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Minimising haemodynamic lability during changeover of syringes infusing norepinephrine in adult critical care patients: a multicentre randomised controlled trial

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Abstract

Background: Arterial pressure lability is common during the process of replacing syringes used for norepinephrine infusions in critically ill patients. It is unclear if there is an optimal approach to minimise arterial pressure instability during this procedures. We investigated whether 'double pumping' changeover (DPC) or automated changeover (AC) reduced blood pressure lability in critically ill adults compared with quick syringe changeover (QC).

Methods: Patients requiring a norepinephrine infusion syringe change were randomised in a non-blinded trial undertaken in six ICUs. Randomisation was minimised by norepinephrine flow rate at inclusion and centre. The primary outcome was the frequency of increased/decreased mean arterial pressure (defined by </>15 mm Hg from baseline measurements) within 15 min of switching the syringe compared with QC.

Results: Patients (mean age: 64 (range:18–88)) yr were randomly assigned to QC (n=95), DPC (n=95), or AC (n=96). Increased MAP was the commonest consequence of syringe changeovers. MAP variability was most frequent after DPC (89/224 changeovers; 39.7%) compared with 57/223 (25.6%) changeovers after quick syringe switch and 46/181 (25.4%) in patients randomised to receive automated changeover (P=0.001). Fewer events occurred with QC compared with DPC (P=0.002). Sensitivity analysis based on mixed models showed that performing several changeovers on a single patient had no impact. Both type of changeover and norepinephrine dose before syringe changeover were independently associated with MAP variations >15 mm Hg.

Conclusions: Quick changeover of norepinephrine syringes was associated with less blood pressure lability compared with DPC. The prevalence of MAP variations was the same between AC and QC.

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Keywords: blood pressure; changeover; critical care; critical care nursing; infusion pump; norepinephrine; shock; vasopressor

Editor's key points

- Blood pressure lability is associated with worse outcomes in critical illness.
- Replacing syringes required to infuse vasoactive agent may contribute to blood pressure lability.
- The optimal method of replacing syringes delivering vasoactive drugs in critically ill patients is unclear.
- In a randomised, controlled, open-label trial, the authors compared the effect of three methods of changing syringes required for infusing norepinephrine on blood pressure lability in critically ill subjects.
- Blood pressure lability was most frequent after 'double pumping' changeover, compared with a quick syringe switch or automated syringe changeover (relative risk: 1.93 [95% confidence intervals: 1.36–2.73]).

Norepinephrine is the first-line vasopressor agent used in patients with shock.[1–4] Because the half-life of norepinephrine is short,[5,6] syringes that deliver continuous infusions need to be replaced frequently.[6–8] Haemodynamic instability is frequent during syringe changeovers.[9–13] Three changeover approaches have been described.[6–16] The quick syringe changeover (QC) approach consists of a quick replacement of the nearly empty syringe with a full syringe. 'Double pumping' changeover (DPC) requires the brief use of two syringes in parallel. Automated syringe changeover (AC) uses 'smart' infusion technology that links two syringes.

In vitro AC efficiently maintains a constant norepinephrine infusion compared with QC,[17] which may result in less haemodynamic instability in patients.[10] However, previous studies have generated a mixed picture as to which syringe changeover procedure is most likely to contribute to a higher risk of haemodynamic instability in critically ill adults[9,12,13] and children.[14,15]

As these three changeover techniques have never been directly compared, we performed an RCT to compare the effect of the three changeover techniques on blood pressure variability in critically ill adult patients.

Methods

Trial design

We conducted a randomised, controlled, open-label trial between April 2015 and April 2017 in six ICUs in France registered at ClinicalTrials.gov (NCT02304939). The participating ICUs, the number of inclusions, the number of changeovers assessed and the reference changeover technique for each ICU are mentioned in the Supplementary material (Supplementary Table S1). The study protocol was approved by the leading human research ethics committee (Comité de Protection des Persones Ouest II). According to French law at this time, no formal written informed consent was required. The patients or their relatives were informed of the study details (orally and with a written document) and that withdrawing their participation could occur at any time.

Inclusion criteria

Critically ill patients in whom invasive arterial monitoring was necessary to guide norepinephrine therapy were eligible.

Exclusion criteria

Patients who were pregnant, <18 yr old, or receiving palliative care were ineligible.

