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APPARATUS

Accurate continuous drug delivery at low infusion rate with a novel microvolumetric infusion pump (MVIP): pump design, evaluation and comparison to the current standard

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Summary

Infusion devices for continuous and precise drug administration are indispensable tools in anaesthesia and critical care medicine. Problems such as start-up delays, non-continuous flow and susceptibility to hydrostatic pressure changes at low infusion rates resulting in accidental bolus release or prolonged flow interruption are inherent to current infusion technology. In order to improve precise drug delivery, an innovative technical concept has been realised in a novel microvolumetric infusion pump (MVIP) device. The MVIP principle includes repeated filling and emptying of a non-compliant microsyringe without the use of valves. The performance of the MVIP prototype has been evaluated and compared with standard syringe infusion pump assemblies. The novel MVIP concept has thereby proven to eliminate most problems during infusion start-up, steady state flow and vertical pump displacement, and has the potential of revolutionising infusion technology and setting a new dimension in patient safety.

Keywords *Equipment*; infusion pump, microvolumetric.

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Instantaneous infusion start-up and precise delivery of highly concentrated, short-acting drugs at low infusion rates from pressure controlled infusion pumps is hampered by intrinsic compliance and mechanical gaps [1–5]. Although improvements in syringe pump design have nearly eliminated mechanical gaps [2, 4, 6], the intrinsic compliance still facilitates fluid pooling into the infusion system, or accidental fluid emptying from the system during infusion start-up, vertical pump displacement and following infusion line occlusion [7–9]. The magnitude of these effects depends directly on the compliance of the infusion line, the infusion syringe and the infusion pump driver mechanism [8–11].

Various countermeasures and strategies have been introduced to minimise these effects [12,13]; however, technical improvements and new infusion pump technologies are desirable [13,14]. We present a novel technical concept that has been realised in the microvolumetric infusion pump (MVIP) device. The MVIP is particularly designed for precise continuous intravenous drug delivery at low infusion rates.

The aim of this study was to evaluate the performance of the first MVIP prototype during start-up, at steady state flow, and after vertical displacement in comparison to a modern syringe infusion pump assembly.

Methods

Functional principle

The MVIP prototype model was built at the Interstate University of Applied Sciences of Technology Buchs, Switzerland. It is a stand-alone device simply interposed between a non-pressurised fluid reservoir and an infusion catheter through afferent and efferent infusion lines (Fig. 1). Its basic functional unit consists of a stiff tubular micro chamber of 10 μl volume (microsyringe) and a

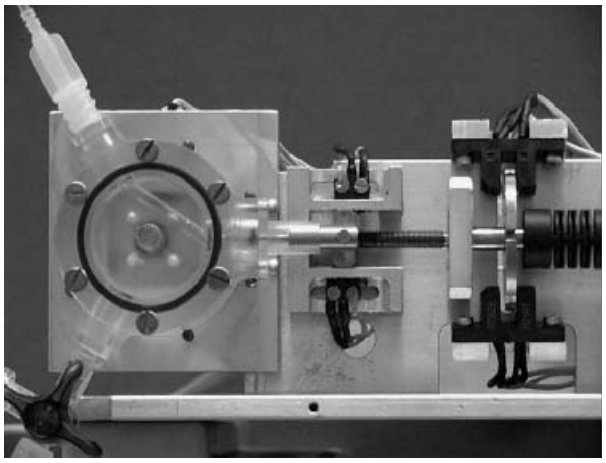

Figure 1 The MVIP prototype-model with a stiff dosing chamber of 10 μl volume (microsyringe).

single borehole rotating disc-valve that allows unidirectional, incremental microvolumetric dosing. The 120°-design of the rotating disc-valve allows fast bypass-flow in order to flush the infusion line (bypass mode). In the function mode, the microvolumetric chamber undergoes repetitive extrusion and refill cycles (Fig. 2). For example, at a flow rate of 0.5 $ml.h^{-1}$, 50 cycles of 72 s duration are performed per hour. Each cycle comprises 67 s for emptying the 10 μl microchamber and 5 s for rotations of the borehole and filling of the microchamber. The current prototype pump is driven by two motors, one for rotating the disc-valve, the other to operate the microsyringe. The use of two separate driver units is by no means a technical requirement and was only chosen for simplicity of the mechanical construction. A small steering unit controls circular motion and exact positioning of the disc-valve as well as the critical filling and extrusion periods of the microchamber.

