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Flow variability and its physical causes in infusion technology: a systematic review of *in vitro* measurement and modeling studies

DOI 10.1515/bmt-2014-0148
Received November 3, 2014; accepted July 10, 2015

Abstract: Infusion therapy is medically and technically challenging and frequently associated with medical errors. When administering pharmaceuticals by means of infusion, dosing errors can occur due to flow rate variability. These dosing errors may lead to adverse effects. We aimed to systematically review the available biomedical literature for *in vitro* measurement and modeling studies that investigated the physical causes of flow rate variability. Special focus was given to syringe pump setups, which are typically used if very accurate drug delivery is required. We aimed to extract from literature the component with the highest mechanical compliance in syringe pump setups. We included 53 studies, six of which were theoretical models, two articles were earlier reviews of infusion literature, and 45 were *in vitro* measurement studies. Mechanical compliance, flow resistance, and dead volume of infusion systems were stated as the most important and frequently identified physical causes of flow rate variability. The syringe was indicated as the most important source of mechanical compliance in syringe pump setups (9.0×10^{-9} to 2.1×10^{-8} l/Pa). Mechanical compliance caused longer flow rate start-up times (from several minutes up to approximately 70 min) and delayed occlusion alarm times (up to 117 min).

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Keywords: compliance; drug delivery; *in vitro*; infusion; metrology; pumps; review.

Introduction

Background

Infusion technology is among the most frequent sources of technology-related medical errors [12]. Intravenous (IV) drug administration by infusion is especially challenging for critical applications because stable infusion flow rates are necessary. Variability in flow rate leads to dosing errors, which may lead to adverse clinical effects. These clinical effects can be classified as either insufficient efficacy (underdosing) or increased toxicity (overdosing). There are several reasons for this. First of all, patients, especially those on the intensive care, often need very concentrated pharmaceuticals (drugs) that are delivered with flow rates as low as 0.1 ml/h to minimize excess fluid delivery [48]. Secondly, IV access sites should be limited for reasons of infection risk. Usually, only one catheter is used for multiple IV drug delivery. Consequently, multiple pumps are combined on this single catheter, causing the flows originating from each individual pump to interact with each other due to pressure differences and mixing effects. This principle of joining multiple infusion pumps on one central line has been named multi-infusion or co-infusion and may be the source of considerable flow rate variability [7]. Thirdly, the total infusion setup consists of several components, many of which are disposable medical devices. While the syringe pumps should produce a relatively accurate flow rate, it has been suggested that the physical properties of the other components in an infusion setup may still cause an instable and seemingly unpredictable flow rate [3, 50]. The flow rate is especially unpredictable after pressure changes [17]. These pressure changes appear, for example, after the pump is started; the flow rate is changed; or the pump height is altered. There

has been an increased awareness that flow rate variability may be responsible for medical errors associated with medical technology. Therefore, in recent years, research has been conducted to trace and assess the origin of infusion flow rate variability. Most of the studies found were *in vitro* laboratory investigations, using several measurement methods [7, 11, 16, 23, 27, 32, 50, 55].

Nowadays, it is generally recognized that the actual drug serum concentrations in the patients involve more than the pharmacokinetics of the drug inside the patients alone. The dynamics of the infusion systems outside the patient plays a significant role in drug delivery as well [31]. Timmerman et al. [47] found three major physical causes explaining the dynamics of the infusion system: mechanical compliance, flow resistance, and dead volume. Previous studies have already summarized flow rate variability studies from a clinical perspective [49] but do not elaborate about the underlying physical causes found in literature. Recently, Sherwin et al. [46] explored infusion studies and stated that the physical variables/causes that affect drug delivery in infusion systems require further exploration. In order to facilitate further research in the area of drug metrology, we aim to systemically review the biomedical literature for *in vitro* measurement and modeling studies that investigated the physical causes of flow rate variability.

Mechanical compliance

Mechanical compliance (or compressibility) is described as the volume change caused by changing pressure. The underlying cause is the elasticity of the infusion components. Consequently, volume is stored due to the stretching of non-rigid infusion components as a result of the rising pressure applied by the pump. Mechanical compliance is defined according to Eq. 1:

$$C=\frac{\Delta V}{\Delta P} \tag{1}$$

where C (l/Pa) is the mechanical compliance, ΔV (l) is the volume increase, and ΔP (Pa) is the applied pressure difference. Pressure changes may be caused by changing the nominal flow rate. For example, relatively large pressure changes occur inside the infusion system when the pump is started from a standstill. Another possible cause of pressure change is the vertical displacement of an infusion pump. When the pump is moved up, with respect to the output, i.e. the patient, the pressure increases because the pressure produced by a water column is only dependent on its height. In case of a volumetric pump, regulated by gravity only, the flow rate will increase after increasing the height of the pump. The only limitation is caused by the flow resistance of the tubing and the viscosity of the fluid. However, in case of a syringe pump, merely a bolus (temporary increase of flow rate) is expected. Most syringe pumps simply push the plunger a certain amount per unit time forwards upstream, towards the patient, while preventing the plunger to move backwards, towards the pump. Because of the mechanical compliance, however, some amount of fluid can be stored or released if the pressure is changed. For example, when the pump moves upwards, the pressure is increased at the lower end of the system. As a result, the pressure on the syringe is decreased, which causes the syringe to contract. This decrease in volume causes a small bolus. Conversely, a downwards motion causes a temporary underdosing because the syringe expands. This effect is not related to the velocity of motion during the very act of vertical displacement of the pumps, so the kinetic energy remains irrelevant. It is only the change in position (height) that matters (before and after the vertical displacement of the pump, respectively), not the vertical motion itself that is needed to implement this change in height. The time it takes for the outflow from the syringe in the pump to reach the nominal value is dependent not only on the mechanical compliance but also on the flow resistance. The magnitude of the resistance is determined mainly by the diameter of infusion lines (tubing). Infusion devices with small diameters, for example, a catheter with an inner diameters of 1.0 mm, have a relatively high resistance, i.e. approximately 0.1 mbar per ml/h (10 Pa per ml/h). Of all the infusion components, these relatively small diameters are often found in vascular access devices, such as catheters and cannulae. Viscosity has influence on the effects of the resistance, as with more viscous liquids, the effects of resistance are expected to be more pronounced. Temperature, in turn, may alter the magnitude of the viscosity.

In the infusion setup, mechanical compliance causes deviations in flow rate changes that are opposite with respect to any flow rate change. For example, when the pump is started from a standstill, the pump requires time to reach the nominal flow rate at the catheter tip, where the pharmaceutical enters the patient. This delay between the flow rate and the nominal flow rate is caused by mechanical compliance. Another potential danger, caused by compliance, is a delayed occlusion alarm. When an infusion line is occluded (obstructed), the pressure in the infusion system will increase. If this happens, the pumps should stop and trigger an alarm signal. However, because the pressure increase expands the infusion components first, the force transducer in the pump, usually located at

the plunger in syringe pumps to measure an increase in pressure, does not measure this pressure increase until the components are not able to expand any further. In a multi-infusion situation, a flow rate change in one pump may cause flow rate deviations in the output from other pumps that are connected to the same central line or catheter. When the flow differences are relatively large or when the central line is occluded beyond the mixing point (upstream), backflow may occur. In such a case, the liquid flows back towards a syringe or infusion bag [7, 36].

Dead volume

Dead volume is a term first described in the field of infusion technology by Lovich et al. [28, 29]. Dead volume is the total volume between the mixing point and the outflow into the patient at the catheter tip, also called drug reservoir, internal volume, or dead space volume. When a certain drug concentration is introduced into the infusion line, it travels through the dead volume into the patient. In clinical practice, there is approximately 1 m of distance between the patient and the pump. With the use of typical infusion lines, this results in about 1.6 ml of dead volume. If multiple infusion pumps are combined on one central line and catheter, the dead space volume is shared between those pumps. In this case, a flow rate change in one pump introduces changes to the entire combined mixture in the central line (Figure 1). A concentration ratio of multiple medications is introduced at the mixing point, where multiple pumps are combined. This concentration ratio is based on the current flow rates produced by the pumps. For example, if pump 1 has a flow rate of 20 ml/h and pump 2 has a flow rate of 30 ml/h, then the ratio of medication originating from pump 1 will be 2/5 and the ratio of medication originating from pump 2 will be 3/5. This ratio remains unaltered between the mixing point and the patient once it is inside the tube between the mixing point and the patient at the catheter tip. Therefore, this mixing ratio administered to the patient at the catheter tip is a mixing ratio that was produced in the past. Consequently, if the nominal flow rate of pump 1 is increased to 30 ml/h, a new ratio of 3/6 is introduced at the mixing point, for both pump 1 and pump 2. However, the ratio of 2/5 and 3/5, for pumps 1 and 2, respectively, is still inside the line between mixing point and the catheter tip. This mixture, introduced in the past, will be infused with a new combined flow rate of 60 ml/h, which produces a temporary unwanted bolus until the old concentration ratio has been flushed out. The time it lasts for a concentration mixture to be flushed out of the dead volume (the dead volume time) can be calculated as [t (s)=dead volume (l)/flow rate (l/s)], where the flow rate is the cumulative new flow rate originating from all the pumps connected to the same central line.

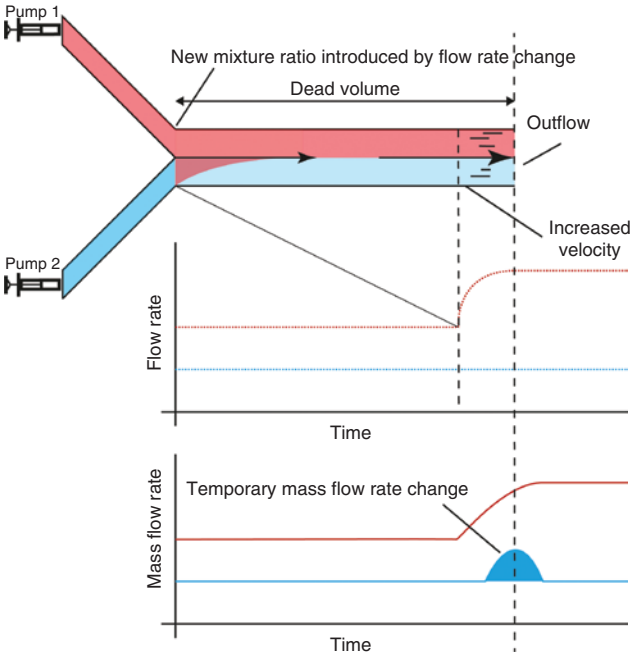

Figure 1: Schematic explaining the effect of dead volume in a multi-infusion system. When the flow rate of the red pump is increased, an excess bolus of pharmaceuticals from the blue pump enters into the patient. This bolus occurs due to the fact that the concentration mixture within the "dead volume," which has been based on the "old" situation before the flow rate increase in the red pump, is now propelled out from the dead volume into the patient with the new increased total flow rate of the red and blue pumps.

In practice, the phenomena of mechanical compliance, resistance, and dead volume are superimposed on each other. Consequently, the pharmaceutical dose per unit time administered to the patient is not just related to the nominal flow rate but may also be affected by the physical effects of mechanical compliance, resistance, and dead volume.

Infusion components and equipment

For each study, we categorized the pumps that were used. Pumps can mostly be categorized as syringe pumps or volumetric (peristaltic) pumps. Syringe pumps are commonly used for the accurate delivery of relatively low flow rates. Volumetric pumps are used for higher flow rates. The flow in volumetric pumps can be regulated in several ways such as drip chambers or counters or peristaltic methods. These methods are generally less accurate than

syringe pumps. In many cases, a combination of syringe and volumetric pumps is used, where the volumetric pump is used as a faster (i.e. higher flow rate) "carrier" for the slower syringe pumps containing critical pharmaceuticals. For example, a volumetric pump with a high flow rate containing a sodium chloride (NaCl) solution may be used to "push out" an older concentration ratio, produced by multiple slower pumps combined on the same central line. The volumetric pump containing the NaCl is called a carrier flow, i.e. the faster flow "carries" the drug mixture, originating from several slower pumps, through the dead volume of the central line, between the mixing point and the patient at the catheter tip. Moreover, because the concentrations of the critical pharmaceuticals from the slower pumps are reduced by the faster carrier flow, the impact of flow rate variability is smaller. Conversely, the dosing error will be larger if the concentration of the critical medication is higher. Consequently, the impact for the patient will be more severe. However, many patients are unable to tolerate large quantities of fluid; the use of a carrier flow is therefore not always possible.

Infusion components include stop cocks, manifolds, anti-reflux and anti-syphon valves, infusion lines (tubing), catheters, cannulae, filters, and syringes. The mechanical properties of these components are associated with the physical causes described earlier.

