An in vitro evaluation of infusion methods using a syringe pump to improve noradrenaline administration

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Conflict of interest
Stéphanie Genay, Bertrand Décaudin, Bertrand Debaene and Pascal Odou report receiving travel expense reimbursements from Doran International.

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Background: International guidelines recommend noradrenaline (NA) as the vasopressor of choice to treat septic shock. The aim of this study was to determine the best way to infuse patients with NA.
Methods: The in vitro study was designed to measure NA concentration at the end of each studied assembly line. Three infusion systems used the double pump method and three single pumps, which differed as regards NA concentrations (0,2 – 0,5 – 1 mg/h), dead space volume of the devices and the use of saline. Infusion systems were compared according to the time necessary to reach an NA mass flow rate steady-state plateau after the onset of infusion or after a flow change.
Results: Times were significantly different between the six methods for infusing NA. The system using the double syringe method with a standard extension set was the longest to reach the steady state after the onset of infusion [40.00 min (19.57 – 49.22)]. The steady-state plateau was obtained most rapidly with the double-syringe pump systems using very low dead-space volume extension sets and single-syringe pump systems containing diluted noradrenaline at the beginning of NA infusion.
Conclusion: A combination of a low dead-space volume extension set and a double pump method with a constant saline flow rate at 5 ml/h might be the solution to provide the most reliable NA infusion delivery.

Editorial comment: what this article tells us
Noradrenalin infusion is often the primary choice when a vasopressor is considered. Safety in administration may become an issue, in particular when there are multiple infusions and/or when high doses are given. Several infusion systems were assessed in this vitro study, and the authors advocate that a double pump system with low dead space is prospectively evaluated in the clinical setting.

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The recent update in 'Surviving Sepsis Campaign Guideline for the Management of Severe Sepsis and Septic Shock' reinforces the early quantitative resuscitation of the septic patient during the first 6 h and considers noradrenaline (NA) as the first choice vasopressor to obtain and maintain a mean arterial pressure (MAP) of over 65 mmHg.[1] In this context, NA must be infused to stabilise MAP rapidly. Infusion is usually continuous through a central venous catheter (CVC), preferentially on the proximal line of a double-lumen CVC, although no specific guidelines exist, and each intensive care unite (ICU) has to establish its own method using simultaneous saline infusion or not, a high concentration of NA with a slow infusion rate or a low concentration of NA with a high infusion rate and different infusion devices. Some infusion steps are particularly critical: infusion onset, syringe changeover, flow rate changes, weaning.[2–7]

Several in vitro studies have highlighted the existence of mass flow rate disturbances during these stages depending on the characteristics of the infusion line (anti-reflux valve and dead-space volume) but have not assessed the clinical implications of these results.[8–11] Our previous results highlighted the impact of the dead-space volume extension line when NA was concomitantly infused with saline, but only two current infusion systems (IS) were compared.[12,13]

This study was designed to assess the accuracy of NA delivery respecting administrative protocols and current ICU usage in French hospitals and to define methods to ensure the most reliable NA delivery.

Methods

Infusion systems are presented in Fig. 1.

The first series of experiments required connecting an NA syringe directly to a tube mimicking a CVC volume (16 gauge). Three concentrations of NA were evaluated: 0.2 mg/ml (IS1), 0.5 mg/ml (IS2) and 1.0 mg/ml (IS3).

The second series of experiments used NA at a common concentration of 0.5 mg/ml. Infusion was performed through a double syringe pump system with an NA syringe and a saline syringe as carrier. The different arrangements were:

- IS4: the NA syringe and saline syringe were both connected to a standard Y-extension set flushed with NA (Cair LGL, Civrieux d'azergues, France). Saline flow was adapted according to NA flow to obtain a sum of the two flow rates (NA and saline) always equal to 10 ml/h.
- IS5: the NA syringe and saline syringe were both connected to a very low dead-space volume Y-extension set (Edelvaiss-Vset + M, Doran International, Toussieu, France). Each line was flushed with its own fluid. The sum of the two flow rates was always equal to 10 ml/h.
- IS6: the NA syringe and saline syringe were both connected to a very low dead-space volume Y-extension set (Edelvaiss-Vset + M, Doran International, Toussieu, France). Each line was flushed with its own fluid. The saline flow rate was fixed at 5 ml/h.