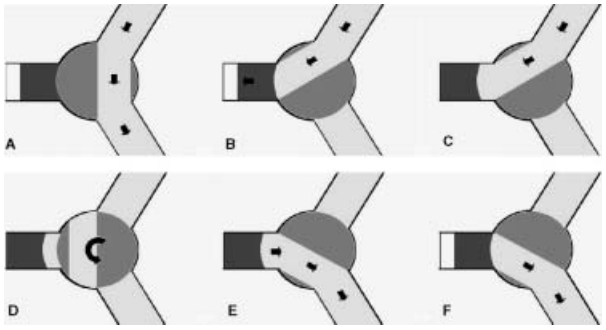

Figure 2 Functional principle of the microvolumetric infusion pump. A 120° single borehole rotating disk-valve allows flushing of the infusion line as well as repeated depletion and refill of the small microchamber. A: bypass mode; B-E: functional mode; B: start of filling the microchamber from the afferent infusion line; C: microchamber filled with fluid; D: rotating disc valve with borehole in intermediate position; E: start emptying of fluid from the microchamber into the efferent infusion line; F: microchamber fully emptied.

Experimental set-up

In an in-vitro set-up, start-up and steady state performance, and susceptibility to hydrostatic pressures changes were evaluated for the MVIP device and compared to a standard syringe infusion pump.

For the MVIP test assembly a 1000-ml, non-pressurised infusion bag containing sterile distilled water (Sterile Water for irrigation, Laboratorium Dr G. Bichsel AG, Interlaken, Switzerland) was positioned 50 cm above the MVIP unit and connected through an infusion line with dropping chamber (Bag Infusion Set, Codan Medical ApS, Rodby, DK) to the MVIP inlet. A stiff infusion line (200 cm; PE-Infusion Line, Clinico Medical GmbH, Bad Mersfeld, Germany) was attached to the MVIP outlet. Prior to the experiments, the system was flushed to remove any air from the infusion pathway (Fig. 2A), the microchamber was filled (Fig. 2C) and set into the start position (Fig. 2E).

The standard pump test assembly consisted of an Alaris Asena® GH syringe pump (IVAC Medical Systems, Hampshire, United Kingdom), low-compliant infusion syringes of three different volumes (single use syringe, 10-ml, 20-ml, 50-ml; CODAN Medical ApS, Rodby, DK), and a 200 cm non-compliant infusion line (PE-Infusion Line, Clinico Medical GmbH, Bad Mersfeld, Germany), which was connected to the syringe. For each experiment, the respective syringe was filled with distilled water and inserted into the syringe pump. An automated priming procedure, including the extrusion of a 1-ml fluid bolus, was performed prior to the start in order to overcome any mechanical gaps within the system.

For all experiments with both the MVIP and standard assemblies, the distal end of the non-compliant infusion line was connected to an additional stiff infusion tubing (50 cm) that was immersed with its distal tip by 13 cm in a sampling glass filled with distilled water. In order to simulate a central venous pressure of 10 mmHg, the pump outlet was positioned at the level of the immersed infusion line tip (−13 cm relative to the liquid surface). A thin layer of oil covered the water surface to avoid any fluid evaporation. Assuming a specific weight of distilled water of 1 $g.ml^{-1}$ at room temperature, fluid delivery ($ml.h^{-1}$) into the sampling beaker was gravimetrically determined using an electronic balance (AG 204-Delta-Range®, Mettler Toledo, Schwerzenbach, Switzerland; Sensitivity 0.0001 g) [15]. The balance data output was recorded in 1-s intervals by an IBM-compatible personal computer employing software specifically written for this purpose (MCPS V2.6-CAD, Software GmbH, Mönchengladbach, Germany).