Methods

Search strategy and selection of studies

We searched for *in vitro*, i.e. laboratory studies, in Medline related to infusion flow rate variability, published between August 1994 and August 2014. Flow rate variability was considered to be any phenomenon that was measured in terms of flow rate. Common phenomena and causes of infusion flow rate variability were used as our inclusion criteria. These phenomena included start-up and fluctuations of flow rates, back flow, and dead volume. These phenomena are generally related to infusion component such as syringes, tubing, valves, catheters, etc. In addition to measurement studies, we also searched for theoretical modeling studies. Figure 2 illustrates the rationale for the keywords used. The keywords were grouped as "effects," "components," and "methodology." The keywords within each group were combined with logical OR operators. Other keywords that were attempted included "compliance," which was too generic and gave too many results. The keywords "pressure," "flow," and "*in vitro*" returned too many unwanted results as well. Flow AND variability returned insufficient results, while flow OR variability returned too many results. Metrology was not a common keyword in biomedical literature and returned no relevant additional results.

Accordingly, the following search string was used in Medline (Pubmed): (infusion) AND (flow rate OR start-up OR backflow OR dead volume) AND (infusion line OR stop cock OR syringe OR tubing OR filter OR valve OR pump OR catheter OR measuring OR model).

The following options were activated in Pubmed: "Full text," "Abstract," "English only." Checking "review" or "*in vitro*" as a search option did not give the expected results and was not used.

When reading the studies, we focused on the following four questions:

1. How are the physical effects causing flow rate variability, especially the physical causes of mechanical compliance, flow resistance, and dead volume, explained?
2. Which physical effects were indicated as the most important causes of flow rate variability?
3. When the role of mechanical compliance was mentioned, which component of the infusion device chain was identified as the most compliant element?
4. What has been the purpose for theoretical modeling studies and what physical effects were studied?

Only full-text English papers with abstracts were considered. We screened titles and abstracts before reading the entire article. In case other reviews were found that investigated infusion flow variability studies, we cross-checked our results with the results of the other reviews. The condition was that all studies from these reviews matching our inclusion criteria should show up with our search query. The classifications of the included studies are stated under the Data extraction section. We also used a classification for the excluded studies after reading and interpreting the title. The excluded studies were categorized in one of the following categories:

***In vivo*:** These are studies concerned with the effects of infusion flow rate variability inside humans or animal subjects;

Non-flow: non-flow studies were all studies that were not evaluating flow rates in any way. For example, studies aimed at measuring only pressure or the assessment of non-continuous infusion were excluded. Studies evaluating the flow outside the infusion system such as the distribution to tissue were also excluded. These studies were classified as non-flow.

N/A: These are studies that we were not able to obtain.

Miscellaneous excluded studies: These are studies in which no measurement method or theoretical models were used to evaluate continues infusion flow rate. Studies that differed entirely from the subject were also categorized as miscellaneous excluded studies.

Studies investigating the properties of drugs such as mixing and absorption by infusion components were not included.

Data extraction

From the included articles, we extracted to following data: (1) objective; (2) year of publication; (3) details about the measurement method used: setup, sensitivity, sample time, etc.; (4) details about the pump used: type of infusion pump, brand; (5) infusion disposable type, if this was specifically associated with a physical cause; (6) nominal flow rates; (7) the physical parameters/causes that were investigated. If this was not specifically stated, the physical parameters/causes were interpreted.

We classified the measurement studies according to the physical causes of flow rate variability. Measurement studies that could not specifically be classified according to a general physical cause were categorized as miscellaneous; these studies usually evaluate the performance of specific infusion pumps.

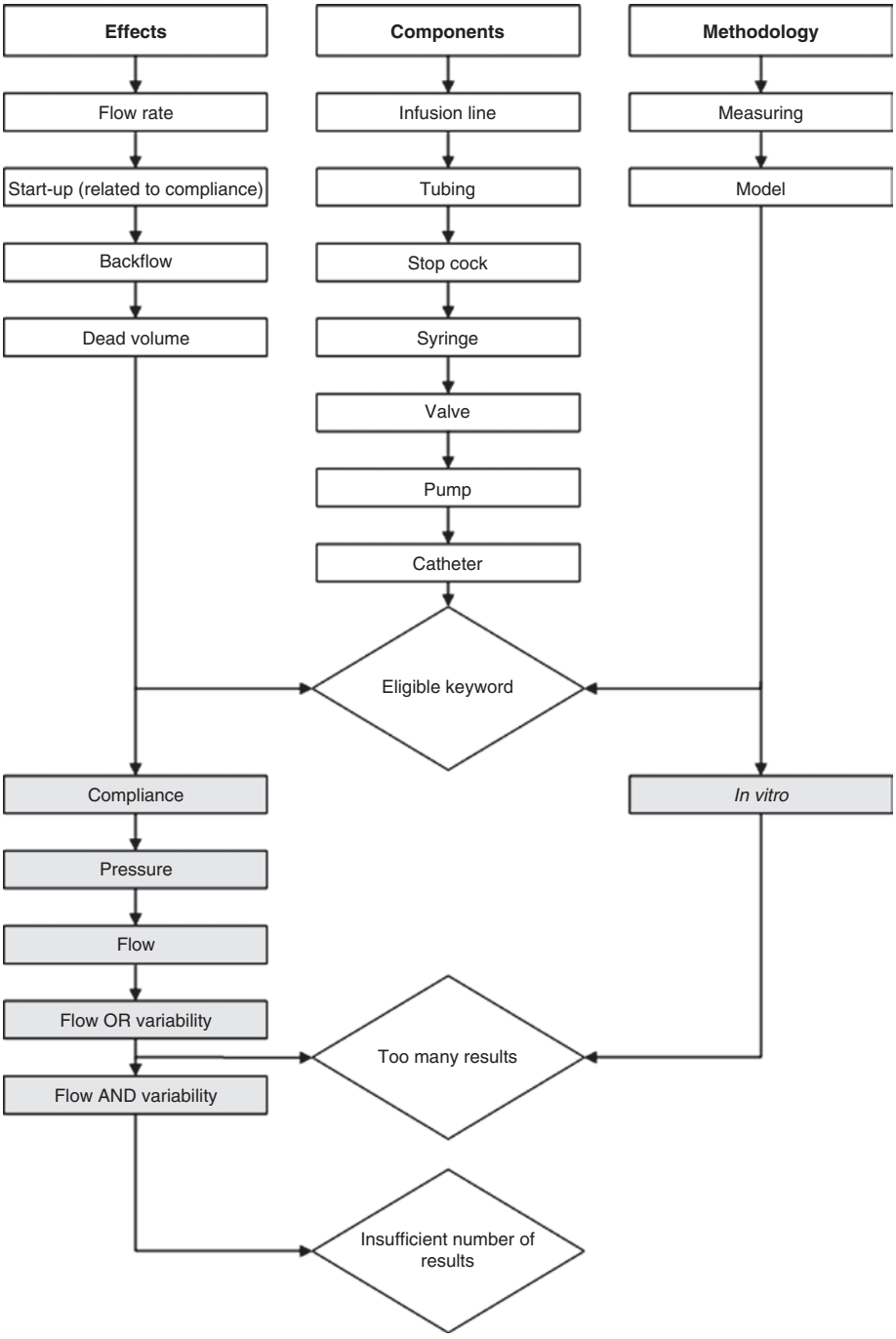

Figure 2: Flowchart of the keywords that were either used or attempted in the search strategy. The keywords were categorized as "effect" studied, "component" studied, and "methodology" used to conduct the study.

Results

The search resulted in 1498 publications from which 1368 were excluded. From most of the excluded studies, it was found that the subject differed entirely after reviewing the title. Another 29 studies were non-English, and one study did not provide an abstract; these 30 studies were excluded as well. After this, we reviewed the abstracts and excluded 52 studies on the basis of the specific criteria stated before. Five studies were added after cross-checking references of the studies found (Figure 3).

We included 53 studies, of which six were theoretical models, two were other reviews, and 45 were *in vitro* measurement studies. Table 1 shows a complete overview of the studies found in our review.

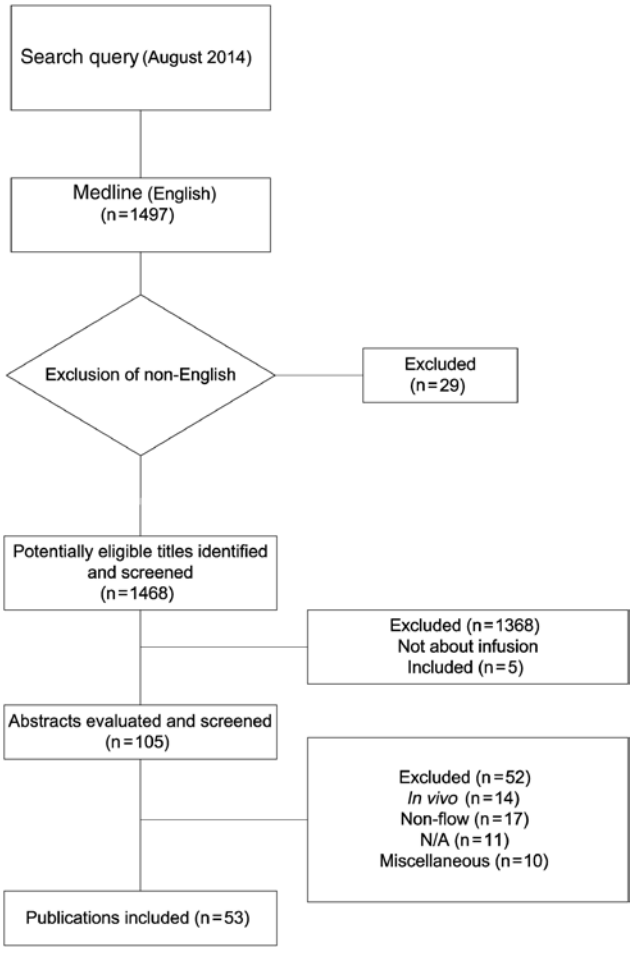

Figure 3: Systematic review query. Fourteen *in vivo* studies were excluded. Seventeen studies were not about flow measurement (non-flow). Eleven studies were not available (N/A), and ten studies were not included for miscellaneous reasons. Fifty-three papers were included, of which six were theoretical modeling studies and two papers were other reviews about infusion flow rate variability.

Study characteristics

We found several measurement methods used for investigating flow rate variability in infusion. Figure 4 shows the number of publications by year and the measurement methods that were used. Gravimetric methods were commonly used for single flows investigating flow rate start-up and mechanical compliance. Spectrometric methods were mostly used for the assessment of dead volume. Spectrometric methods include any method using a spectrometer to obtain the concentration output originating from a specific pump. Absorption spectrophotometry was common. In many cases, dye analogues were used. However, we also found studies in which actual pharmaceutical concentrations were measured using similar spectrometric techniques. Further study characteristics can be found in Figure 5.

Physical causes

From the 45 measurement studies, 33 explicitly investigated flow rate variability due to the physical causes of mechanical compliance, flow resistance, or dead volume. The other measurement studies focused on the performance of specific infusion pumps. Fifteen studies primarily investigated the role of mechanical compliance caused by infusion components as a cause of flow rate variability. Of all the studies investigating the role of mechanical compliance, 10 associated the mechanical compliance with syringes. Seven studies investigated the physical effect of resistance caused by infusion components. Of these studies, four explicitly stated that the physical effect of resistance was investigated. Eleven studies investigated dead volume, and all studies explicitly stated that the physical effect of dead volume was investigated. Besides these major physical effects, turbulence in relation to air bubbles was mentioned as a possible source of flow variability [15]. Also temperature and viscosity of the infused liquid were indicated as factors influencing the flow rate [14, 16]. Studies investigating mechanical compliance in relation to start-up time were common and mostly measured gravimetrically. Start-up or onset (time) is defined as the time required to reach the nominal flow rate or a certain pre-defined fraction of the nominal flow rate. However, dead volume studies, usually using spectrometric methods for measuring drug concentrations, became increasingly numerous during the last years.

Mechanical compliance and flow resistance

Mechanical compliance and resistance were mostly investigated in relation to start-up time. However, we have also found several studies in which compliance was specifically analyzed [17, 39, 52, 53, 56]. Neff et al. [39] found a mechanical compliance of approximately 1.2–1.8 µl/mm Hg (9.0×10^{-9} to 1.35×10^{-8} l/Pa) for several different pumps using an Injectomat Syringe (Fresenius, Bad Homburg, Germany) 50 ml. Weiss et al. [53] found approximately 1.24–1.85 µl/mm Hg (9.3×10^{-9} to 1.38×10^{-8} l/Pa) for four different 50-ml syringes: CODAN Medical ApS (Rødby, Denmark), IVAC Medical Systems (San Diego, CA, USA), Becton Dickinson (Plymouth, Ireland) and Fresenius AG (Bad Homburg, Germany). We found 1.5×10^{-8} to 2.1×10^{-8}

Table 1: Overview of the studies found in the review.