Fifty-milliliter syringes (Beckton Dickinson, Le Pont-de-Claix, France) were filled with either 0.2, 0.5 or 1.0 mg/ml noradrenaline bitartrate (Noradrenaline, Aguettant, Lyon, France) diluted in saline (0.9% NaCl, Maco Pharma, Tourcoing, France) or with saline (as carrier). Both were infused together using syringe pumps (Pilote A2, Fresenius Vial, Brézins, France). The single-syringe pump systems were flushed with the NA solution and directly connected to the UV spectrophotometer. The double-syringe pump systems were connected either to a standard Y-extension set consisting of a stopcock placed on an extension set (Cair LGL, Civrieux d'azergues, France) flushed with 0.5 mg/ml noradrenaline, or to a very low dead-space volume set (Edelvaiss-Vset + M, Doran International, Toussieu, France) flushed with either NA or saline. Infusion lines were flushed using the purge function of syringe pumps.

Infusion parameters are described in Table 1. All experiments made use of a tubing system mimicking a CVC volume (16 gauge) added at the distal end of each infusion line. The infusion line egress was connected to a 10-mm flow-through UV spectrophotometer quartz cell (Suprasil, Hellma, Germany) to measure NA concentration continuously.

The analytic spectrophotometric UV method (UV 2450, Shimadzu, France) was validated using seven concentrations of between 6.25 and 200 μg/

