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► To cite this version:

Laurent Poiroux, Cyril Le Roy, Anne-Sylvie Ramelet, Méline Le Brazic, Leslie Messenger, et al.. Minimising haemodynamic lability during changeover of syringes infusing norepinephrine in adult critical care patients: a multicentre randomised controlled trial. *British Journal of Anaesthesia*, 2020, 125, pp.622 - 628. 10.1016/j.bja.2020.06.041 . hal-03491667

HAL Id: hal-03491667

<https://hal.science/hal-03491667>

Submitted on 21 Sep 2022

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Minimising haemodynamic disturbance during changeover of syringe pumps infusing norepinephrine in adult critical care patients: a multicentre randomized controlled trial.

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SHORT RUNNING TITLE: Norepinephrine changeovers impact blood pressure

ABSTRACT

Background Blood 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. We investigated whether “double-pumping” or automated changeover reduced blood pressure lability in critically ill adults, compared to a quick syringe changeover.

Methods Patients requiring a norepinephrine infusion syringe change were randomized in a non-blinded trial undertaken in six intensive care units. Randomization was minimised by norepinephrine flow rate at inclusion and centre. The primary

outcome was the frequency of increased/decreased mean arterial pressure (defined by \leq / \geq 15mmHg from baseline measurements) within 15 minutes of switching the syringe, compared to quick syringe changeover.

Results Patients (mean age: were randomly assigned to quick (n=95), “double-pumping” (n=95) or automated syringe changeover (n=96). Increased MAP was the commonest consequence of syringe changeovers. MAP variability was most frequent after “double-pumping” (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 changeovers ($p=0.001$). Less events occurred with quick syringe changeover compared to double-pumping ($p=0.002$). 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 mmHg.

Conclusions Quick-changeover of norepinephrine syringes was associated with blood pressure lability compared to double-pumping. The prevalence of MAP variations was the same between AC and quick syringe changeover.

KEYWORDS: Norepinephrine, changeover, infusion pump, blood pressure, critical care, critical care nursing

EDITORS KEYPOINTS

- 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 three methods of changing syringes required for infusing norepinephrine.
- Blood pressure variability was most frequent after “double-pumping”, compared to a quick syringe switch and automated syringe changeover (relative risk:1.93 (95% confidence intervals:1.36-2.73)).

INTRODUCTION

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. Hemodynamic instability is frequent during syringe changeovers ⁹⁻¹³. Three changeovers approaches have been described.⁶⁻¹⁶ The quick syringe changeover approach quickly replaces the nearly empty syringe with a full syringe. “Double-pumping” requires the brief use of two syringes in parallel. Automated syringe changeovers employ “smart” infusion technology that links two syringes.

In vitro, automated changeovers efficiently maintain a constant norepinephrine infusion compared to quick syringe changeovers,¹⁷ which may result in less haemodynamic instability in patients.¹⁰ However, observational 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 ^{12 9 13} and children. ^{14 15}

Since these three changeover techniques have never been directly compared, we performed a randomised controlled trial to compare the effect of the three changeover techniques on blood pressure variability in critically ill adult patients.

METHODS

Trial design

We conducted a randomized, controlled, open-label trial between April 2015 to April 2017 in six intensive care units (ICUs) in France registered with ClinicalTrials.gov (NCT02304939). The study protocol was approved by the leading human research ethics committee (Comité de Protection des Personnes 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).

The study was

Inclusion criteria

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

Exclusion criteria

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

Interventions

Normal local ICU practice is detailed in Supplementary Material. Norepinephrine administration was standardized in the 3 arms. ICU nurses were trained to the standardized changeover procedures before the beginning of the study (supplementary data). A randomization computer based system was used for allocation, minimised by centre and the norepinephrine infusion rate at inclusion (\leq or

>0.5µg kg min). After randomisation, but before first syringe changeover was required, a standardized infusion setup was installed (Supplementary data).

Patients were randomly assigned to one of three groups:

1. Quick-changeover: rapidly changing the nearly empty syringe with a full norepinephrine syringe.
2. Double-pumping: starting the norepinephrine full syringe before the nearly empty syringe ended (which requires a brief period of parallel infusions).
3. Automated changeover: 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 mmHg in absolute value (increase or decrease) within the 15 minutes following the start of the changeover, compared to the baseline MAP recorded once one minute before the start of the changeover. In the absence of a consensual definition for significant MAP variation, an absolute change in MAP of 15 mmHg, as described in similar previous studies.^{10 13}

Secondary outcomes

Two secondary outcomes were recorded.