No.	Author	Measurement method	Nominal flow rates	Pump type[a]	Objective	Physical cause[b]
1	Weisman (2014) [51]	Gravimetrically – Readability: 0.1 g – Repeatability: 0.1 g – Sample time: 1 h – Capacity: 4000 g	7–10 ml/h	Elastomeric pump (five different types) ACTion Pump (Ambu, Glen Burnie, MA, USA), GoBlock-SF (B. Braun, Bethlehem, PA, USA), ON-Q C-bloc (I-Flow, Lake Forest, CA, USA) MedFlo MultiRate (MR) (Acacia Inc., Brea, CA, USA), Infusor LV Multirate (Baxter, Round Lake, IL, USA)	Pump evaluation for accuracy [51]	–
2	Mohseni (2014) [34]	Gravimetrically – Capacity: 100 ml	5 ml/h	Elastomeric pump (BOT-802, Nanchang Biotek Medical Device Company, China)	Pump evaluation for accuracy after repeated use [34]	–
3	Le Noel (2014) [22]	Gravimetrically – Sample time: 30 s	100–400 ml/min	Peristaltic pump (TGV 600, Gamidatech, Eaubonne, France)	Testing of influence of two-catheter diameters using a fast infusion pump en solvent related to the blood viscosity [22]	Resistance Temperature
4	Eijk (2014) [50]	Flowmetry Thermal mass flowmeter Coriolis mass flowmeter – Sample time: 0.01 s	0.1 ml/h	Syringe pump Perfusor fm (B. Braun, Melsungen, Germany)	Evaluation of check valves [50].	Resistance
5	Sarraf (2014) [43]	TRN001 isometric transducer – Sample time: 0.1 s	20–400 ml/h	Syringe pump Graseby 3400 pump (Marcal Medical, Millersville, MD, USA)	Pump benchmark and syringe evaluation. Start-up time, update time evaluated [43]	Compliance Resistance
6	Lovich (2013) [30]	Spectrometry –Sample time: 60 s	3, 10 ml/h	Syringe pump (Medfusion 3500, Smiths Medical, Lower Pemberton, UK)	Dead volume assessment of manifold using carrier flow [30]	Dead volume
7	Seo (2014) [45]	Infrared drip chamber measurement / “measuring volume in reservoir”	40–100 ml/h	A wearable ambulatory intravenous infusion device (AIVD) prototype	Pump evaluation on errors [45]	–
8	Foinard (2013) [10]	Spectrometry gravimetrically – Readability: 0.1 mg – Sample rate: 60 s (for both)	Carrier: 90 ml/h Other: 7–14 ml/h	Syringe pump (Module DPS, Fresenius, Bad Homburg, Germany) Volumetric pump one volumetric pump for the carrier fluid infusion (Module MVP, Fresenius, Bad Homburg, Germany)	New disposable evaluation [10]	Dead volume
9	Oualha (2014) [41]	HPLC (retrospective measurement)	2–4 ml/h	Syringe pump DPS, Fresenius Vial, Brezins, France)	Evaluation of dead volume in CVC [41]	Dead volume
10	Kim (2013) [19]	Gravimetrically	–	Syringe pump (PILOTE ANETHESIE 2 IS, Fresenius Vial, Le Grand Chemin, Brezins, France)	Evaluating the effect of priming on TCI (target-controlled infusion) performance [19]	Compliance

Table 1 (continued)

No.	Author	Measurement method	Nominal flow rates	Pump type[a]	Objective	Physical cause[b]
11	Medlicott (2013) [33]	Spectroscopy – Sample time: 5 min – Mixture: dyes	3.8, 18.7 ml/h	Syringe pump Colleague volumetric neonatal infusion pump (Baxter Healthcare, Auckland, New Zealand) Volumetric pump Graseby syringe driver (Graseby Medical, Hertfordshire, UK), T34 syringe pump (REM systems Ltd, Auckland, New Zealand) and Asena CC syringe pump (CareFusion, Auckland, New Zealand)	Simulation of gentamicin delivery to neonates [33]	–
12	Pierce (2013) [42]	Gravimetrically Graduated cylinder – Accuracy: 0.5 ml Balance – Accuracy: 0.01 ml	0–1998 ml/min	Volumetric pump (Sigma Spectrum, Medina, NY, USA)	Evaluation of drip chamber (benchmark) [42]	–
13	Liu (2013) [25]	Time until empty	~50–400 ml/min	Volumetric pump	Influence on flow rate of cannula [25]	Resistance
14	Tsao (2013) [48]	Spectrometry – Sample time: 1 min – Mixture: dyes	Carrier: 10 ml/h Other: 5 ml/h	Syringe pump Medfusion 3500 (Smiths Medical, Dublin, OH, USA)	Flow rate interaction in low flow NICU simulation [48]	Dead volume
15	Brotschi (2012) [4]	Gravimetrically – Sensitivity 0.1 mg – Sample time: 10 s	0.5, 1, 2 ml/h	Syringe pump Alaris Asena GH syringe pump (IVAC Medical Systems, Hampshire, UK)	Influence of in-line filter. Start-up time, variability, Influence of vertical pump displacement evaluated [4]	Resistance Compliance
16	Lannoy (2012) [21]	Spectrometry – Mixture: pharmaceuticals – Sample time: 6 s – UV spectrum Gravimetrically	Protocol 1: Carrier: 90 ml/h Other: 7 ml/h Protocol 2: Carrier: 350 ml/h Other: 65 ml/h	Syringe pump (Pilote A2; Fresenius Vial, Brezins, France) (accuracy 2% of the set flow rate) Volumetric pump (Optima MS; Fresenius Vial, Brezins, France)	Interrupting and resuming carrier flow with an inotropic on the syringe pump [21]	Dead volume
17	Kawabata (2012) [16]	Total volume measurement and time measurement	~5 ml/h	Elastomeric pump Portable disposable infusion pump (SUREFUSER®A, Nipro Corporation, Osaka, Japan)	Influence of temperature and viscosity on the total volume of the drug solution in SUREFUSER®A and the duration of infusion [16]	Temperature Viscosity
18	Ellger (2011) [9]	–	0.1, 1.0 ml/h	Syringe pump	Test of non-return valves in preventing backflow [9]	–
19	Lannoy (2010) [20]	Spectrometry –Mixture: pharmaceuticals –UV spectrum Gravimetrically	Carrier: 35, 70, 115 ml/h Other: 7 ml/h	Syringe pump (Pilote A2, Fresenius Vial, Brézins, France) Volumetric pump (Optima MS, Fresenius Vial, Brézins, France)	Testing the characteristics of several infusion sets, varying in dead volume and an anti-reflux valve [20]	Dead volume Resistance

Table 1 (continued)

No.	Author	Measurement method	Nominal flow rates	Pump type[a]	Objective	Physical cause[b]
20	Levi (2010) [23]	Spectrometry – Mixture: dyes – Sample time: 1 min (for the "infusion pump")	Carrier: 8.0 ml/h Other: 0.1, 0.2 ml/h	Syringe pump Baxter, Model Automatic Syringe 50 (Baxter Inc., Deerfield, IL, USA) Volumetric pump Baxter Colleague 3cx (Baxter Inc., Deerfield, IL, USA) quoted as "infusion pumps"	Evaluation of syringe and volumetric pump for accuracy and precision [23].	Dead volume
21	Schmidt (2010) [44]	Gravimetrically – d=0.1 mg – Sample time: 1 min	0.4, 0.8, 1.0 ml/h	Syringe pumps Pump A, Terumo Terufusion Infusion Pump TE-331 (Terumo, Tokyo, Japan) Pump B, Braun Perfusor Compact (B. Braun, Melsungen, Germany)	Testing different syringes for start-up time [44]	Compliance Resistance
22	Moss (2009) [35]	Spectrometry – Mixture: dyes – Sample time: 1 min	Carrier: 10 ml/h Other: 3 ml/h	Syringe pump Dual channel syringe pump (Harvard Clinical Pump, Harvard Clinical Technology, South Natick, MA, USA)	Analysis of traditional stopcock manifold against a micro infusion set. Onset time evaluated [35]	Dead volume
23	Bartels (2009) [2]	Spectrometry – Mixture: dyes – Sample time: 1 min	Carrier: 2, 2 ml/h Other: 0.5 ml/h	Syringe pump dual-channel syringe pump (Harvard Clinical 2 pump, Harvard Clinical Technology, South Natick, MA, USA)	Analysis of double lumen catheter. Onset time evaluated [2]	Dead volume
24	Décaudin (2009) [7]	Spectrophotometric – Mixture: pharmaceuticals – Sample time: 30 s – Recovery: 99.5%–101.0% – UV spectrum	Carrier: 90 ml/h Other: 15, 10, 7 ml/h	Syringe pump Pilote A2 (Fresenius Vial France; flow rate accuracy 1% on drive mechanism) Volumetric pump 1 Lbag (Maco Pharma, Tourcoing, France)	Evaluation of infusion set length, dead volume and the presence of an anti-reflux valve [7]	Dead volume
25	Ilan (2008) [13]	Pump occlusion alarm time	2, 10, 100 ml/h	Peristaltic pump Sigma 8000-plus (Sigma, Medina, NY, USA) Graseby 3000 (Smiths Medical, Watford, Herts, UK) Baxter colleague (Baxter, Deerfield, IL, USA) Alaris 7230B (Alaris Medical Systems, San Diego, CA, USA)	Analysis of occlusion: time-to-alarm in four peristaltic infusion devices [13]	–
26	Lovich (2007) [29]	Spectrometry – Mixture: dyes – Sample time 1 min	Carrier: 10, 60 ml/h Other: 3 ml/h	Syringe pump Harvard 2 Clinical Pump (Harvard Clinical Technology, South Natick, MA, USA)	Analysis of dead volume of several central venous catheters [29]	Dead volume
27	Neff (2007) [40]	Gravimetrically – Sensitivity: 0.1 mg	0.1, 0.5, 1 ml/h	Syringe pump Asena GH syringe pump (Alariss Medical Systems, Hampshire, UK)	Syringe analysis on size and architecture [40]	Compliance
28	Hall (2005) [11]	Flowmeter – Accuracy: 1% The flowmeter was calibrated to a certain volume	2.8–8.6 ml/h	Volumetric pump (Macroflex, Macro Pharma, London, UK) was connected to a blood administration set (C2071B, Baxter Healthcare Ltd, Newbury, UK)	Analysis of flow rate reduction by anti-reflux valves and cannulae [11]	Resistance

Table 1 (continued)

No.	Author	Measurement method	Nominal flow rates	Pump type[a]	Objective	Physical cause[b]
29	Davey (2005) [6]	Gravimetrically – Sensitivity: 0.01 mg – Sample time: 30 s	1.0 ml/h		Evaluation of influence of air bubbles on delivery [6]	Compliance
30	Dönmez (2005) [8]	Pump occlusion alarm	0.5, 1.0, 2.0, 5.0 ml/h	Syringe pump 20 JMS SP-100 and 20 JMS SP-500 (JMS, Hiroshima, Japan)	Pump bench test of occlusion alarms with different syringe sizes [8]	Compliance Resistance
31	Weiss (2004) [55]	Gravimetrically – Sensitivity: 0.1 mg – Sample time: 1 s	0.5 ml/h	Microvolumetric infusion pump (MVIP) Prototype microfluidic device using an infusion bag Syringe pump Alaris Asena GH syringe pump (IVAC Medical Systems, Hampshire, UK)	Influence of vertical displacement on low flows [55]	Compliance
32	Ilfeld (2002) [14]	Gravimetrically – Sample time: 1 min	5.0, 4.16, 4.0 ml/h	Portable pump (various technologies) Accufuser (McKinley Medical Wheat Ridge, CO, USA) C-Bloc (I-Flow Corp. Lake Forest, CA, USA) MedFlo II (MPS Acacia Brea, CA, USA) Microject (PCA Sorenson Medical West Jordan, UT, USA) Pain Pump (Stryker Instruments Kalamazoo, MI, USA) Sgarlato Labs (Los Gatos, CA, USA)	Test flow rate accuracy, consistency, and profiles of various portable pumps. Total time was measured and compared to the expected time of an empty pump. The tests were done at body temperature and higher temperatures [14].	Temperature Others
33	Neff (2001) [37]	Gravimetrically – Sensitivity: 0.1 mg	1 ml/h	Syringe pump Braun Perfusor compact (Braun, Melsungen, Germany) IVAC P4000 Anaesthesia Syringe Pump (IVAC Corporation, Hampshire, UK) Fresenius Injectomat cp-IS (Fresenius Hemocare GmbH, Bad Homburg, Germany) Arcomed Syramed lSP6000 (Arcomed, Regensdorf, Switzerland)	Evaluation of start-up delays [37]	Pump design
34	Kern (2001) [17]	Gravimetrically No further specifications Pressure was also measured.	1, 2, 3, 5, 10 ml/h	Syringe pump Injectomat-C (Fresenious, Oberusel, Germany) Ivac 770 (Ivac, San Diego, CA, USA) Perfusor fm (B. Braun Melsungen Medical, Melsungen, Germany)	Analysis of the effect of lowering the pump (vertical displacement) in a neonatal and adult setting [17]	Compliance
35	Weiss (2001) [54]	Gravimetrically – Sensitivity: 0.1 mg – Sample time: 1 s	0.5–1 ml/h	Syringe pump Fresenius Injectomat (cp-IS, Fresenius AG, Bad Homburg, Germany) Pressure flushing bag	Effects of different flush techniques of arterial line in a pediatric setting [54]	Compliance Resistance