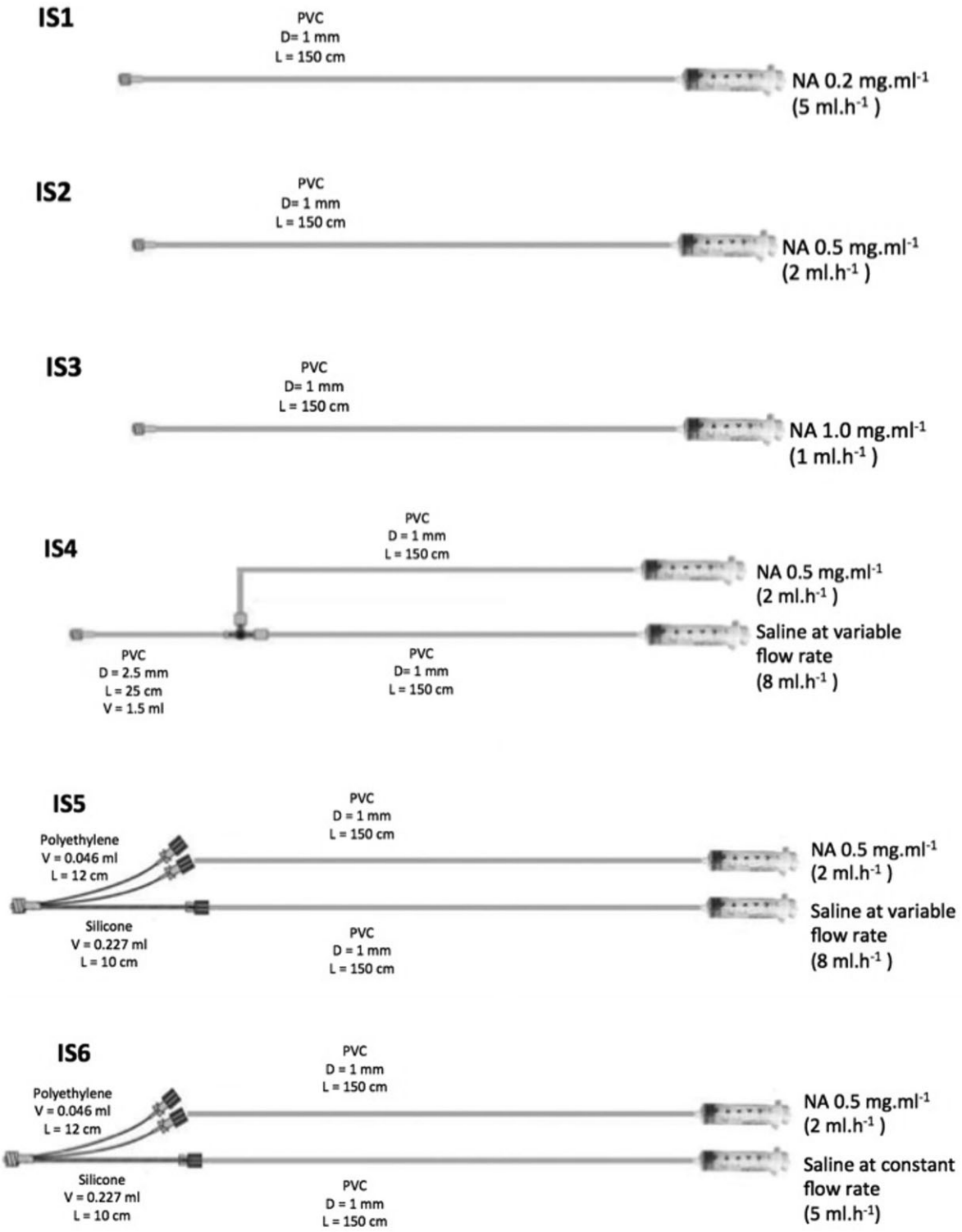

Fig. 1. Characteristics and design of the six studied noradrenaline infusion systems (IS).

Table 1 Infusion parameters.

Infusion system	Syringe pump	Concentration of NA solution	Saline flow rate	Y-extension sets characteristics
IS 1	Single syringe pump	0.2 mg/ml	No saline syringe	–
IS 2	Single syringe pump	0.5 mg/ml	No saline syringe	–
IS 3	Single syringe pump	1 mg/ml	No saline syringe	–
IS 4	Double syringe pump	0.5 mg/ml	Adapted according to NA flow rate*	L:25 cm, V:1.5 ml, PVC
IS 5	Double syringe pump	0.5 mg/ml	Adapted according to NA flow rate*	L:12 cm, V:0.046 ml, PE
IS 6	Double syringe pump	0.5 mg/ml	Fixed at 5 ml/h	L:12 cm, V:0.046 ml, PE

*So that the sum of the two flow rates was equal to 10 ml/h. IS, infusion system; L, length; V, volume; PVC, polyvinyl chloride; PE, polyethylene; NA, noradrenaline.

Table 2 In vitro flow changes protocol.

Time (s)			0–3500	3500–5000	5000–6500	6500–8000	8000–10000
Desired mass flow rate (mg/h)			1.00	1.25	1.50	1.25	1.00
IS 1	NA	**Flow rates (ml/h)**	5.00	6.00	7.50	6.00	5.00
IS 2	NA		2.00	2.50	3.00	2.50	2.00
IS 3	NA		1.00	1.20	1.50	1.20	1.00
IS 4 and IS 5	NA		2.00	2.50	3.00	2.50	2.00
	Saline		8.00	7.50	7.00	7.50	8.00
IS 6	NA		2.00	2.50	3.00	2.50	2.00
	Saline		5.00	5.00	5.00	5.00	5.00

NA, noradrenaline; IS, infusion system.

ml, prepared six times by two different operators. The total flow rate (saline flow plus NA flow) was checked using a flowmeter (Metron QA-IDS Metron Lagu, France). Drug mass flow rate (expressed as $\mu g.h^{-1}$) was calculated every second as the product of NA concentration against total flow rate. Ten experiments were completed for each system, with newly prepared NA and saline syringes.

NA infusion started at 1.0 mg/h with simultaneous saline infusion if necessary. Two 0.25 mg/h flow increases and two 0.25 mg/h flow decreases were initiated (Table 2). Infusion rates were altered four times: at 3500 s (58 min 33 s), at 5000 s (1 h 23 min 20 s), at 6500 s (1 h 48 min 20 s) and at 8000 s (2 h 13 min 20 s). Infusion was halted at 10,000 s (2 h 46 min 40 s).