Start-up performance

The pumps were started at an infusion rate of 0.5 ml.h^{-1}. Elapsed time from depressing the start button to first fluid delivery as indicated by the electronic balance (T_1) and time until achieving 95% of steady state flow (T_2) was recorded.

Steady state flow

Mean flow rate, flow variance and time periods of zero fluid delivery were assessed during steady state flow conditions (0.5 ml.h^{-1}).

Vertical pump displacement

At 0.5 ml.h^{-1} steady state flow conditions, the pumps were lowered by 50 cm and the resulting retrograde aspiration volume (RAV; amount of fluid backflow into the syringe-infusion line assembly), zero-drug delivery time (ZDDT), and time to re-establishment of 95% steady state flow were assessed. Since the pump-lowering manoeuvre is followed by an immediate weight drop on the balance due to fluid backflow from the beaker towards the tubing, ZDDT was defined as the time interval between pump lowering and re-attainment of the beaker weight that was measured immediately before vertical pump displacement. ZDDT indicates therefore the time needed to extrude the pooled backflow volume from the system. After steady state flow delivery was re-established, the pump was elevated to its original vertical position resulting in the release of an infusion bolus (IB) and an overshooting flow rate as a result of the immediate hydrostatic pressure relief. IB and elapsed time to re-establishment of steady state flow rate (105%) was recorded.

Each experiment was performed in quadruplicates with both the MVIP and the standard syringe infusion pump device. The standard pump assembly (Asena® GH) was tested with three syringe sizes (10-ml, 20-ml, 50-ml) and with two exemplars of the identical syringe pump type (total = 4 × 3 × 2 measurements). All experiments were done at 22–24 °C ambient temperature.

Data were compared for the MVIP and the Asena GH/10-ml pump assemblies by Welch's t-statistics. Data are presented as mean (SD). A *P*-value of less than 0.05 was considered statistically significant. Data analysis was performed using Mathematica V 5.0 (Wolfram Research, Inc, Champaign, IL).

Results

The various parameters that were either measured or calculated are shown in Table 1. The mean flow was slightly higher in the MVIP than in the conventional syringe pump assemblies and demonstrated lower variance at steady state flow conditions.

After start-up, first fluid was delivered within 2.0 s in the MVIP and within 10.5–12.9 s in the conventional syringe pump assemblies. A 95% steady state flow at 0.5 ml.h^{-1} infusion rate was achieved in the MVIP after 8.8 (3.9) s, which was 6 times faster than in the Asena GH/10-ml syringe pump assembly: 59.0 (34.4) s; $P = 0.0022$ and 49-fold reduced in comparison to the Asena GH/50-ml assembly: 391.0 (157.9) s; see Fig. 3. The course of start-up fluid delivery is demonstrated in Fig. 4 for the MVIP and an Asena GH/50-ml system with and without syringe sticking.

Similarly, ZDDT and time to 95% steady state flow rate after MVIP-lowering by 50 cm amounted to 3.0 (0.0) and 7.8 (1.7) s, which was 10 times and 7 times faster than in the Asena GH/10-ml syringe pump assembly: ZDDT = 29.1 (6.9) s, $P < 0.0001$ and 95% steady state flow = 57.3 (14.2) s, $P < 0.0001$. The same measurements performed with the Asena GH/50-ml device revealed a 49-fold (ZDDT = 242.9 [28.3] s) and 81-fold (95% steady state flow = 381.9 [111.6] s) prolongation relative to the MVIP (Fig. 3).

Table 1 Measured and calculated parameters obtained from the MVIP device and the Alaris Asena® GH syringe infusion pump evaluated with different Codan infusion syringes at an infusion rate of 0.5 ml.h^{-1}. Values are mean (SD). ⋆Welch's *t*-test for the comparison of the MVIP with the Asena GH/10-ml pump assembly. Abbreviations: RAV = retrograde aspiration volume; ZDDT = zero drug delivery time; IB = infusion bolus.