Table 1 (continued)

No.	Author	Measurement method	Nominal flow rates	Pump type[a]	Objective	Physical cause[b]
36	Neff (2001) [38]	Gravimetrically – Sensitivity: 0.1 mg	1 ml/h	Syringe pump IVAC P7000 syringe pump (Alaris Medical Systems, Hampshire, UK)	Evaluation of FASTSTART mode in specific pump [38]	Compliance
37	Neff (2001) [39]	Gravimetrically – Sample time: 1 s	1 ml/h	Syringe pumps Fresenius Injectomat-S (Fresenius, Bad Homburg, Germany) Fresenius Injectomat-IS (Fresenius, Bad Homburg, Germany) IVAC P4000 Anaesthesia Syringe Pump (IVAC, Hampshire, UK)	Analysis of the effects of vertical displacement for different infusion pump models [39]	–
38	Weiss (2000) [56]	Gravimetrically – Sensitivity: 0.1 mg – Sample time: 1 s	0.5, 1, 2 ml/h	Syringe pump IVAC syringe pump (IVAC-Alaris, IVAC Medical Systems, Hampshire, UK)	Evaluation of the effects of syringe size [56]	Compliance
39	Kim (1999) [18]	Gravimetrically Time to occlusion alarm	1 ml/h	Syringe pump Medfusion pump, model 2001 (Medifusion, Medex Inc, Duluth, GA, USA)	Three different syringe sizes investigated on the accuracy of delivery and the time to occlusion alarm [18]	Compliance
40	Weis (2000) [52]	Gravimetrically – Sensitivity: 0.1 mg – Sample time: 1 s	0.5, 1, 1.5 ml/h	Syringe pump (Model 711±1G, IVAC, San Diego, CA, USA)	Evaluation of infusion line compliance under influence of vertical displacement [52]	Compliance
41	Weiss (2000) [53]	Gravimetrically – Sensitivity: 0.1 mg – Sample time: 1 s	1 ml/h	Syringe pump (IVAC Syringe Pump P4000, IVAC Medical Systems, Hampshire, UK)	Evaluating the effects of syringe plunger design on vertical displacement. Four syringes were evaluated [53]	Compliance
42	McCarroll (2000) [32]	Time to first drop (observer)	2, 10, 50 ml/h	Syringe pump Syringe driver IVAC P2000 (IVAC, San Diego, CA, USA)	Evaluation of the effects of anti-syphon valves on start-up time (time to first drop) [32]	Resistance
43	Capes (1997) [5]	Gravimetrically	0.388, 1.25 ml/h	Syringe pump MS16A syringe drivers (Graseby Medical, Watford, UK; serial numbers 261. 6293. and 31007) Springfusor 30 short model syringe drivers (Go Medical Industries Pty., Ltd., Subiaco, Australia)	Evaluation of a subcutaneous syringe pump accuracy [5]	–
44	Lönnqvist (1997) [26]	Gravimetrically – Detection limit: 10 mg – Sensitivity: 10 mg	1 ml/h	Syringe pump BD Modular and BD Pilot C (Becton-Dickenson, Brezins, France) Perfusor Securra FT and Perfusor (FM, B. Braun, Melsungen, Germany) IVAC P 4000 (IVAC, San Diego, CA, USA)	Vertical displacement evaluation [26]	Gap in infusion pump Compliance

Table 1 (continued)

No.	Author	Measurement method	Nominal flow rates	Pump type[a]	Objective	Physical cause[b]
45	Angle (1997) [1]	Pressure conversion "model"	25, 65, 135, 270 ml/h	Volumetric pump (Harvard Apparatus, South Natick, MA, USA)	Evaluation of infusion PICC lines [1]	Resistance
46	Levine (2013) [24]	*Model* and time for defined aliquots of fluid to pass into the open burette (validation)	0–700 ml/min	Volumetric pump (for validation)	Evaluation of multi-lumen extension resistance according to the Poiseuille equation [24]	Resistance
47	Ma (2011) [31]	*Model*	–	–	Using model of Lovich et al. to evaluate infusions in pediatric anesthesia [31]	Dead volume
48	Murphy (2010) [36]	*Model*	1–50 ml/h	–	Effects of volume storage after occlusion [36]	Compliance Resistance
49	Lovich (2006) [28]	*Model*	0, 1.2, 5, 10, 15, 100, 500 ml/h	–	Further investigation of dead volume and carrier flow by alternating the quantities [28]	Dead volume
50	Jayanthi (2005) [15]	*Model*		–	Investigating effects of cannulae length [15]	Resistance
51	51 Lovich (2005) [27]	*Model* and spectrometry (validation)	3–640 ml/h	–	Investigating dead volume effects [27]	Dead volume
52	Sherwin (2014) [46]	*Review*	–	–	–	–
53	Eijk van der (2013) [50]	*Review*	–	–	–	–

[a]Volumetric pumps include any volumetric pump using a bag, gravity, and an optional flow regulator such as peristaltic techniques.

[b]Primary cause investigated.

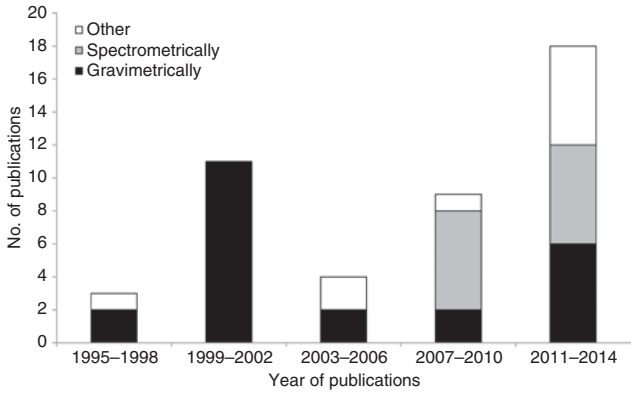

Figure 4: Overview of measurement methods used in the included publications (n=45). Measurement methodologies included gravimetric methods, spectrometric methods, and others.

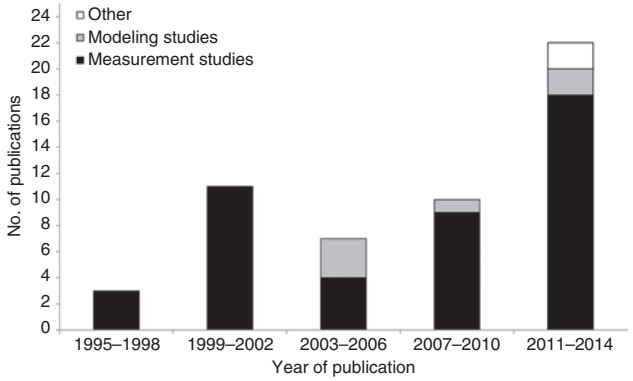

Figure 5: Overview of study characteristics. Modeling studies that were tested using a laboratory setup were categorized as a modeling study.

l/Pa for a B. Braun (Melsungen, Germany) 50-ml syringe using a pressure gauge and a balance [3]. Kim and Steward [18] found that the syringe was the most compliant component in a syringe infusion setup and specifically stated that the mechanical compliance is located in the latex plunger of the syringe. Kim and Steward also found that the accuracy of the flow rate was not significantly improved with smaller syringes but that larger syringes delayed the time to reach an occlusion alarm from 7.4 to 84 min for the 10- and 60-ml syringes, respectively. The experiments were performed with the model 2001 (Medifusion, Medex Inc, Duluth, GA, USA) pump [18]. Priming the infusion set with some pressure may decrease the effects of mechanical compliance, thereby decreasing the flow rate onset time. However, a bolus may occur at start-up [19]. Neff et al., Weiss et al., and Schmidt et al. [37, 40, 44, 53] evaluated start-up times gravimetrically for different syringes and syringe sizes. All stated the influence of mechanical compliance explicitly and found that smaller syringe sizes, i.e. syringes with smaller diameters and therefore smaller volumes, showed shorter onset delays and shorter "zero-drug delivery times" in which there was no flow rate at all. It was found that start-up time was at least 60 min with the 50-ml syringe. With the 10-ml syringe, start-up time was <20 min. However, these start-up times could not entirely be attributed to compliance, although it was attempted to remove other influences [44]. Neff et al. [40] found between 3.6±0.9 min (10-ml syringe, 1.0 ml/h nominal flow rate) and 74.5±26.6 min (50-ml syringe, 0.1 nominal flow rate) start-up time. The start-up times as well as the no-flow times after lowering the pump were in correlation with the calculated mechanical compliance and the elastic nature of the plunger material [43, 56]. Moreover, lower flow rates were associated with longer start-up delays [40, 43, 44, 56].

Another cause of pressure changes in an infusion system, which exploits compliance, is the vertical displacement of the pump. This has been investigated in several studies. It was generally found that an upward motion is followed by a bolus delivery, and a downward motion is followed by temporary reduced flow output [4, 17, 26, 39, 50, 52, 55]. This effect is not related to the velocity of motion during the act of vertical displacement of the pumps. Only the difference in height between the pump and the point of outflow causes the temporary flow deviation. Infusion lines were also stated as a source of mechanical compliance [43, 52]. Weiss et al. [52] evaluated gravimetrically the influence of infusion lines on mechanical compliance due to vertical displacement. The flow rate onset time, i.e. the time in which there was no flow rate, varied between 5.1±1.5 s and 44.0±6.8 s (mean±SD), depending on the type of infusion line, after lowering the middle part of the infusion lines 70 cm below the infusion pump, at a nominal flow rate of 0.5 ml/h. The infusion lines tested were Syringe Extension Set (IVAC Medical SYSTEMS, San Diego, CA, USA, Ref G30402M/652403), Injectomat-Line (Fresenius, Bad Homburg, Germany, Ref 9011971), Syringe Extension Set (IVAC Medical SYSTEMS, San Diego, CA, USA, Ref G30402/652393), Syringe Extension Set (IVAC Medical SYSTEMS, San Diego, CA, USA, Ref G30402/652393), and Injectomat Line PEL (Fresenius, Bad Homburg, Germany, Ref 9000951). The variation of the results showed a close correlation between the variation of the infusion line mechanical compliances, which varied between 0.48±0.17 µl/mm Hg (3.6×10^{-9} $\pm1.3\times10^{-9}$ l/Pa) and 2.15±0.26 µl/mm Hg ($1.6\times10^{-8}\pm2.0\times10^{-9}$ l/Pa). These mechanical compliances were obtained using a blood pressure transducer [52]. Brotschi et al. [4] evaluated the influence a neonatal Pall in-line filter device (Pall Posidyne Neo Filter 0.2 lm, Pall AG Switzerland, Basel, Switzerland) on start-up times and flow rate irregularities during

vertical displacement of the syringe pump. The experiments were performed with nominal flow rates of 0.5, 1.0, and 2.0 ml/h. The time to first drop was registered as well as the time required to reach 95% of the nominal flow rate. For each of these end points, a comparison between using an in-line filter and not using an in-line filter was made. The values, resulting from four repeated experiments, were presented as median values; the range is denoted between parentheses. The time required to reach 95% of the nominal flow rate (95% time) differed significantly when using a filter and not using a filter for the nominal flow rates of 0.5 ml/h ($p=0.02$) and 2.0 ml/h ($p=0.003$) but not for 1.0 ml/h ($p=0.7$). For a nominal flow rate of 0.5 ml/h, the time to first drop was 355.5 s (0–660 s) without the filter and 115 s (0–320 s) with the filter; the difference was not statistically significant. Ninety-five percent of the nominal flow rate was reached in 580 s (360–870 s) without a filter and reduced to 284 s (130–650 s) with the filter. For a nominal flow rate of 1.0 ml/h, the time to first drop was 0 s (0–172 s) without the filter and 0 s (0–160 s) with the filter; the difference was not statistically significant. Ninety-five percent of the nominal flow rate was reached in 230 s (220–350 s) without the filter and 210 s (120–520 s) with the filter; the difference was not statistically significant. For a nominal flow rate of 2.0 ml/h, the time to first drop was 0 s (0 s) without the filter and 0 s (0–60 s) with the filter; the difference was not statistically significant. Ninety-five percent of the nominal flow rate was reached in 249.5 s (153–393 s) without the filter and 62 s (0–200 s) with the filter. It was concluded that the start-up time was reduced after introducing an in-line filter. However, the differences were diminished at higher flow rates, i.e. 1.0 and 2.0 ml/h, and the time to first drop differences were not statistically significant. The storing of fluid into the compliant disposables of a system was reduced using an in-line filter after lowering the pump. The bolus resulting from elevation of the pump was not reduced using an in-line filter. Experiments were performed gravimetrically, and a thin layer of oil was used to prevent evaporation [4].

Yet another compliant element in the infusion system is air. The influence of air bubbles was gravimetrically evaluated by Davey et al. [6] at 1.0 ml/h. Davey et al. stated that "[s]mall air bubbles can become lodged in the pressure-sensing disc part of syringe pump delivery lines. This can give rise to serious disturbances in fluid delivery from minute to minute, but does not trigger pump alarms. Small air bubbles being delivered through non-horizontal sections of delivery line can also cause significant transient disturbances to fluid delivery. Flow rate fluctuated between 1 and 3 ml/h" [6].