Three different times were calculated as previously by Genay et al.[12] so that the six infusion systems could be compared:

1. T1 or the time from the moment when the syringe pump start button is pressed until a steady-state plateau is obtained at a mass flow rate of 1.0 mg/h. The steady state plateau was defined as the constant mass flow rate.
2. T2 or the time to reach the steady-state plateau after an increase in mass flow rate.
3. T3 or the time to reach the steady-state plateau after a decrease in mass flow rate.

Times to reach the steady-state plateau were compared with the Kruskal–Wallis test. In the presence of a significant P value ($P < 0.05$), an analysis using the Conover and Iman method was made to detect significant differences between couples of infusion methods. XLSTAT v2011.2.01 (Addinsoft, Paris, France) was used for data analysis. Results were expressed as median values (range) of time values (minutes : seconds). Data from the two flow increases was pooled to calculate the T2 median values as it was for flow decreases and T3.

Results

Times to reach the steady-state plateau from the moment the syringe pump start button was

Table 3 Times to reach the steady-state plateau after infusion onset (T1) and after two increases (T2) or decreases (T3) in flow rate (n = 10). Results are expressed as median values (min–max) of time values (minutes : seconds).

Time	IS 1	IS 2	IS 3	IS 4	IS 5	IS 6
T1	14:35 [12:50–18:10]	15:30 [13:40–19:50]	22:40† [8.20–27.20]	40:00* [19:57–49:22]	12:34 [6:34–17:33]	15:05 [10:01–22:29]
T2	11:25 [8:50–14:30]	10:00 [5:20–14:20]	11:25 [8:30–20:30]	14.31‡ [10:12–19:27]	9.29 [3:27–16:40]	8.03§ [2:33–13:52]
T3	11:45†† [7:00–15:10]	9:25 [7:40–15:50]	8:45 [6:20–13:10]	17.04¶ [12:13–21:36]	10.47** [4:49–15:14]	7.59 [3:28–10:45]

*Significant differences vs. IS1, IS2, IS3, IS5 and IS6 ($P < 0.0001$). †Significant differences vs. IS1 ($P < 0.001$), IS2 ($P = 0.001$), IS5 ($P < 0.0001$) and IS6 ($P = 0.009$). ‡Significant differences vs. IS2, IS5, IS6 ($P < 0.0001$), IS1 ($P = 0.02$) and IS3 ($P = 0.004$). §Significant differences vs. IS1 ($P < 0.001$) and IS3 ($P = 0.002$). ¶Significant differences vs. IS2, IS3, IS5, IS6 ($P < 0.0001$) and IS1 ($P = 0.0003$). **Significant difference vs. IS6 ($P = 0.007$). ††Significant differences vs. IS3 ($P = 0.027$) and IS6 ($P = 0.001$).