Interventions

Normal local ICU practice is detailed in Supplementary material. Norepinephrine administration was standardised in the three arms. ICU nurses were trained to the standardised changeover procedures before the beginning of the study (Supplementary data). A randomisation computer-based system was used for allocation, minimised by centre and the norepinephrine infusion rate at inclusion ($\leq$or >0.5 μg kg^{-1} min^{-1}). After randomisation, but before first syringe changeover was required, a standardised infusion set-up was installed (Supplementary data and Supplementary Figure S1).

Patients were randomly assigned to one of three groups:

(i) QC: rapidly changing the nearly empty syringe with a full norepinephrine syringe
(ii) DPC: starting the norepinephrine full syringe before the nearly empty syringe ended (which requires a brief period of parallel infusions)
(iii) AC: using smart infusion pumps (Orchestra®; Fresenius Kabi, Bad Homburg, Germany)

Primary outcome

The primary outcome was the percentage of changeovers associated with at least one MAP variation >15 mm Hg in absolute value (increase or decrease) within the 15 min after the start of the changeover compared with the baseline MAP recorded once 1 min before the start of the changeover. In the absence of a "gold-standard" definition for significant MAP variation, an absolute change in MAP of 15 mm Hg was arbitrarily selected, as described in similar previous studies.[10,13]

Secondary outcomes

Two secondary outcomes were recorded:

(i) Number of syringe changeovers associated with at least one MAP increase >15 mm Hg
(ii) Adverse clinical events occurring during, and for 15 min after, the study procedure

Data collection

The MAP data from the first norepinephrine changeover after inclusion up to a maximum of four further changeovers were recorded. The MAP recordings were made 1 min before the start of the changeover, and then every minute during 15 min. Data were analysed offline by a study investigator masked to

group allocation. The nurse in charge of the patient recorded the changeover duration using a stopwatch timer.

Sample size estimation

The expected prevalence of changeovers with MAP variations >15 mm Hg was 25% in the QC arm,[10–13]. A reduction of 50% of this prevalence was clinically deemed to be relevant in the DPC and AC arms. The sample size calculation was performed using a global comparison test (χ^2 with two degrees of freedom; superiority analysis) and two *post hoc* pairwise comparisons (χ^2 with one degree of freedom) (to compare the incidence of MAP variations between DPC and QC, and between AC and QC). To avoid an alpha error inflation risk, a Bonferroni correction was used (P=0.017); 214 changeovers in each group corresponding to a total of 642 changeovers were therefore required (1-β=0.2; α=0.05).

Statistical analyses

Categorical data were described using numbers and percentages, and compared using χ^2 tests or Fisher's exact tests when required. Continuous data were described using mean (standard deviation) and compared using Kruskal–Wallis or analysis of variance (with *post hoc* pairwise comparisons by Bonferroni adjustment). Intention-to-treat analyses were performed.

As up to four syringe changeovers were permitted on a single patient, *post hoc* sensitivity analyses were performed using logistic mixed models to establish whether there was a correlation between repeated observations made in the same patient. For these models, the effect of the randomisation arm was studied, taking into account fixed effects (delay since randomisation; norepinephrine infusion rate before each changeover) and random effects (individual patients). For syringe changeovers associated with MAP increase/decrease >15 mm Hg, the numbers of patients with at least one MAP change and mean MAP changes were analysed. *Post hoc* analyses for norepinephrine infusion rate (</>0.5 μg kg^{-1} min^{-1}) at the beginning of the changeovers were also performed.

Results

Participant characteristics

Patients (286) were randomly assigned to either QC (n=95), AC (n=96), or DPC (n=95) (Table 1). In addition, 628/657 changeovers were analysed after missing data were excluded (Fig. 1). Other than the baseline norepinephrine infusion rate, the time until the first syringe change and baseline MAP were similar between each group (Table 2).

Primary outcome

MAP variability was most frequent after DPC (89/224 changeovers; 39.7%) compared with 57/223 (25.6%) changeovers after a quick syringe switch and 46/181 (25.4%) in patients randomised to receive ACs (P=0.001; Table 3, Supplementary Figure S2-a).

Secondary outcomes

Changeovers associated with at least one MAP decrease > 15 mm Hg: No significant difference was found between the three groups; Table 3, Supplementary figure S2-b.

Adverse clinical events

Reductions in MAP were more likely to require vasopressor support from ICU nurses (Supplementary Table S2).