Resistance was also evaluated. Angle et al. [1] measured the pressure using a pressure gauge for several peripherally inserted central catheter (PICC) lines, a common vascular access device. The flow rate was calculated according the Poiseuille law. Flow rate capacity was related to the inner diameter. Resistance was specifically given for each PICC line ranging from approximately 0.05 to 1.5 mm Hg per ml/h (7 Pa per ml/h to 200 Pa per ml/h) [1]. Non-linear resistance occurs with several types of valves to prevent backflow. It has been shown that this causes flow rate variability [7, 9, 11, 25, 27, 32, 50]. Liu et al. [25] measured the effect of using several sizes of cannulae in combination with a SmartSite Needle-Free (CareFusion, San Diego, CA, USA) anti-reflux valve on the time required to empty an infusion bag of a volumetric infusion pump. Experiments were performed under a gravity-only condition, where the bag was emptied due to gravity alone. Furthermore, a pressure infuser was used; in this case, the bag was squeezed with a pressure of 0.4 bar (4×10^4 Pa). Each experiment was performed with and without an anti-reflux valve and repeated five times. Results were presented with a 95% confidence interval (95% CI). For the biggest cannula (14 G), flow rates of 82 (79–86, 95% CI) and 126 (116–135, 95% CI) ml/min were measured with and without an anti-reflux valve, respectively, for the gravity-only condition. For the smallest cannula (20 G), flow rates of 43 (41–44, 95% CI) and 47 (46–48, 95% CI) ml/min were measured with and without an anti-reflux valve, respectively, for the gravity-only condition. Smaller cannulae and the presence of an anti-reflux valve delayed the emptying of the infusion bag and thus delayed the flow rate under gravity-only condition as well as with the use of a pressure infuser [25]. Weiss et al. [54] investigated different flush techniques for arterial lines and cannulae and found that, when using a syringe pump, the onset time of flow rate was significantly longer than when using a pressure bag system. Start-up time (zero flow time) was 0.1 ± 0.01 and 7.7 ± 0.5 min for the bag flush system and syringe pump, respectively [54]. Le Noel et al. [22] tested the influence of several catheters with different lengths (42–200 mm) and inner diameters (0.9–1.6 mm) on the flow rate using a peristaltic pump. The pump contained a fluid with a viscosity similar to that of blood. Nominal flow rates of 100, 200, 300, and 400 ml/min were used. The experiments were performed according to the ISO 10555-3 standard using a gravimetric measurement setup. The study showed that these relatively high flow rates were not reached and that the error of the underestimation increased with decreasing catheter inner-diameters, longer catheter lengths, and higher fluid viscosity. These findings indicate that the lower than expected flow rates were related to the flow resistance caused by the catheter [22]. Van der Eijk et al. [50] investigated the effects of three different types of check valves [BBraun Infuvalve (Melsungen, Germany),

Filtertek BV SyphonSafe (Co., Limerick, Ireland), BBraun BC1000 (Melsungen, Germany)], on start-up time and the total delivered volume during measurement; these effects can be related to flow resistance. A thermal flow meter was used for a pump with a nominal flow rate of 0.1 ml/h. An additional pump with a nominal flow rate of 2.5 ml/h was also measured simultaneously using a Coriolis Flowmeter. The pumps were connected to a common central line with a three-way stopcock. The results were presented as mean±SD. Start-up time was defined as reaching 75% of the nominal flow rate. Van der Eijk et al. found longer start-up times with check valves (up to 43.7±2.7 min) than without check valves (27.6±3.8 min) for the pump with a nominal flow rate of 0.1 ml/h. A lower than expected total volume delivery was found in the pump with a nominal flow rate of 2.5 ml/h. The lowest value found with a check valve was 12±24% of the expected total volume compared to 52±21% without a check valve. It can be concluded from the results that check valves may cause flow reduction [50]. Hall and Roberts [11] used a flow meter to observe flow rate reduction caused by three different anti-reflux valves [Protect-a-Line 3 (Vygon (UK) Ltd, Cirencester, UK), Wescott Sae-flo (Wescott Medical Ltd, Chester-le-Street, UK), B. Braun Back flow valve (B. Braun Medical, Melsungen, Germany)]. The experiments were performed with a volumetric pump under gravity (150-cm height difference) or an applied pressure of 0.4 bar (4×10^4 Pa) and measured using a flowmeter. In addition, the influence of two different cannulae with different diameters (16 G and 20 G) was investigated. Flow rate decreased for all valves with a 16-G cannula; the highest reductions were -38% under gravity and -23% (both with the Protect-a-Line 3) under the applied pressure. For the 20-G cannula, no statistically significant flow rate reductions were found [11]. McCarroll et al. [32] evaluated three anti-syphon valves [B. Braun Medical (Melsungen, Germany) BC1000 Backcheck Valve, Wescott Medical 200 cm (Wescott Medical Ltd, Chester-le-Street, UK), Vygon Protect-A-Line (Vygon (UK) Ltd, Cirencester, UK)] at nominal flow rates of 2, 10, and 50 ml/h, using syringe pumps. An observer recorded the time between depressing the start button and the first drop that fell from the infusion line. All results were compared to a "control" situation without an anti-syphon valve. The results were presented as mean±SD. The time to first drop was longer when an anti-siphon valve was used at lower nominal flow rates. The longest time until the first drop was observed was 18.4±9.26 min, as opposed to 3.5±2.09 min in the control situation, with a nominal flow rate of 2 ml/h. At the higher nominal flow rates of 10 and 50 ml/h, the times to first drop were less pronounced. In these cases, none of the difference with the control group was statistically significant, except for the Wescott valve for which a start-up time of 0.6±0.33 min was found as opposed to 0.3±0.14 min for the control situation. Overall, all the valves performed similarly within the uncertainties that were presented [32]. At low flow rates, time to first drop was significantly longer using an anti-syphon valve as opposed to the control group. At the faster rates, this difference was less pronounced but still observed in some cases.

Dead volume and multi-infusion

Dead volume or internal volume has been related to central infusion lines, manifold or the entire infusion set [7, 10, 20, 21, 23, 30, 35, 48]. Dead volume was also associated with vascular access devices such as catheters [2, 29, 41]. Lowering the dead volume was practically unanimously recommended in the literature reviewed. However, lowering the volume of tubing by reducing the diameter increases the resistance [7, 29].

Dead volume is especially important for relatively low flow rates, i.e. between 0.1 and 10 ml/h. Low flow rates are typically used on the neonatal intensive care unit (NICU), because the small infants cannot tolerate large quantities of fluid [48]. Consequently, the concentrations of the pharmaceuticals are high. However, this is also the reason that small deviation can easily cause dosing errors. Therefore, there has been a focus on flow rate variability in the NICU setting [17, 33, 50]. However, we also found flow variability studies outside the NICU setting.

A research group led by Décaudin [7] conducted a series of studies to investigate the effects of, among other effects, dead volume. Décaudin et al. investigated two different multiple-in, single-out infusion sets (both from Doran International, Toussieu, France) used for multi-infusion. The sets differed in length and dead volume, i.e. the volume between the mixing point and the distal end of the infusion set. In addition, the presence and position of an anti-reflux valve were varied between the tests. Depending on the access position of the infusion set (i.e. distal or proximal with respect the infusion pump), the dead volumes were between 0.046 and 8.01 ml. Drug concentration at the end of the infusion set was measured using an UV spectrometer. The mass flow rate and mass flow rate plateau (µg/min) were investigated, where the mass flow rate plateau was defined as the mean amount of drug delivered to the patient per unit time in steady state, i.e. the stage where a concentration equilibrium has been reached. A deviation in the "drug delivery plateau" (in percentages) was evaluated, where 100% corresponded to the expected mass flow rate plateau. It was hypothesized that values lower than 100% were caused by backflow from the other pumps connected

to the same infusion set. In addition, the flow change efficiency (FCE) was calculated. The FCE is the ratio (in percentages) of the expected delivered drug and the measured drug delivered. The "drug delivered" is defined as the "area under curve" of the mass flow rate during a specific time period, usually after a flow rate change was initiated. For example, if during a flow rate start-up period of 30 min, the mass flow rate corresponds for 100% to the expected mass flow rate, the FCE is 100%. Three syringe pumps with nominal flow rate between 7 and 15 ml/h and one carrier flow volumetric pump with a nominal flow rate of 50 ml/h were used. The results were presented in mean±SD. The FCE values were 53.0%±15.4% and 5.6%±8.2%, for dead volumes of 0.046 and 6.16 ml, respectively. It was therefore found that infusion sets with lower dead volume resulted in higher FCE values. This finding was true for any flow rate change. The presence of an anti-reflux valve increased the mass flow rate plateau from 92.4% to 99.3% of the theoretical curve of the nominal flow rate, without and with an anti-reflux valve, respectively. This showed that an anti-reflux valve reduced backflow into the tubing of another infusion pump, which was connected to the same infusion set as the infusion pump from which the fluid originated [7]. From the same group, Lannoy et al. [21] conducted similar experiments using the same infusion sets as Decaudin et al. [7]. However, in this case, the effects of carrier flow were investigated. The influence of a 10-min carrier flow interruption, as well as two different nominal carrier flow rates of 90 and 350 ml/h, was investigated. The nominal flow rates of the pump used to simulate drug delivery, noradrenaline in this case, were varied between a "low flow" and "high flow" regime of 7 and 65 ml/h, respectively. For the "low flow" regimen, the FCE values of noradrenaline were 6.7%±0.5% and 63.5%±0.8% for dead volumes of 6.16 and 0.046 ml, respectively, during a 10-mi period after stopping the carrier fluid. The FCE values were 257.8%±25.0% and 119.9%±0.6% for dead volumes of 6.16 and 0.046 ml, respectively, during a 10-min period after restarting the carrier flow. For the "high flow" regime, the FCE values of noradrenaline were 56.2%±1.8% and 94.7%±4.4% for dead volumes of 6.16 and 0.046 ml, respectively, during a 10-min period after stopping the carrier fluid. The FCE values were 146.0%±6.9% and 102.2%±3.7%, respectively, for dead volumes of 6.16 and 0.046 ml during a 10-min period after restarting the carrier flow. This is similar to the conclusion of Décaudin et al. [48] that a smaller dead volume is providing a better FCE, which means that the delivered amount of drugs is closer to the expected value [21].

In another study, Lannoy et al. [20] investigated several infusion sets with dead volumes between 6.16, 3.70, 1.85, 0.93, and 0.046 ml with and without anti-reflux valves. The drug (Noradrenaline) was set to a nominal flow rate of 7 ml/h. The nominal carrier flow rates were 35, 70, and 115 ml/h. The FCE values varied between 5.6% and 53% for 6.16 to 0.046 ml dead volume, respectively, during the period of the first 5 min. After 10–15 min, FCE was around 100% for all dead volumes; so after 15 min, the mass flow rate of noradrenaline was as expected. The FCE increased in a non-linear fashion with increasing dead volume. Anti-reflux valves improved the drug delivery (FCE) by approximately 10% for the low carrier flow after a duration of 10 min from the start. It was found that flow rate variability was less for the infusion set with a low dead volume [20]. Foinard et al. [10] evaluated a new low dead volume disposable, 150-cm extension line (Cair LGL, Civrieux d'Azergues, France), and a nine-lumen infusion device (Edelvaiss-Multiline®, Doran International, Toussieu-Lyon, France) in a similar fashion as the studies conducted by Décaudin et al. [7] and Lannoy et al. [21, 20] and found a different FCE for the new disposable when increasing and decreasing the flow rate in the pump containing noradrenaline. After increasing the nominal flow rate of the noradrenaline from 7 to 14 ml/h, the FCE values were 58.4%±5.3% and 84.3%±5.2% for the conventional and new infusion set, respectively. After decreasing the nominal flow rate from 7 to 14 ml/h, the FCE values were 175.3%±8.9% and 108.2%±4.4% for the conventional and new infusion set, respectively [10]. It was concluded that the new disposable showed significantly less drug delivery disturbances. In the studies conducted by the group of Décaudin (including Lannoy et al. and Foinard et al.) [7, 20, 21], a balance was often used to obtain the cumulative fluid quantity at the end of the infusion setup.