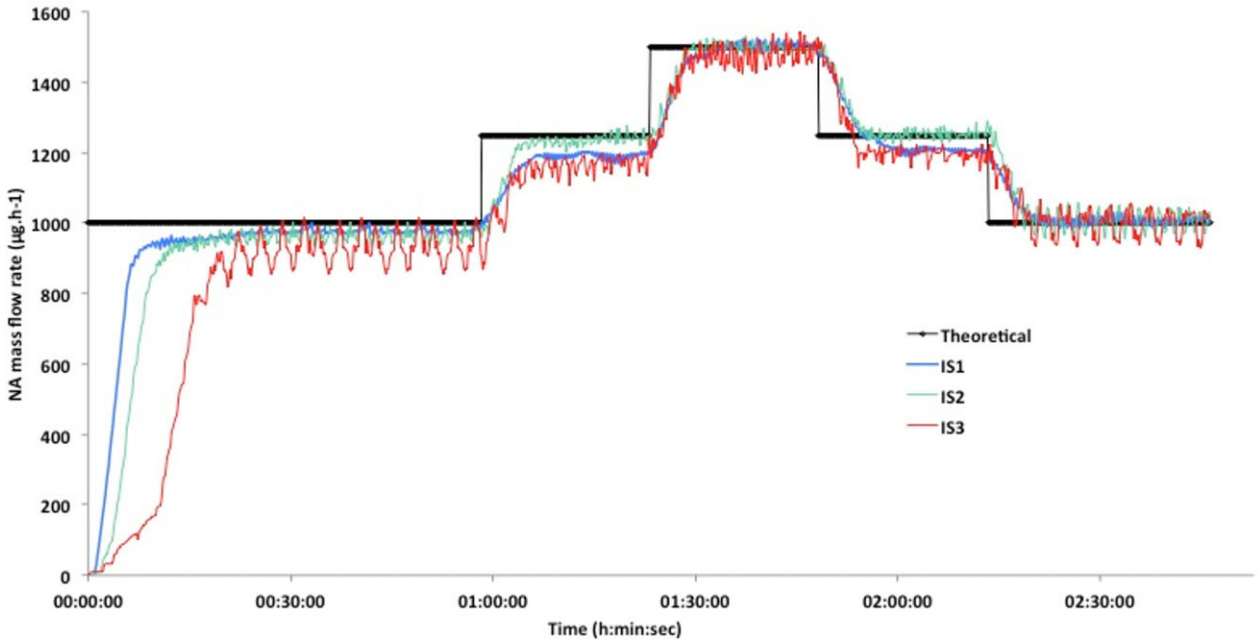

Fig. 2. Evolution of the noradrenaline mass flow rate according to the three single-syringe pump infusion systems (IS1 to IS3).

pressed (T1), after increases (T2) or decreases (T3) in flow rates were significantly different from one method to the other (Table 3). There was a high NA peak with the double-syringe infusion system using a standard Y-extension set (IS4), whereas this phenomenon was not observed with the five other systems. Figure 2 shows the evolution of the NA mass flow rate obtained with the three single syringe pump systems, and Fig. 3 with the three double-syringe pump systems. The peak lasted 34.53 ± 8.10 min with a maximum of 4.3 ± 0.1 mg/ml for a targeted mass flow rate of 1.0 mg/h. The double-syringe infusion system using a standard Y-extension set (IS4) was the longest to reach the mass flow rate steady-state plateau at the onset of infusion and at a flow increase or decrease.

The steady-state plateau was obtained most rapidly with the double-syringe pump systems using very low dead-space volume extension sets (IS5 and IS6) and single-syringe pump systems containing diluted noradrenaline (IS1 and IS2) at the beginning of NA infusion. There were significant differences after flow increases or decreases