1. Number of syringe changeovers associated with at least one MAP increase >15 mmHg
2. Adverse clinical events occurring during, and for 15 minutes after, the study procedure.

Data collection

MAP data from the first norepinephrine changeover after inclusion up to a maximum of four further changeovers were recorded. MAP recordings were made one minute before the start of the changeover and then every minute during 15 minutes. 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 mmHg was 25% after quick syringe changeovers,¹⁰⁻¹³ and predicted to be up to 50% in double-pump automated changeover arms. The sample size calculation was performed using a global comparison test (chi-square with 2 degrees of freedom, superiority analysis). Two post-hoc pairwise comparisons (chi-square with 1 degree of freedom) were then performed to compare the incidence of MAP variations between DPC and quick syringe changeover and between AC and quick syringe changeover. 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 required ($1-\beta=20\%$; $\alpha=0.05$).

Statistical analyses

Categorical data were described using numbers and percentages and compared using chi-square tests or Fisher exact tests when required. Continuous data were described using mean (standard deviation) and compared using Kruskal-Wallis or ANOVA (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 randomization arm was studied taking into account fixed effects (delay since randomization; norepinephrine infusion rate before each changeover) and random effects (individual patients). For syringe changeovers associated with MAP increase/decrease >15 mmHg, the number of patients with at least one MAP change and mean MAP changes were analysed. Post-hoc analyses for norepinephrine infusion rate ($\leq/ >0.5$ $\mu\text{g kg min}$) at the beginning of the changeovers were also performed.

RESULTS

Participant characteristics.

286 patients were randomly assigned to either quick (n=95), automated (n=96) or double-pump (n=95) syringe changeover (Table 1). 628/657 changeovers were analysed after missing data were excluded (Figure 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 “double-pumping” (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 changeovers (p=0.001; Table 3).

Secondary outcomes

Changeovers associated with at least one MAP increase >15 mmHg

“Double-pumping” was associated with more changeovers (n=64; 28.6%) associated with at least one MAP increase >15 mmHg, compared to changeovers after quick syringe switch 24 (10.8%) and automated changeovers (28 (15.5%); p=0.001; Table 3).

Adverse clinical events

Falls in MAP were more likely to require vasopressor support from ICU nurses (Supplementary data).

Post hoc analyses

Sensitivity analysis showed that there were more MAP variations >15 mmHg following double-pump compared to quick syringe changeover ($p=0.009$), but automated changeover was similar to quick syringe changeover ($p=0.932$; Table 4; supplementary data). Both study group allocation and norepinephrine flow rate at the beginning of the changeovers were independently associated with MAP variations >15 mmHg (Table 4). The time between randomization and the start of the changeovers was not associated with MAP variation >15 mmHg (Table 4). Mean increases and decreases in MAP were similar for each syringe changeover arm (supplementary data). MAP changes >15 mmHg in relation to the norepinephrine infusion rate at the beginning of the syringe changeover were more frequent in patients randomised to double-pump changeover (supplementary data).

DISCUSSION

This study is the first prospective randomized controlled trial assessing the three most commonly used norepinephrine changeover techniques. According to previously published data⁹⁻¹³ significant MAP variations were frequent in the three study groups. Our results showed that MAP lability was more frequent after double-pump syringe changes compared to quick syringe changeover. Increases in MAP after syringe changeover were most common. In contrast to previous studies^{9 14 15}, our results suggest that quick syringe changeover is superior to compared to double-pumping, since there were more MAP deviations after double-pumping. However, automated and quick syringe changeovers were similar. Because double-pumping is still extensively used, our data provide clinically relevant, updated information on the optimal choice for syringe changeover.

We also found that declines in $MAP > 15 \text{ mmHg}$ were less likely to occur after automated and quick syringe changeover. Perhaps surprisingly, the time required for syringe changeover was longer with automated rather than quick syringe changeover. 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 randomized controlled study has several strengths. norepinephrine administration was standardized based on previous publications^{6 18–28} and the same infusion setup was used in the three arms. Patient mortality in this study was representative of recently published data on septic shock patients,²⁹ and therefore generalisable. However, the following study limitations should also be noted. First, several changeovers were performed in many patients, which may influenced our results. However, similar results were found when repeated changeovers in the same patients were taken into account. Second, despite randomization taking into account the norepinephrine flow rate at inclusion, patients randomised to automated syringe changeover had higher norepinephrine requirements which may have influenced our results. However, the clinical severity (assessed using SAPS II score 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 >15mmHg, suggesting that double-pumping remained independently associated with more frequent MAP lability. Gréau et al¹³ 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 hemodynamic 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 heart rate variations were not recorded in our study, we cannot thus exclude an impact of the changeover techniques on heart rate. Sixth, our study was not

designed to take into account various human factors, including previous nurses' working experience 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 quick syringe changeovers 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.