Tsao et al. [27] found that dead volume in a multi-infusion setting caused flow rate variability after changing the nominal flow rate. Flow rates used were 10 ml/h for the carrier and 5 ml/h for the syringe pump containing the drug. A bolus lasting about 10 min of approximately 20% above the nominal flow rate was found. A spectrometric setup was used, and the medication schedule was based on a neonatal regimen. Moss et al. [35] evaluated a traditional manifold (4-stopcock Hi-Flo manifold, Arrow International, Reading, PA, USA) against a new infusion disposable six-port Multi Line Extension Set (Summit Medical Products, Worcester, MA, USA). The new infusion disposables were specifically designed to reduce the dead volume. Experiments were performed using a carrier flow of 10 and 3 ml/h for the flow of the pump containing the model drug; results were presented as mean±SD. The start-up time (50% of the nominal value) of the model drug was found to be proportional to the dead volume. The shortest start-up time (3.53±0.11) was found for the new disposable, the longest start-up was found for the traditional manifold

(9.21±0.33) [35]. Bartels et al. [2] investigated a double lumen catheter (#AK-15402, Arrow, Reading, PA, USA) with similar flow rate and regimens as moss, using a spectrometric method. Bartels et al. found that start-up time until the drug concentration was reached was significantly longer with lower flow rates. Also priming, i.e. filling, reduced the onset time. Lovich et al. [29] investigated the dead volume of several central venous catheters using a carrier flow of 10 and 60 ml/h and a drug flow of 3 ml/h. The time necessary to reach steady state in the mass flow rate of the model drug differed between central venous catheters. The differences were related to dead volume. However, Lovich et al. stated that besides dead volume, vascular access sizes are distinguished by their resistance. Oualha et al. [41] evaluated delay time due to dead volume in a central venous catheter (#CS-16402, Arrow, Teleflex, PA, USA) using retrospective HPLC analysis. A dead volume time was calculated, which amounted to 6 min for a dead volume of 0.3 ml and a nominal flow rate of 2 ml/h. However, 100% of the expected concentration of the drug was only reached in 15–18 min, which is longer than the expected time calculated on the dead volume [41].

Miscellaneous

An early study performed by Lönnqvist et al. [26] attributed a bolus followed after vertical displacement to design flaws in syringe pumps. After a change in pressure, mechanical compliance may store or release some additional fluid. In this case, a gap between the plunger and the syringe driver was indicated as a source for the flow rate variability after vertical displacement. This means that the syringe is able to move slightly forward (upstream, towards the patient) or backward (towards the pump) as a result of increasing and decreasing the height of the pump, respectively [26]. Neff et al. [37] found a similar problem. They also found that pump design caused significantly different flow rate variability during vertical displacements of several types of pumps with the same syringe [39]. Ilan et al. [13] investigated the time until an occlusion alarm was released for the Sigma 8000-plus (Sigma, Medina, NY, USA), Graseby 3000 (Smiths Medical, Watford, Herts, UK), Baxter colleague (Baxter, Deerfield, IL, USA), and Alaris 7230B (Alaris Medical Systems, San Diego, CA, USA) peristaltic pumps. Nominal flow rates of 2, 10 and 100 ml/h were used. Time to occlusion alarm was 0.3±0.1, 2.3±0.5 and 11.7±3.1 (mean±SD) min for nominal flow rates of 100, 10 and 2 ml/h, respectively [13].

Levi et al. [23] evaluated a combination of low flow syringe and volumetric "infusion" pumps for accuracy and precision using a spectrometric setup. In addition, a multiple-in/single-out stopcock array was evaluated. Levi et al. found that the infusion pump was more accurate than a 60-ml syringe pump in generating infusion rates of both 0.1 and 0.2 ml/h. Also the multiple-in/single-out stopcock array caused significant delays of at least 30 min for the concentration to double after the flow rate was doubled. This was due to dead volume [23]. Neff et al. [39] investigated three different syringe pumps from two different manufacturers (Fresenius, Bad Homburg, Germany and IVAC Medical Systems, San Diego, CA, USA) and found significant differences in zero drug delivery time between the pumps after vertical displacement while keeping the same syringe type. The zero drug delivery time varied from 2.78±0.29 to 5.99±1.09 min. Because the syringe types were kept constant, the differences in zero drug delivery time were attributed to the difference in mechanical compliance of the syringe pump itself, which varied from 1.22±0.01 to 1.75±0.02 µg/mm Hg ($9.2\times10^{-9}\pm7.5\times10^{-11}$ l/Pa to $1.3\times10^{-8}\pm1.5\times10^{-10}$ l/Pa) [39]. Dönmez et al. [8] evaluated 40 syringe pumps (two types) using a variety of syringe sizes, measuring the time to reach the occlusion alarm at relatively low flow rates of 0.5–5.0 ml/h. Time to occlusion was longer with lower flow rates and shorter for higher flow rates, up to 117.3±9.4 min for 0.5 ml/h and 15.0±7.1 min for 5 ml/h (mean±SD). Syringe type had no statistically significant effect on the time to occlusion alarm [8]. Neff et al. [37] evaluated four syringe pumps at 1 ml/h for start-up times gravimetrically. Time to first fluid delivery and time to steady state (time between first fluid delivery and reaching the nominal flow rate) were evaluated. Significant differences were found between the syringe pumps. The times to first fluid delivery ranged from 0.3±0.1 to 1.1±0.8 min, and the times to steady state ranged from 6.0±3.1 to 11.1±4.3 min after eliminating the gap in the pump by giving a bolus first. When this bolus was not given, the time to first fluid delivery and the time to steady state were 57.2±28.6 and 76.3±29.0 min, respectively [37]. Neff et al. [38] also evaluated FASTSTART mode in the IVAC P7000 syringe pump (Alaris Medical Systems, Hampshire, UK) in a similar kind. FASTSTART delivers an intelligent bolus to lower start-up times. "FASTSTART significantly reduced time to first delivery and times to steady state in the unprimed syringe pump infusion System." The greatest improvement was obtained after priming the pump. The time to steady state was reduced by about 50% from 1.4±1.4 to 0.7±0.6 (mean±SD) min. The experiments were performed gravimetrically [38]. Sarraf and Mandel [43] performed a benchmark test for a specific syringe pump (Graseby 3400, Marcal Medical, Millersville, MD, USA) using a TRN001 isometric transducer (Kent Scientific,

Torrington, CT, USA). The isomeric transducer was used to measure a downwards force and was therefore able to measure the weight of water ejected from the syringe. "Start-up loss" was measured. Start-up loss was defined as the difference in mass measured after 25 s compared with an ideal, instantaneous, start-up curve. Results were presented as mean±SD. Sarraf and Mandel found "mass lost" between 29.8±1.31 and 937.7±32.36 mg, compared with the ideal curve, for nominal flow rates between 20 and 400 ml/h, respectively [43].

Miscellaneous infusion pump setups

Although the vast majority of the studies found were based on syringe or volumetric pumps in an intensive care setting, we found some studies evaluating the performance of less common types of infusion setups.

Pierce et al. [42] evaluated a drip chamber under specific conditions. Drip chambers monitor the flow rate of gravity driven volumetric pumps by counting and regulating drops, ideally independent from physical factors such as height or resistance. However, it was hypothesized that if the drip chamber was in a "wide open" condition, the drops can no longer be quantified and the physical factors start to influence the flow rate. Under "wide open" conditions, flow rate varied significantly as a result of changing the height of the infusion bag from 60 to 120 cm above the point of outflow. The flow rate increased with 61.2%±0.01% from 25.0±0.0 to 40.3±0.5 ml/min (mean±SD) for a 14-G catheter. This catheter had the largest diameter of the catheters tested. Catheter diameter size also influenced the flow rate significantly; the largest difference was 2.9-fold (95% CI, 2.84–2.96) between the 14-G and 22-G catheter when the pump was placed 120 cm above the point of outflow. It was not recommended to use gravity-driven pumps for administration of drugs that require accurate delivery such as vasoactive drugs [42]. Kawabata [16] tested the influence of temperature and viscosity on the time required to deliver the total volume of the infusion reservoir. Cancer treatment regimens were simulated, using actual cytostatic medication. Viscosity of the cytostatic medications was related to temperature. The pump evaluated was the SUREFUSER 23, which is a portable disposable infusion pump. The largest deviation was found for a total volume (volume to be delivered) of 250 ml, which was infused in 63 and 55 h for 25°C and 30°C, respectively [16]. Weiss et al. [55] tested a new microvolumetric infusion pump (MVIP) at a nominal flow rate of 0.5 ml/h against a conventional (Alaris Asena GH, IVAC Medical Systems, Hampshire, UK) syringe pump gravimetrically. Time to first fluid and time until achieving 95% of the steady state nominal flow rate value were assessed. Results were presented in mean±SD. Times to first fluid delivery were 10.5±4.1 and 10.8±4.0 s with a low mechanical compliance 20-ml and a 10-ml syringe, respectively, for the conventional pump. For the conventional pump, times until achieving steady state (95% of nominal flow) were 2.0±0.8 and 12.9±7.4 s for the 10- and 20-ml syringe. The fastest steady state start-up was 8.8±3.9 s for the MVIP. It was found that the novel MVIP concept showed to eliminate most of the problems during the initial start-up. In addition, most problems during steady state flow and vertical pump displacement were improved [55]. Capes et al. [5] investigated two pumps: the Graseby MS16A (Watford, UK) syringe driver and the spring driven Springfusor 30 (Go Medical Industries Pty. Ltd. Subiaco, Australia). These pumps were used for patient-controlled subcutaneous analgesia infusion. The percentage that the flow rate was within 20% of the nominal flow rate over 35 min was measured. This was 91.9% and 100% for the Graseby and Springfusor, respectively. The percentage within 5% of the nominal flow rate over 35 h resulted in 58.2±13.2% and 100% for the Graseby and Springfusor, respectively. However, the Sprinfusor deviated from +10% to -10% over 35 h in an almost linear fashion. Temperature had some effect on the Springfusor. The accuracy was 100% within the 20% of the nominal flow rate and 97.4±3.0 for 25°C and 30°C, respectively. Measurements were performed according to an adaptation of the Association for the Advancement of Medical Instrumentation, the International Organization for Standardization, and the International Electrotechnical Commission method [5]. Seo et al. [45] evaluated a wearable AIVD prototype using an infrared drip chamber measurement method. The device was able to deliver flow rates between 36 and 90 ml/h with <10% error [45]. Ilfeld et al. [14] tested six portable pumps for flow rate accuracy and consistency using a gravimetric setup. The pumps provided ±15% of the nominal rate for 18%–100% of their infusion duration. Increasing the temperature by steps of 4°C had different effects on the infusion rates for each model. However, generally, the flow rates increased for each model tested, with ranges from 0% to 33% flow rate increase [14]. Two benchmark studies investigating elastomeric pumps were found. Mohseni and Ebneshahidi [34] measured the flow rate accuracy after repeated use of 10 different elastomeric pumps (BOT-802, Nanchang Biotek Medical Device Company, Nanchang, China) because erroneous delivery times of analgesia were reported after repeated use of the same elastomeric pump. To simulate the repeated use, the same elastomeric pump was refilled and re-used three times. The flow rates were measured gravimetrically using a microset with 100-ml capacity. Significance of

evaporation was considered, and temperature was kept at body temperature. Elastomeric pumps tend to start higher than the nominal flow rate; this was also the case with the pumps evaluated in this study. At the start, the flow rate was about 6.75 ml/h, while the nominal flow rate was 5 ml/h. After about 4 h, the flow rate remained within 5.75 and 4.75 ml/h for the rest of the total infusion time of 20 h. This profile was similar after repeated use; therefore, it was concluded that repeated use of elastomeric pumps is safe [34]. Weisman et al. [51] evaluated five different elastomeric pumps for accuracy during a total infusion time of about 40–70 h, gravimetrically. The flow rates varied typically between -30% and +30% of the nominal flow rate for almost all of the pumps for the total infusion time. However, the ACTion pump AMBU Inc. (Glen Burnie, MA, USA) was the most accurate pump, as it infused within ±15% from the beginning to the end of investigation [51].

Theoretical modeling studies

We also found six studies that investigated flow rate variability theoretically. For Lovich et al. [27, 28], the reason for modeling was to formally investigate the effects of dead volume and carrier flow. Moreover, Lovich et al aimed to raise awareness that the dead volume is a "drug reservoir."