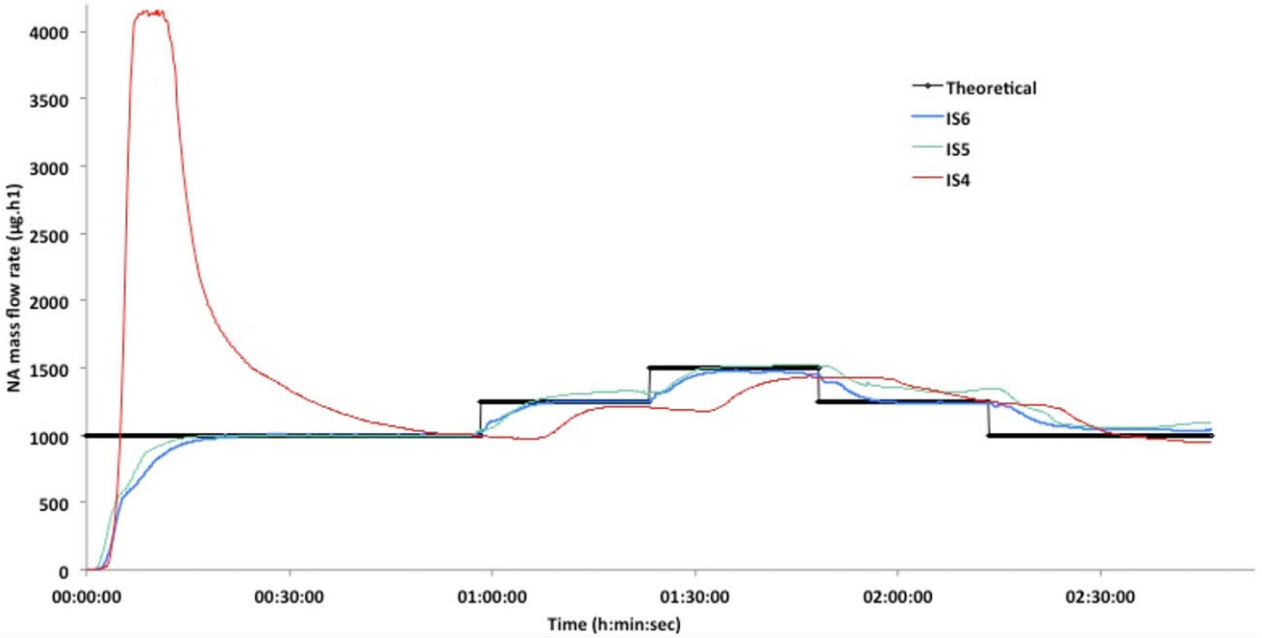

Fig. 3. Evolution of the noradrenaline mass flow rate according to the three double-syringe pump infusion systems (IS4 to IS6).

with the double-syringe pump system using a very low dead-space extension set vs. a standard Y-extension set.

Discussion

This in vitro study is the first to evaluate the main parameters of an NA infusion method on NA infusion accuracy: drug dilution, infusion system characteristics, use of a carrier. The first part of the study showed the impact of drug dilution on obtaining the expected drug delivery. The use of concentrated noradrenaline caused significant delays to reach the steady-state plateau from the beginning of infusion compared to the two other systems using more diluted noradrenaline. An NA dilution at 1 mg/ml causes infusion to be too slow. At very low flow rates (i.e. 1 ml/h for infusion system 3), the drug flow was not driven smoothly by the syringe pump, and instantaneous flow irregularities were noticeable. A single-syringe pump infusion system with diluted NA (0.2 or 0.5 mg/ml) appeared to be the best way to obtain satisfactory drug delivery. However, NA dilution means that NA syringes have to be changed frequently just as when patients require large daily doses. Such changeovers generate important haemodynamic disturbances,[3–6] which can be prevented by using smart pumps.[7] Intermediary dilution (0.5 mg/ml) seems therefore to be a good compromise between an inert infusion system and another which is difficult to manage. The double-syringe pump system may be a way to master NA delivery. We previously showed that extension set characteristics had a considerable impact on system reactivity.[9,12] Infusion of NA with a double-syringe pump using a very low dead-space volume infusion set means the steady state can be reached faster after infusion onset or change in flow rate. These results are in accordance with previous studies.[14] According to Lovich et al.,[8] the time to reach the steady state can be estimated, with the Plug-Flow and Well-Mixed models, to be approximately one to three times the ratio of dead-space volume to the sum of flow rates. Our previous works have demonstrated that the use of a very low dead-space volume infusion set with anti-reflux valve improves the accuracy of drug delivery. Lovich et al. have demonstrated that the architecture of an IV infusion system impacts the in vivo biological response to drug infusion.[15] There were substantial differences between the double pump infusion systems according to extension set. With the standard extension set, there was considerable NA bolus at the onset of infusion, due to the

initial NA flush. The dead space volume of the Y-extension set delayed the obtention of mass flow rate stabilisation after infusion onset. Another point to consider is the plastic material of the infusion device. Noradrenaline interacts with neither PVC nor PE. However, infusion line compliance, which differs between PE and PVC lines, affects syringe pump performance, especially flow rate variability.[16]

No difference was observed between the two double pump infusion systems with a very low dead-space volume infusion set. As a constant saline flow rate is more convenient than adapting saline flow to the rate of NA, this method seems highly suitable as fluid intakes are limited, while the benefits of a double pump system are retained.

There are however limitations to this study as our assessment considers only six different ways of infusing an NA solution frequently used in French ICUs. These methods use high concentrations of noradrenaline to reduce flow rate and consequently involve syringe changeovers when patients require large daily doses. As the use of high concentrations of noradrenaline is considered as hazardous by some practitioners, other methods exist using low concentrations of noradrenaline in bags infused by volumetric pump. Analysis of this study must take into account two main sources of variability. First, we worked on instantaneous flow rates, whereas manufacturer's data indicates a 5-min average flow rate. Second, we used a spectrophotometer flow cell with an internal volume of 390 µl. This internal volume affects the measured time required to reach the steady state in the cell, which may vary between one and three times the ratio of internal volume to the sum of flow rates.

