( \tau = 0.16s \) for the case without air bubble entrainment to \( \tau =0.31s \) for the case with a ~1.0 mm long air bubble entrained in the infusion tubing system. Such measurement results suggest that air bubbles in the infusion capillary tubing system would soften the flow decay process in the same manner as shock-absorbers.
Concluding Remarks

An experimental study was conducted to investigate the pulsed flow inside the micro-sized infusion tubing system in continuous subcutaneous insulin infusion (CSII) therapy. A micro-PIV system was used to provide detailed flow velocity field measurements inside the capillary tubing system to characterize the behavior of the transient micro-flows upon the pulsed actuation of the insulin pump in CSII therapy. It was found that the microflow inside the infusion tubing system is a highly unsteady process, which is much more interesting than the creeping flow that the nominal averaged flow rates would suggest. While the period of the insulin pump operation cycle was 180s at the basal rate of 2.0U/H, the duration of the operation pulse of the insulin pump was found to be only 0.25s to generate tremendous pressure gradient inside the infusion tubing system to push the fluid flow downstream for insulin delivery. As a result, the flow velocity inside the infusion tubing system was found to vary significantly during the operation cycle of the insulin pump. As the operation pulse of the insulin pump starts to build up tremendous pressure gradient, the flow velocity within the infusion tubing system was found to increase rapidly. The instantaneous flow velocity within the infusion tubing system at the end of the insulin pump operation pulse was found to be about 20mm/s, which is about 200 times higher than the time-averaged flow velocity during the operation cycle of the insulin pump. The flow velocity within the infusion tubing system was found to decrease rapidly after the operation pulse of the insulin pump, the initial decay process of the flow velocity was found to be represented well by an exponential function with the characteristic time of 0.16s, which is on the same order as the duration time of the operation pulse of the insulin pump. Interestingly, although the magnitude of the flow velocity inside the infusion tubing system was found to decrease rapidly in the decay process, the normalized velocity profiles within the capillary tubing system were found to be self-similar, which can be fitted reasonably well by a parabolic curve.

An experimental study was also conducted to investigate the effects of air bubbles entrained inside the infusion tubing system on the insulin delivery in CSII therapy. It was found that the flow patterns near the interfaces between the fluid flow and air bubbles were changed dramatically due to the existences of the air bubbles inside the capillary tubing system. The fluid flow was found to diverge along the interfaces at the rear ends of the migrating air bubbles, and converge towards the centerline of the capillary tubing system at the front ends of the air bubbles. As a result, the velocity profiles across the micro-channel were found to change from parabolic to bimodal as the fluid flow approaching the air bubbles. It was also found that the air bubbles entrained in the infusion capillary tubing system would slow down the flow decay process after the operation pulse of the insulin pump in the same manner as shock-absorbers.

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References