DETAILS OF AUTHORS' CONTRIBUTIONS

Study design: LaP, CLR, JFH, 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, JFH, LiP

Writing paper: LaP, LiP CLR, SR, JFH, AM

Revising final draft: all authors.

ACKNOWLEDGMENTS

The authors would like to thank all the professionals of the Research department of the University Hospital of Angers who participated in the implementation and the conduct of this study. Special thanks to Marion Guyon and Jean-Baptiste Pelletier for their commitments throughout the CHIC project. We also thank Johanna Chupin for designing the study standardized setup displayed in Figure ESM-1.

DECLARATION OF INTERESTS

All authors have no conflict of interests to declare.

FUNDING

Grant awarded by the French Ministry of Health within the Programme Hospitalier de Recherche Infirmière et Paramédicale (PHRIP 2013)

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Table 1: Patient characteristics.

BMI: Body Mass Index. ICU: Intensive Care Unit. SAPS: Simplified Acute Physiology Score. SOFA: sequential organ failure assessment.

Variables	quick syringe changeover (n=95)	DPC (n=95)	AC (n=96)	p value
Age (years), mean (range)	63.9 (18-88)	63.3 (27-88)	63.8 (22-87)	0.84
Male gender, 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 ($\mu\text{g kg}^{-1} \text{min}^{-1}$), mean (SD)	0.7 (0.8)	0.7 (0.7)	0.6 (0.5)	0.80
Norepinephrine indication:				0.89
- Hemodynamic instability after cardiac arrest, n (%)	10 (10.5)	12 (12.6)	10 (10.4)	
- Hemorrhagic 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

Table 2: Syringe changeover characteristics.

a: $p < 0.05$ compared to AC. b: $p < 0.05$ compared to quick syringe changeover. c: $p < 0.05$ compared to DPC .

	quick syringe changeover (n=235)	DPC (n=229)	AC (n=193)	p value (Kruskal- Wallis)
Time between inclusion and first changeover (hour), mean (SD)	6.1 (6.5)	9.3 (15.2)	7.3 (7.4)	$p = 0.324$
MAP at baseline (mm Hg), mean (SD)	74.7 (13.3)	74.1 (12.5)	75.7 (12.4)	$p = 0.196$
Norepinephrine infusion rate at the beginning of the changeovers ($\mu\text{g kg}^{-1}$ min^{-1}), mean (SD)	1.07 (1.10) ^a	1.11 (1.14)	0.73 (0.63) ^b	$p = 0.001$
Norepinephrine infusion rate at the beginning of the changeovers (mL h^{-1}), mean (SD)	1.37 (1.81) ^a	1.41 (1.45)	1.04 (2.09) ^b	$p = 0.001$

Table 3: Numbers and percentages of changeovers with at least one mean arterial pressure variations > 15 mmHg in absolute value (increase or decrease), with at least one mean arterial pressure increases > 15 mmHg and with at least one mean arterial pressure decreases > 15 mmHg.

QC: quick syringe changeover, DPC: double pump changeover, AC: automated changeover. a: $p < 0.05$ compared to DPC. b: $p < 0.05$ compared to AC. c: $p < 0.05$ compared to quick syringe changeover.

	QC	DPC	AC	P value
Primary outcome				
Changeovers associated with at least one MAP variations >15 mmHg in absolute (increase or decrease) value, n (%)	57 (25.6) ^a	89 (39.7) ^c	46 (25.4)	$p=0.001$
Secondary outcomes				
Changeovers associated with at least one MAP increases >15 mmHg, n (%)	24 (10.8) ^a	64 (28.6) ^c	28 (15.5)	$p=0.001$
Changeovers associated with at least one MAP decreases >15 mmHg, n (%)	39 (17.5)	33 (14.7)	25 (13.8)	$p=0.001$

Table 4: Sensitivity analysis (mixed model) to identify factors independently associated with MAP variation (increase or decrease) >15 mmHg. Reference arm is the quick syringe changeover technique.