Lovich et al. [27] derived relatively simple mathematical models, a plug-flow model and a well-mixed model, to describe the flow of drugs within the dead volume. The model simulated two pumps, one carrier flow pump and one drug flow pump. In the plug-flow model, the drug and carrier flow mix instantaneously at the mixing point. In the well-mixed model, the mixture inside the dead volume is always uniform. The model was tested by measuring the concentration of a model drug using a spectrometric setup. The experimental data generally showed features of the plug-flow model as well as the well-mixed model. Lovich et al. stated that "[t]he models predict a lag in response time to changes in carrier or drug flow, which is proportional to the dead-volume and inversely related to the total flow rate." Increasing the carrier flow rate caused a temporary bolus [27]. Lovich et al. [28] also used a similar approach to investigate a specific clinical case, involving the infusion of phenylephrine as a model drug. However, the model developed was generic and describes the effects on the mass of drug delivered to the patient after flow rate interventions for any of the two pumps. Cutting off the carrier flow was found to reduce drug delivery profoundly. Moreover, after flow rate interventions disrupted the drug delivery, it was found that it took longer to reach the steady state flow rate with a large dead volume, slower carrier flow or larger stock-drug concentrations. Lovich et al. stated that "after a change in carrier flow or drug dosing, a significant lag is possible before drug delivery achieves steady state" [28]. Murphy and Wilcox [36] developed a mathematical model to conveniently alter infusion component parameters in order to study flow dynamics that would otherwise be difficult to observe in an *in vitro* situation. Murphy and Wilcox applied mechanical compliance and flow resistance. The model was compared to experimental results conducted in an earlier experiment, in which two syringe pumps were connected to a common central line. The end of the infusion line was occluded while the pumps continued to deliver fluid. This simulated the occlusion of a cannula, which may occur in clinical practice. The nominal flow rates were 10 and 1 ml/h. Although the line is occluded, "internal flow" was possible because of the mechanical compliance of the system, in which the excess fluid is accommodated for by the expanding compliant infusion components. After the occlusion was released, the expanded infusion components typically convert the excess fluid into a bolus until the pressure inside the system is balanced again. Mechanical compliance and resistance of the syringes and infusion lines were partly calculated and partly experimentally determined. A mechanical compliance of 0.8×10^{-11} m^3/Pa (0.8×10^{-8} l/Pa) was found for a representative 50-ml intensive care syringe pump with a Alaris 1.5-m extension line with an internal diameter of 1.5 mm (CareFusion, San Diego, CA, USA). After the infusion line was released, the experiment found a bolus of 0.8 ml, and the simulation model predicted 0.9 ml [36]. Jayanthi and Dabke [15] studied the effects of cannula length. IV cannulae had the following sizes: 14 G, 16 G, 18 G, and 20 G ("Venflon" Becton Dickinson, Helsingborg, Sweden). "Stitch cutter blades" (Swann Morton Ltd., Sheffield, UK) were used to shorten the cannulae. The 20-G cannula was 32 mm in length, the rest were 45 mm in length. Flow rates between approximately 90 and 400 ml/min were observed. Jayanthi and Dabke stated that "[m]athematical calculations performed using Hagen-Poiseuille's law predicted an increase of 40% in flow rates when the IV cannulae were shortened by 13 mm" [15]. However, *in vitro* measurement results showed an increase of only 4%–18%. Jayanthi and Dabke attributed the difference to turbulence. In-line air bubbles were stated as a possible cause for turbulence, although it was attempted to remove air bubbles. Measurements for the *in vitro* validation measurements were performed using an Urodyn 1000 flowmeter (Dantec, UK) [15]. Ma et al. [31] used the previously developed mathematical derivations of Lovich et al. [27, 28] to analyze "continuous intravenous infusions in pediatric anesthesia" [31]. The effects of "patient weight, infusion system dead volume, drug and carrier flow rates, along with drug stock concentration and dose, on

propofol and remifentanil delivery to the circulation" [31] were studied. A lag time related to dead volume and flow rate was found; the effects were the most prominent for neonates. The analysis showed the "potential importance of factors influencing drug delivery to the patient's circulation, focusing on propofol and remifentanil administration to small patients" [31]. Levine et al. [24] constructed low-pressure and high-pressure models and compared to two difference multi-lumen stets, TIVA three-way set with two anti-syphon valves and back-check valve (Cardinal Health, Dublin, OH, USA, product number 500-003 AMS) and the "Trifuse, 3 clave" (ICU Medical Inc., San Clemente, CA, USA, product number 011-C4290). The Cardinal consisted of three arms; the longest was 8 cm with an inner diameter of 1.68 mm. The ICU Medical also consisted of three arms of 18 cm length and an inner diameter of 1.19 mm. The experiments were performed with and without BD (BD Medical, Franklin Lakes, NJ, USA) Insyte IV cannulae (14 G, 16 G, 18 G, 20 G, and 22 G). The hypothesis was that according to the Poiseuille equation, narrow and long multi-lumen extensions would impede the flow rate. A pressurized infusion system was tested *in vitro* by measuring the different times of a certain amount of fluid to flow into an open burette. It was found that the flows were reduced using both multi-lumen extensions by maximally 76%; the effects were the most prominent for large cannulae. Moreover, Levine et al. [24] advised manufacturers to provide information on the diameters with their disposables.

Discussion

We found 53 studies of which six were theoretical modeling studies and 45 were *in vitro* measurement studies. From the measurement studies, the majority explicitly investigated a physical cause of either mechanical compliance, flow resistance, or dead volume. In the following subsections, we discuss the findings from the literature, focusing on the physical causes of flow rate variability, in the light of the four questions stated in the methods section.

Role of mechanical compliance, flow resistance, and dead volume in flow rate variability

Mechanical compliance and resistance were mostly investigated not only in relation to start-up of the flow rate [17, 39, 40, 43, 53, 56] but also in relation to a delayed occlusion alarm [8, 13, 18]. However, other effects affecting start-up times were also found. Lönnqvist et al. [26] attributed a bolus after vertical displacement of the pump to design flaws in syringe pumps. Mechanical compliance was not stated as a physical cause; instead, a gap between the plunger and the syringe driver was indicated as a source for the flow rate variability after vertical displacement. The disposables used were not specifically rigid, and the mechanical compliance of the disposables was not given either. It remains, therefore, unclear what fraction of the delay is contributed by the gap and what fraction is contributed by the mechanical compliance. However, Neff et al. [37] found a similar design problem with a pump using non-compliant disposables. Besides pump start-up and other flow rate changes, vertical displacement causes flow rate variability due the mechanical compliance in the system. It was generally found that an upward motion is followed by a bolus, i.e. a temporary flow rate increase, and downward motion is followed by reduced flow output [4, 17, 26, 39, 50, 52, 55].

Resistance accentuates the effects of mechanical compliance; Neff et al. [40] stated that a combination of resistance and mechanical compliance may prolong start-up times. This statement is supported by modeling studies that use the RC time as a measure for duration of the start-up effects, in which the RC time is the product of flow resistance R and mechanical compliance C [47]. Resistance is largely related to the diameter and the length of the infusion tubing. Especially vascular access devices such as catheters are resistant. For example, Angle et al. [1] measured the pressure using a pressure gauge for several peripherally inserted central catheter (PICC) lines. PICC lines are specific central venous vascular access devices. The flow rate was calculated according the Poiseuille law, with the assumption that the PICC lines were not significantly compliant. Angle et al. found that the inner diameter of the PICC line was related to the flow capacity. Resistance was specifically given for each PICC line [1]. Le Noel et al. [22] found that the actual flow rate in a fast peristaltic infusion pump was lower than the preset nominal flow rate using different catheters with different diameters. Resistance was explicitly stated as the cause [22]. Non-linear resistance occurs with several types of valves, used to prevent backflow. It has been shown that this causes flow rate variability, usually in the form of flow rate reduction or an additional delay in start-up time [7, 9, 11, 32, 50]. McCarroll et al. [32] explicitly recognized that the valves provided a high resistance to flow. However, the resistant effects of valves are non-linear, and the effects of valves on flow rate were not always recognized as resistance in all studies found.

Dead volume or internal volume was related to central infusion lines, manifold or the entire infusion set [7, 10, 20, 21, 23, 30, 35, 48]. Dead volume was also associated

with vascular access devices such as catheters [2, 29, 41]. Oualha et al. [41] found that the measured delay time due to dead volume was longer than the theoretical delay time. Oualha et al. attributed the difference to shear forces. It was also theorized that diffusion might be responsible [41]. However, it is unlikely that this has a significant impact, given the flow rate and fluid properties of the watery fluid as predicted by the number of Péclet. Moreover, other differences in the uniformity of the drug concentration in the dead volume, described earlier by Lovich et al. [27], may explain the differences found delay. Another possibility is that the compliance of the infusion setup plays a significant role. Modeling studies found that a combination of flow resistance and mechanical compliance may alter the flow rate onset. Therefore, this delay is superimposed with the dead volume effects [47]. If the setup becomes more complex, it is expected that it can still be simulated by a more advanced model incorporating mechanical compliance, flow resistance, and dead volume effects. This has been done to some extent [27, 28, 36].

Besides the major physical effects of mechanical compliance, resistance, and dead volume, turbulence in relation with air bubbles was mentioned as a possible source of flow rate variability [15]. However, in most infusion applications, the flows are too low. In these cases, the Reynolds number predicts that there will be no turbulence. Also temperature and viscosity of the infused liquid were found as factors influencing the flow rate [5, 14, 16, 22]. Large temperature changes and viscous medication are not common, at least on the intensive care, where critical medications are ordinarily used. The design flaws stated earlier [26, 37] are also an effect not directly related to mechanical compliance, resistance, or dead volume. However, design flaws such as gaps between the syringe drivers and the syringe have been improved in the newer models of syringe pumps. Furthermore, Sarraf and Mandel found that the start-up delays were correlated to flow rates in an asymptotic fashion, which is expected from the elastic stress/strain properties of the infusion material [43].

In summary, it is likely that mechanical compliance, resistance, and dead volume remain the most important physical causes of flow variability in infusion.

Components with the largest contribution to the system's mechanical compliance

Kim and Steward [18] found that the syringe was the most compliant component in a syringe infusion setup and stated that the largest portion of the mechanical compliance is located in the latex plunger of the syringe. We also found that syringes were the most important source of mechanical compliance [3, 47].

Some other sources of mechanical compliance were found too. Infusion lines were also stated as a source for mechanical compliance [43, 52] as well as air bubbles [6]. Besides the syringe, the infusion lines may also act as a reservoir for fluid after lowering the pump, which causes the flow rate to reduce. Weiss et al. demonstrated that some brands of infusion lines clearly contributed to the total mechanical compliance of the whole system after vertical displacement of the pump [52]. To what extent the infusion lines contribute to the entire system mechanical compliance as opposed to other components was not quantified. Air bubbles can be a relatively large source of mechanical compliance as well. However, we were not able to find a source about the regularity of significantly compliant in-line air bubbles in clinical practice. Furthermore, the pump itself was mentioned as a source of mechanical compliance [37]. Neff et al. also found that pump design caused significantly different flow rate variability during vertical displacements of several types of pumps with the same syringe [39]. Whether this was due to mechanical compliance in the syringe driver or another problem was not specifically stated. The start-up times obtained by Weiss et al., Neff et al., and Schmidt et al. [40, 44, 53, 56] for different syringes and syringe sizes were in correlation with the calculated mechanical compliance. Moreover, the mechanical compliance was closely related to the syringe plunger area [56]. However, it was also found that for some brands of syringes, the mechanical compliance was related to the filling volume. It was concluded that some syringe walls are also compliant. Nevertheless, Weiss et al. concluded that the plunger accounted for at least two-thirds of the mechanical compliance [53]. The correlations between syringe properties such as syringe size, plunger area, and flow rate onset time demonstrated that the syringe is the most probable source of mechanical compliance in syringe pump infusion systems. The mechanical compliance values varied from 9.0×10^{-9} to 2.1×10^{-8} l/Pa [3, 39, 53, 56]. It should be noted that the precise values of mechanical compliance that were presented are based on the entire infusion setup. However, as the syringe was found to be the most important source of mechanical compliance [18], syringes with similar volumes are eligible for inter-comparison between studies.

Theoretical models of infusion systems

We have presented the main purposes for developing theoretical models for infusion systems in the results.

In addition, Ma et al. [31] stated that managing continuous drug infusion requires not only an understanding of pharmacokinetics inside the patient. It also requires an understanding of the system delivering the drug into the bloodstream outside the patient. This can be accomplished by modeling. In our opinion, another reason, not stated in literature, can be that modeling studies are able to conveniently isolate, e.g. physical effects associated with mechanical compliance, from other physical effects. This is more difficult in *in vitro* laboratory experiments.

The studies from Lovich et al. [27, 28] and Ma et al. [31] describe a straight-forward description of the dead volume effect. However, an effort was made to accommodate for different mixing effects when drug flow mixes with carrier flow at the mixing point. A plug-flow model assumed that the drug and carrier flow mix perfectly at the mixing point and, subsequently, travel as a plug toward the patient. Conversely, a well-mixed model assumed that the concentration in the drug is uniform everywhere in the dead volume. The time required to reach steady state was three times longer in well-mixed model compared with the plug-flow model. It was found that the actual time required to reach steady state was between the boundaries defined by the plug-flow and well-mixed models [27]. It is also stated that carrier flows might introduce diffusion, for which the model was not able to accommodate. It remains controversial whether diffusion is actually a significant effect at the flow rates typically used on the intensive care or operation room. Another limitation of the model was that it was unable to account for variable carrier flow rates, while carrier pumps are often gravity-driven volumetric pumps, in which the flow rates fluctuate [27, 28]. Mechanical compliance and resistance of the infusion system were also not incorporated in the model used by Lovich et al. and Ma et al. [27, 28, 31]. It was shown that these effects do play a significant role in flow rate variability in infusion systems [47]. Conversely, Murphy and Wilcox [36] were able to simulate the flow rate variability due to the properties of mechanical compliance and resistance of the infusion setup but did not incorporate the dead volume effect. However, to simulate the actual resulting drug delivery of a clinically relevant infusion setup, the dead volume of the central infusion line and catheter has to be included in the model as well. The modeling studies found in this literature study typically considered a simplified two-pump multi-infusion situation. Although this makes the physical effects that were investigated comprehensible, in clinical practice, a multi-infusion setup usually consists of much more than two pumps. A model incorporating more than two pumps might therefore give useful insights in realistic clinical medication schedules.