Post hoc analyses

The sensitivity analysis showed that there were more MAP variations >15 mm Hg after a DPC compared with QC (P=0.009), but AC was similar to QC (P=0.932; Table 4;

Table 1 Patient characteristics. AC, automated changeover; DPC, double-pumping changeover; QC, quick syringe changeover; SAPS, Simplified Acute Physiology Score; SD, standard deviation; SOFA, sequential organ failure assessment.

Variable	QC (n=95)	DPC (n=95)	AC (n=96)	P-value
Age (yr), mean (range)	63.9 (18–88)	63.3 (27–88)	63.8 (22–87)	0.84
Male sex, n (%)	69 (72.6)	67 (70.5)	68 (70.8)	0.96
Weight (kg), mean (SD)	78.7 (17.8)	79.1 (20.0)	78.5 (18.0)	0.99
BMI (kg m^{-2}), mean (SD)	27.6 (5.4)	27.9 (7.1)	27.5 (6.3)	0.98
SAPS II, mean (SD)	60.5 (21.5)	58.9 (17.8)	56.3 (17.7)	0.54
SOFA score at inclusion, mean (SD)	11.1 (3.9)	10.5(3.7)	10.4 (3.5)	0.47
Norepinephrine dose at inclusion (μg kg^{-1} min^{-1}), mean (SD)	0.7 (0.8)	0.7 (0.7)	0.6 (0.5)	0.80
Norepinephrine indication				0.89
Haemodynamic instability after cardiac arrest, n (%)	10 (10.5)	12 (12.6)	10 (10.4)	
Haemorrhagic shock, n (%)	8 (8.4)	8 (8.4)	7 (7.3)	
Septic shock, n (%)	47 (49.5)	49 (51.6)	48 (50.0)	
Cardiogenic shock, n (%)	1 (1.1)	2 (2.1)	5 (5.2)	
Others, n (%)	28 (29.5)	23 (24.2)	25 (26.0)	
Missing date, n (%)	1 (1.1)	1 (1.1)	1 (1.1)	
Number of patients with				
0 changeover, n (%)	20 (21.1)	21 (22.1)	28 (29.2)	0.36
1 changeover, n (%)	16 (16.8)	12 (12.6)	14 (14.6)	0.71
2 changeovers, n (%)	7 (7.4)	12 (12.6)	13 (13.5)	0.35
3 changeovers, n (%)	6 (6.3)	8 (8.4)	11 (11.5)	0.45
4 changeovers, n (%)	46 (48.4)	42 (44.2)	30 (31.3)	0.04
ICU mortality, n (%)	31 (33.3)	32 (33.7)	37 (39.0)	0.68