This in vitro study confirms that physicians must consider infusion set characteristics when they decide to infuse patients with NA. In this context, when using a syringe pump, the combination of low dead-space volume and a double pump method with a constant saline flow rate at 5 ml/h provides the most reliable NA delivery. These results need to be confirmed by a randomised clinical trial.

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Authors' contributions

S. G.: Helped design the study, conducted the study, collected and analysed the data and wrote the manuscript.

B. Décaudin: Helped design the study, analysed the data and wrote the manuscript.

S. S.: Helped conduct the in vitro study.

C. B.: Helped design the study and prepared the manuscript.

B. Debaene: Helped design the study, conducted the study, analysed the data and wrote the manuscript.

G. L.: Helped design the study, conducted the study, analysed the data and wrote the manuscript.

P. O.: Helped design the study, analysed the data and wrote the manuscript.

References

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41: 580–637.
2. Ricard J, Martin Y, Botcherby C, Villard S, Kalinowski H, Blivet A, Dreyfuss D. Relais des catécholamines en réanimation. Réanimation 2011; 20: 138–42.
3. Arino M, Barrington JP, Morrison AL, Gillies D. Management of the changeover of inotrope infusions in children. Intensive Crit Care Nurs 2004; 20: 275–80.
4. Argaud L, Cour M, Martin O, Saint-Denis M, Ferry T, Goyatton A, Robert D. Changeovers of vasoactive drug infusion pumps: impact of a quality improvement program. Crit Care 2007; 11: R133.
5. Trim JC, Roe J. Practical considerations in the administration of intravenous vasoactive drugs in the critical care setting: the double pumping or piggyback technique – part one. Intensive Crit Care Nurs 2004; 20: 153–60.

6. De Barbieri I, Frigo AC, Zampieron A. Quick change versus double pump while changing the infusion of inotropes: an experimental study. Nurs Crit Care 2009; 14: 200–6.
7. Cour M, Hernu R, Bénet T, Robert JM, Regad D, Chabert B, Malatray A, Conrozier S, Serra P, Lassaigne M, Vanhems P, Argaud L. Benefits of smart pumps for automated changeovers of vasoactive drug infusion pumps: a quasi-experimental study. Br J Anaesth 2013; 111: 818–24.
8. 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: 1048–55.
9. Décaudin B, Dewulf S, Lannoy D, Simon N, Secq A, Barthélémy C, Debaene B, Odou P. Impact of multiaccess infusion devices on in vitro drug delivery during multi-infusion therapy. Anesth Analg 2009; 109: 1147–55.
10. Lannoy D, Décaudin B, Dewulf S, Simon N, Secq A, Barthélémy C, Debaene B, Odou P. Infusion set characteristics such as antireflux valve and dead-space volume affect drug delivery. Anesth Analg 2010; 111: 1427–31.
11. Lannoy D, Decaudin B, Simon N, Barthelemy C, Debaene B, Odou P. The impact on drug mass flow rate of interrupting and resuming carrier fluid flow. Anesth Analg 2012; 114: 328–32.
12. Genay S, Décaudin B, Ethgen S, Scoccia S, Pinturaud M, Barthélémy C, Lebuffe G, Odou P. Improving noradrenaline infusion technique. Anaesthesia 2013; 68: 647–8.
13. Ethgen S, Genay S, Décaudin B, Odou P, Lebuffe G. Major haemodynamic incident during continuous norepinephrine infusion: beware of the infusion line. An avoidable postoperative hypertensive peak? Ann Fr Anesth Reanim 2012; 31: 550–2.
14. Genay S, Décaudin B, Ethgen S, Barthélémy C, Odou P, Lebuffe G. Impact of noradrenaline infusion set on mean arterial pressure: a retrospective clinical study. Ann Fr Anesth Reanim 2013; 32: e159–62.
15. Lovich MA, Wakim MG, Wei A, Parker MJ, Maslov MY, Pezone MJ, Tsukada H, Peterfreund RA. 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: 1313–8.
16. Weiss M, Neff T, Gerber A, Fischer J. Impact of infusion line compliance on syringe pump performance. Paediatr Anaesth 2000; 10: 595–9.