Action	Parameter	MVIP-Assembly		Asena® GH-Assembly		*p*-value*
Start-Up	Syringe chamber volume	10 µl	50 ml	20 ml	10 ml	
	First Fluid Delivered (s)	2.0 (0.8)	12.9 (7.4)	10.5 (4.1)	10.8 (4.0)	0.0003
	Time to 95% flow (s)	8.8 (3.9)	391.0 (157.9)	181.5 (122.1)	59.0 (34.4)	0.0022
Steady State Flow	Mean flow (ml·h^{-1})	0.511 (0.004)	0.491 (0.014)	0.501 (0.011)	0.489 (0.0123)	0.0011
	Variance (%)	0.74	2.78	2.29	2.51	–
Pump Lowering	RAV (µl)	0.03 (0.05)	9.56 (2.07)	3.34 (0.59)	1.10 (0.39)	<0.0001
(0 cm → −50 cm)	ZDDT (s)	3.0 (0.0)	242.9 (28.3)	87.6 (11.9)	29.1 (6.9)	<0.0001
	Time to 95% flow (s)	7.8 (1.7)	381.9 (111.6)	136.2 (46.8)	57.3 (14.2)	<0.0001
Pump Elevation	IB (µl)	0.38 (0.08)	33.46 (5.05)	11.32 (1.48)	3.78 (0.75)	<0.0001
(−50 cm → 0 cm)	Time to 105% flow (s)	8.5 (1.6)	213.9 (137.5)	76.6 (29.3)	31.0 (10.0)	<0.0001

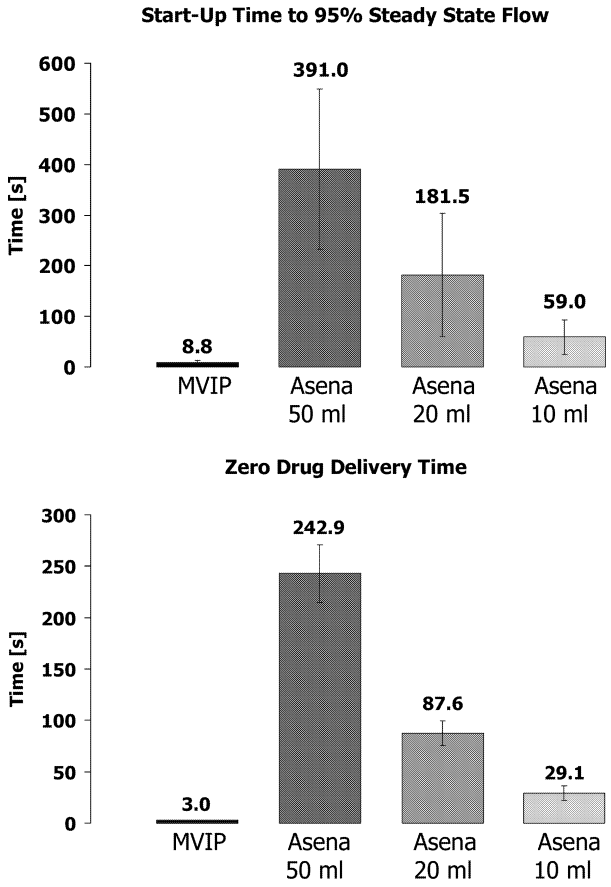

Figure 3 Start-up time to 95% steady state flow and zero drug delivery time (ZDDT) after pump lowering by 50 cm at an infusion rate of 0.5 $ml.h^{-1}$ are plotted for the MVIP and for the conventional syringe pump (Alaris Asena® GH) with three different infusion syringes (CODAN 10-ml, 20-ml, 50-ml syringes). Data are mean, error bars are SD.

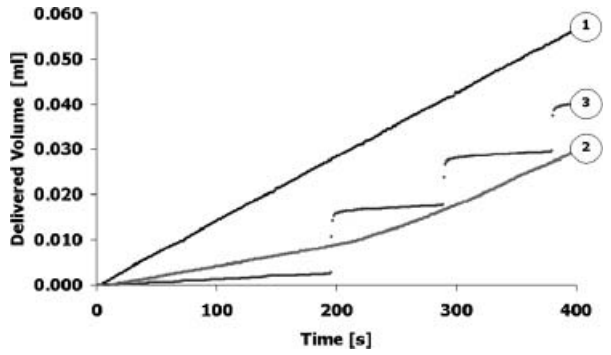

Figure 4 Fluid delivery per time during start-up: MVIP (1), Asena® GH syringe infusion pump with 50-ml Codan syringe without (2) and with (3) syringe sticking.