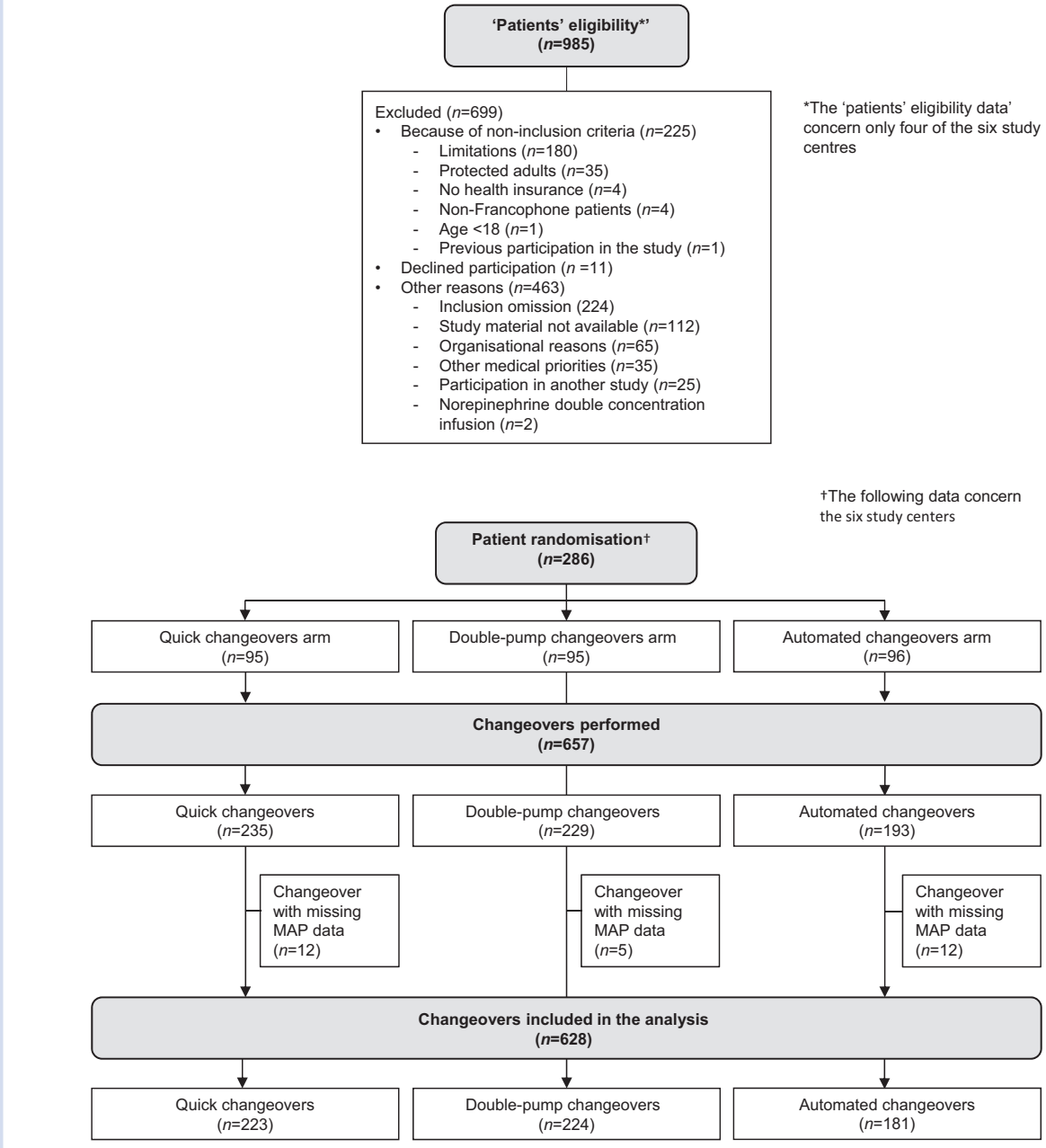

Fig 1. Study flow chart.

Supplementary data). Both study group allocation and norepinephrine flow rate at the beginning of the changeovers were independently associated with MAP variations >15 mm Hg (Table 4). The time between randomisation and the start of the changeovers was not associated with MAP variation >15 mm Hg (Table 4). Mean increases and decreases in MAP were similar for each syringe changeover arm (Supplementary Figure S3). MAP changes >15 mm Hg in relation to the norepinephrine infusion rate at the beginning of the syringe changeover were more frequent in patients randomised to DPC (Supplementary Table S3).

Discussion

This study is the first prospective RCT assessing the three most commonly used norepinephrine changeover techniques. According to previously published data,[9–13] significant MAP variations were frequent in the three study groups. Our results showed that MAP lability was more frequent after DPCs compared with QC. Increases in MAP after a syringe changeover were most common. In contrast to previous studies,[9,14,15] our results suggest that QC is superior compared with DPC, as there were more MAP deviations after DPC. However, AC and

Table 2 Syringe changeover characteristics. *P<0.05 compared with automated changeover (AC). †P<0.05 compared with quick syringe changeover (QC). SD, standard deviation.

	QC (n=235)	DPC (n=229)	AC (n=193)	P-value (Kruskal–Wallis)
Time between inclusion and first changeover (h), mean (SD)	6.1 (6.5)	9.3 (15.2)	7.3 (7.4)	0.324
MAP at baseline (mm Hg), mean (SD)	74.7 (13.3)	74.1 (12.5)	75.7 (12.4)	0.196
Norepinephrine infusion rate at the beginning of the changeovers (μg kg^{-1} min^{-1}), mean (SD)	1.07 (1.10)*	1.11 (1.14)	0.73 (0.63)†	0.001
Norepinephrine infusion rate at the beginning of the changeovers (ml h^{-1}), mean (SD)	1.37 (1.81)*	1.41 (1.45)	1.04 (2.09)†	0.001

Table 3 Numbers and percentages of changeovers with at least one mean arterial pressure variation >15 mm Hg in absolute value (increase or decrease), with at least one mean arterial pressure increase >15 mm Hg, and with at least one mean arterial pressure decrease >15 mm Hg. AC, automated changeover; DPC, double-pumping changeover; QC, quick syringe changeover. *P<0.05 compared with DPC. ‡P<0.05 compared with QC.