Conclusions

In order to minimize the negative effects of flow rate variability, reduction of dead volume [27] and mechanical compliance [56] was recommended. However, this effect cannot be completely removed. First of all, the patient should be able to move. So some distance between the pump and the patient should be maintained, especially in the case of an incubator where the pumps are situated outside the incubator. Thus, there will always be some dead volume. Second, infusion lines should be flexible and therefore at least somewhat compliant. In case of completely rigid lines, vascular access devices such as catheters can easily be damaged as a result of movement. However, using more rigid and small syringes is recommended for very low flows of critical medications such as inotropics. Third, shared dead volume of a multi-infusion setup cannot be avoided in every case. The diameter of a vascular access device is limited because the size of blood vessels where the catheter is inserted is limited. This is especially evident in small children such as neonates. Lowering the volume of tubing by reducing the diameter increases the resistance [7, 29]. Consequently, flow resistance is inevitable.

The physical effects of mechanical compliance, resistance, and dead volume were recognized in the predominant majority of the studies found. Moreover, it was concluded that these physical effects are the principal causes of flow rate variability in infusion. Syringes were the most important source of mechanical compliance and, therefore, the principal cause of the delayed onset of flow rate and delayed occlusion alarm times.

Acknowledgments: The research leading to the results discussed in this report has received funding from the European Metrology Research Programme (EMRP). The EMRP is jointly funded by the EMRP participating countries within EURAMET (Grant/Award number: "EMRP REG NO. HLT07-REG1 MeDD") and the European Union.

References

[1] Angle JF, Matsumoto AH, Skalak TC, O'Brien RF, Hartwell GD, Tegtmeyer CJ. Flow characteristics of peripherally inserted central catheters. J Vasc Interv Radiol 1997; 8: 569–577.

[2] Bartels K, Moss DR, Peterfreund RA. An analysis of drug delivery dynamics via a pediatric central venous infusion system: quantification of delays in achieving intended doses. Anesth Analg 2009; 109: 1156–1161.

[3] Batista E, Almeida N, Furtado A, et al. Assessment of drug delivery devices. Biomed Eng-Biomed Tech 2015; 60: 347–357.

[4] Brotschi B, Grass B, Weiss M, Doell C, Bernet V. In-line filter included into the syringe infusion pump assembly reduces flow irregularities. Intensive Care Med 2012; 38: 518–522.
[5] Capes D, Martin K, Underwood R. Performance of a restrictive flow device and an electronic syringe driver for continuous subcutaneous infusion. J Pain Symptom Manage 1997; 14: 210–217.
[6] Davey C, Stather-Dunn T. Very small air bubbles (10–70 microl) cause clinically significant variability in syringe pump fluid delivery. J Med Eng Technol 2005; 29: 130–136.
[7] Décaudin B, Dewulf S, Lannoy D, et al. Impact of multiaccess infusion devices on in vitro drug delivery during multi-infusion therapy. Anesth Analg 2009; 109: 1147–1155.
[8] Dönmez A, Araz C, Kayhan Z. Syringe pumps take too long to give occlusion alarm. Paediatr Anaesth 2005; 15: 293–296.
[9] Ellger B, Kiski D, Diem E, et al. Non-return valves do not prevent backflow and bacterial contamination of intravenous infusions. J Hosp Infect 2011; 78: 31–35.
[10] Foinard A, Décaudin B, Barthelemy C, Debaene B, Odou P. Prevention of drug delivery disturbances during continuous intravenous infusion: an in vitro study on a new multi-lumen infusion access device. Ann Fr Anesth Reanim 2013; 32: e107–e112.
[11] Hall JM, Roberts FL. An investigation into the reduction in flow rate of intravenous fluid by antireflux valves. Anaesthesia 2005; 60: 797–800.
[12] Husch M, Sullivan C, Rooney D, et al. Insights from the sharp end of intravenous medication errors: implications for infusion pump technology. Qual Saf Health Care 2005; 14: 80–86.
[13] Ilan R, Fowler RA, Ferguson ND, et al. Prolonged time to alarm in infusion devices operated at low flow rates. Crit Care Med 2008; 36: 2763–2765.
[14] Ilfeld BM, Morey TE, Enneking FK. The delivery rate accuracy of portable infusion pumps used for continuous regional analgesia. Anesth Analg 2002; 95: 1331–1336.
[15] Jayanthi NV, Dabke HV. The effect of IV cannula length on the rate of infusion. Injury 2006; 37: 41–45.
[16] Kawabata Y. Effect of coefficient of viscosity and ambient temperature on the flow rate of drug solutions in infusion pumps. Pharm Dev Technol 2012; 17: 755–762.
[17] Kern H, Kuring A, Redlich U, et al. Downward movement of syringe pumps reduces syringe output. Br J Anaesth 2001; 86: 828–831.
[18] Kim DW, Steward DJ. The effect of syringe size on the performance of an infusion pump. Paediatr Anaesth 1999; 9: 335–337.
[19] Kim JY, Moon BK, Lee JH, Jo YY, Min SK. Impact of priming the infusion system on the performance of target-controlled infusion of remifentanil. Korean J Anesthesiol 2013; 64: 407–413.
[20] Lannoy D, Décaudin B, Dewulf S, et al. Infusion set characteristics such as antireflux valve and dead-space volume affect drug delivery: an experimental study designed to enhance infusion sets. Anesth Analg 2010; 111: 1427–1431.
[21] Lannoy D, Décaudin B, Simon N, Barthelemy C, Debaene B, Odou P. The impact on drug mass flow rate of interrupting and resuming carrier fluid flow: an in vitro study on a very low dead-space volume infusion set. Anesth Analg 2012; 114: 328–332.
[22] Le Noel A, Goffrais M, Almayrac A, Riou B, Langeron O, Raux M. Rapid infusion pump overestimates delivered flow during rapid vascular filling: a bench study. Eur J Emerg Med 2015.
[23] Levi DS, Peterson N, Shah SD, Rakholia B, Haught A, Carman G. Connecting multiple low-flow intravenous infusions in the newborn: problems and possible solutions. Pediatr Crit Care Med 2010; 11: 275–281.
[24] Levine DM, Garden AL, Truong HT, Bergemann J, Eames P. Influence of multi-lumen extensions on fluid flow through intravenous cannulae. Anaesthesia 2013; 68: 1239–1242.
[25] Liu D, Keijzers G. Do SmartSite antireflux valves limit the flow rate of 0.9% normal saline through intravenous cannulas? Eur J Emerg Med 2013; 20: 123–125.
[26] Lönnqvist PA, Lofqvist B. Design flaw can convert commercially available continuous syringe pumps to intermittent bolus injectors. Intensive Care Med 1997; 23: 998–1001.
[27] Lovich MA, Doles J, Peterfreund RA. The impact of carrier flow rate and infusion set dead-volume on the dynamics of intravenous drug delivery. Anesth Analg 2005; 100: 1048–1055.
[28] Lovich MA, Kinnealley ME, Sims NM, Peterfreund RA. The delivery of drugs to patients by continuous intravenous infusion: modeling predicts potential dose fluctuations depending on flow rates and infusion system dead volume. Anesth Analg 2006; 102: 1147–1153.
[29] Lovich MA, Peterfreund GL, Sims NM, Peterfreund RA. Central venous catheter infusions: a laboratory model shows large differences in drug delivery dynamics related to catheter dead volume. Crit Care Med 2007; 35: 2792–2798.
[30] Lovich MA, Wakim MG, Wei A, et al. Drug infusion system manifold dead-volume impacts the delivery response time to changes in infused medication doses in vitro and also in vivo in anesthetized swine. Anesth Analg 2013; 117: 1313–1318.
[31] Ma H, Lovich MA, Peterfreund RA. Quantitative analysis of continuous intravenous infusions in pediatric anesthesia: safety implications of dead volume, flow rates, and fluid delivery. Paediatr Anaesth 2011; 21: 78–86.
[32] McCarroll C, McAtamney D, Taylor R. Alteration in flow delivery with antisyphon devices. Anaesthesia 2000; 55: 355–357.
[33] Medlicott NJ, Reith DM, McCaffrey F, Krittaphol W, Broadbent RS. Delayed delivery of intravenous gentamicin in neonates: impact of infusion variables. J Pharm Pharmacol 2013; 65: 370–378.
[34] Mohseni M, Ebneshahidi A. The flow rate accuracy of elastomeric infusion pumps after repeated filling. Anesth Pain Med 2014; 4: e14989.
[35] Moss DR, Bartels K, Peterfreund GL, Lovich MA, Sims NM, Peterfreund RA. An in vitro analysis of central venous drug delivery by continuous infusion: the effect of manifold design and port selection. Anesth Analg 2009; 109: 1524–1529.
[36] Murphy RS, Wilcox SJ. The link between intravenous multiple pump flow errors and infusion system mechanical compliance. Anesth Analg 2010; 110: 1297–1302.
[37] Neff T, Fischer J, Fehr S, Baenziger O, Weiss M. Start-up delays of infusion syringe pumps. Paediatr Anaesth 2001; 11: 561–565.
[38] Neff T, Fischer J, Fehr S, Baenziger O, Weiss M. Evaluation of the FASTSTART mode for reducing start-up delay in syringe pump infusion systems. Swiss Med Wkly 2001; 131: 219–222.
[39] Neff TA, Fischer JE, Schulz G, Baenziger O, Weiss M. Infusion pump performance with vertical displacement: effect of syringe pump and assembly type. Intensive Care Med 2001; 27: 287–291.

[40] Neff SB, Neff TA, Gerber S, Weiss MM. Flow rate, syringe size and architecture are critical to start-up performance of syringe pumps. Eur J Anaesthesiol 2007; 24: 602–608.
[41] Oualha M, Capelo M, Spreux-Varoquaux O, et al. Delay and stability of central venous administration of norepinephrine in children: a bench study. Eur J Pediatr 2014; 173: 69–73.
[42] Pierce ET, Kumar V, Zheng H, Peterfreund RA. Medication and volume delivery by gravity-driven micro-drip intravenous infusion: potential variations during "wide-open" flow. Anesth Analg 2013; 116: 614–618.
[43] Sarraf E, Mandel JE. Time-delay when updating infusion rates in the Graseby 3400 pump results in reduced drug delivery. Anesth Analg 2014; 118: 145–150.
[44] Schmidt N, Saez C, Seri I, Maturana A. Impact of syringe size on the performance of infusion pumps at low flow rates. Pediatr Crit Care Med 2010; 11: 282–286.
[45] Seo WH, Cho KH, Loh BG. A wearable intravenous infusion device facilitating ambulation: a pre-clinical report. J Med Eng Technol 2014; 38: 42–48.
[46] Sherwin CM, Medlicott NJ, Reith DM, Broadbent RS. Intravenous drug delivery in neonates: lessons learnt. Arch Dis Child 2014; 99: 590–594.
[47] Timmerman AM, Snijder RA, Lucas P, Largerweij MC, Radermacher JH, Konings MK. How physical infusion system parameters cause clinically relevant dose deviations after setpoint changes. Biomed Eng-Biomed Tech 2015; 60: 365–376.
[48] Tsao AC, Lovich MA, Parker MJ, Zheng H, Peterfreund RA. Delivery interaction between co-infused medications: an in vitro modeling study of microinfusion. Paediatr Anaesth 2013; 23: 33–39.
[49] van der Eijk AC, van Rens RM, Dankelman J, Smit BJ. A literature review on flow-rate variability in neonatal IV therapy. Paediatr Anaesth 2013; 23: 9–21.
[50] van der Eijk AC, van der Plas AJ, van der Palen CJ, Dankelman J, Smit BJ. In vitro measurement of flow rate variability in neonatal IV therapy with and without the use of check valves. J Neonatal Perinatal Med 2014; 7: 55–64.
[51] Weisman RS, Missair A, Pham P, Gutierrez JF, Gebhard RE. Accuracy and consistency of modern elastomeric pumps. Reg Anesth Pain Med 2014; 39: 423–428.
[52] Weiss M, Banziger O, Neff T, Fanconi S. Influence of infusion line compliance on drug delivery rate during acute line loop formation. Intensive Care Med 2000; 26: 776–779.
[53] Weiss M, Fischer J, Neff T, Baenziger O. The effects of syringe plunger design on drug delivery during vertical displacement of syringe pumps. Anaesthesia 2000; 55: 1094–1098.
[54] Weiss M, Fischer JE, Neff T, Hug MI, Baenziger O. Always flush the sampling port before flushing the arterial cannula in pediatric patients. Acta Anaesthesiol Scand 2001; 45: 729–733.
[55] Weiss M, Gerber S, Fuchslin RM, Neff TA. Accurate continuous drug delivery at low infusion rate with a novel microvolumetric infusion pump (MVIP): pump design, evaluation and comparison to the current standard. Anaesthesia 2004; 59: 1133–1137.
[56] Weiss M, Hug MI, Neff T, Fischer J. Syringe size and flow rate affect drug delivery from syringe pumps. Can J Anaesth 2000; 47: 1031–1035.