Discussion

The principle of the microvolumetric infusion pump is based firstly on the fact that small syringes allow reduction in pressure-induced flow irregularities due to lower syringe compliance and faster speed of the pump driver [7,11]. Second, in conventional syringe pump infusion systems, the volume delivered is not monitored and the exact volume of fluid effectively administered over time cannot be determined with sufficient accuracy from the respective plunger position or running time. In fact, there are only two positions in which this task is easy; namely when the syringe is filled and when it is completely empty (e.g. indicating the administration of 1×50 ml of fluid). Consequently, repetitive extrusion of an extremely small volume from a microsyringe (5000×10 µl) would provide fluid delivery that is less susceptible to pressure changes due to reduced syringe compliance. It would also allow monitoring of the amount of fluid effectively delivered with greatly enhanced precision.

An important element of the MVIP is the non-compliant rotating valve for 'fluid direction'. The proposed 120° disk-valve with a single borehole allows simple evacuation of air from the MVIP in the position where inlet and outlet are directly connected (bypass mode). Furthermore, the rotating disc-valve avoids forward and backward volume displacement as it is usually seen in volumetric infusion pumps with valves that compress soft infusion tubing resulting in forward movement of the fluid column [16]. Finally, the design of the 120° disc-valve avoids any direct connection of inlet and outlet during the pumping procedure, thus eliminating the risk of fluid siphoning [17].

In the MVIP system presented, pressure controlled flow is replaced by discretised flow and integer control: the total applied volume of drug is determined by totalling the number of depletions of the incompliant microsyringe. A major shortcoming of current modern infusion pumps is the fact that the volume actually infused is not based on a real measurement but on an estimate from the set infusion rate [18]. One may argue that this pulsed flow may lead to periodic rather than constant flow. This is true in principle, although we did not detect longer periods than 4 s in the MVIP device compared to considerably larger periods in some of the syringe pump assemblies that are caused by syringe plunger sticking (Fig. 4) [3]. Technically, it is, however, not a problem to give to this periodic flow a frequency ($1/30\ s^{-1}$) well above the inverse of the physiological half-life time of even the most fast-acting drugs used in critical care ($1/150\ s^{-1}$). Under such conditions, periodic flow oscillations would, due to damping, become negligible.

Our measurements were performed in a prototype microvolumetric infusion pump, which needs further technical improvement and miniaturisation. Future design of the MVIP could consist of a disposable 120° rotating

disk-valve including microsyringe (microdosing device) and a reusable pump-driver that is attached to the disposable unit. Thereby, the disposable microdosing device can be part of an infusion line, simply interposed like conventional three-way stopcocks. Although the MVIP presented has been designed for accurate flow and drug delivery at low infusion rates, it is conceivable that the principle of a disposable dosing device in conjunction with an attachable driver unit may become standard in any conventional fluid delivery system. For the administration of larger amounts of fluid and/or high-flow infusion for prolonged periods of time, a macrodosing device (macro-chamber) could be considered. Depending upon the specific infusion conditions, either the disposable micro or macrodosing device could be chosen and attached to the driver unit. Further applications of the MVIP may comprise of intermittent application of accurate drug amounts (electronic syringe), and, since the MVIP in principle can also operate in the opposite direction, aspiration of accurate volumes of blood, cerebrospinal fluid or other body fluids for analysis or drainage.

In conclusion, the MVIP prototype pump demonstrates an outstanding low-flow pump performance during start-up, steady state flow and vertical displacement that is significantly superior to any other modern syringe pump assembly. The proposed separation of the microvolumetric infusion pump in a disposable microdosing unit and an attachable, reusable pump driver may become a simple technology for routine fluid management with a broad spectrum of applications.

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