	QC	DPC	AC	P-value
Primary outcome				
Changeovers associated with at least one MAP variation >15 mm Hg in absolute (increase or decrease) value, *n* (%)	57 (25.6)*	89 (39.7)‡	46 (25.4)	0.001
Secondary outcomes				
Changeovers associated with at least one MAP increase >15 mm Hg, *n* (%)	24 (10.8)*	64 (28.6)‡	28 (15.5)	0.001
Changeovers associated with at least one MAP decrease >15 mm Hg, *n* (%)	39 (17.5)	33 (14.7)	25 (13.8)	0.56

Table 4 Sensitivity analysis (mixed model) to identify factors independently associated with MAP variation (increase or decrease) >15 mm Hg. Reference arm is the quick syringe changeover technique. CI, confidence interval.

Variable	Odds ratio (95% CI)	P-value
Double-pumping changeover	2.47 (1.23–4.95)	0.011
Automated changeover	0.8 (0.38–1.60)	0.557
Norepinephrine rate of infusion at the beginning of the changeover (μg kg^{-1} min^{-1})	0.64 (0.46–0.88)	0.006
Time between randomisation and the beginning of the changeover	1.00 (0.97–1.02)	0.645

QC were similar. Because DPC is still extensively used, our data provide clinically relevant, updated information on the optimal choice for syringe changeover.

We also found that declines in MAP >15 mm Hg were less likely to occur after AC and QC. Perhaps surprisingly, the time required for a syringe changeover was longer with AC rather than QC. This may be attributable to higher levels of vigilance by ICU nurses using the automated syringe system, given that smart pumps were not the standard of care in all the participating centres. Both the study arm and the norepinephrine flow rate at the beginning of the changeovers were independently associated with MAP lability. Although MAP increases may be expected in the presence of higher norepinephrine infusion rates, this has not been formally demonstrated before.

Our multicentre randomised controlled study has several strengths. Norepinephrine administration was standardised based on previous publications,[6,18–28] and the same infusion set-up was used in the three arms. Patient mortality in this study was representative of recently published data on patients with septic shock,[29] and therefore is generalisable. However, the following study limitations should also be noted. First, several changeovers were performed in many patients, which may have influenced our results. However, similar results were found when repeated changeovers in the same patients were taken into account. Second, despite randomisation taking into account the norepinephrine flow rate at inclusion, patients randomised to AC had higher norepinephrine requirements, which may have influenced our results. However, the clinical severity (assessed using the Simplified Acute Physiology Score II at ICU admission) in each arm was similar. In addition, a *post hoc* sensitivity analysis showed that both the study arm and the norepinephrine flow rate at the beginning of the changeovers were independently associated with the prevalence of MAP variations >15 mm Hg, suggesting that DPC remained independently associated with more frequent MAP lability. Greau and colleagues[13] also showed in a *post hoc* multivariate analysis that both the norepinephrine flow rate and the study arm were independently associated with the prevalence of significant haemodynamic events. Third, this study could not be blinded, which could contribute to selection bias. Fourth, it is also possible that other vasoactive drugs were administered in parallel to norepinephrine infusion, but the randomised design should

minimise this influence. Fifth, as HR variations were not recorded in our study, we cannot thus exclude an impact of the changeover techniques on HR. Sixth, our study was not designed to take into account various human factors, including previous working experience of nurses that could potentially have influenced how the changeovers were performed. Finally, our results are not generalisable to other delivery systems.

Conclusion

Our results show that QCs reduce blood pressure lability in critically ill adult patients requiring a continuous infusion of norepinephrine. The clinical impact of reducing the frequency of elevations in blood pressure during norepinephrine syringe changeovers remains to be determined.

Authors' contributions

Study design: LaP, CLR, J-FH, AM
Study coordination: LaP, CLR, LiP
Patient recruitment: CLR, MLB, LM, AG, YA, CH
Data collection: CLR, MLB, LM, AG, YA, CH
Data analysis: LaP, CLR, J-FH, LiP
Writing of paper: LaP, LiP, CLR, A-SR, J-FH, AM
Revising of final draft: all authors.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.06.041.

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