Variables	Odd ratio [95% CI]	p value
Double pump 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 ($\mu\text{g kg}^{-1} \text{min}^{-1}$)	0.64 [0.46-0.88]	0.006
Time between randomization and the beginning of the changeover	1.00 [0.97-1.02]	0.645

LEGENDS TO FIGURES

Figure 1: Study flowchart

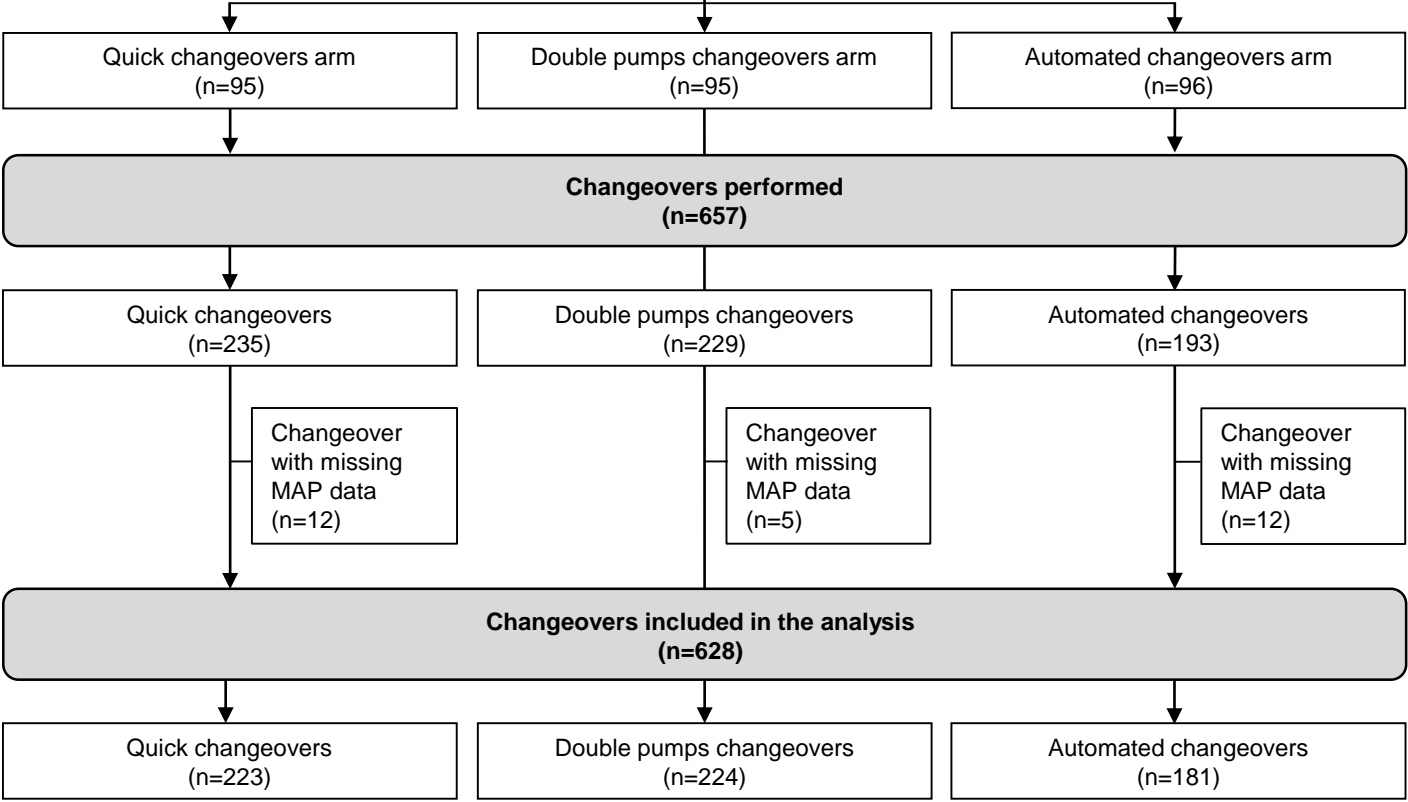
**Patients eligibility *
(n=985)**

- Excluded (n=699)
- Due to non-inclusion criteria (n=225)
 - Limitations (n=180)
 - Protected adults (n=35)
 - No health insurance (n=4)
 - Non-Francophone patients (n=4)
 - Age <18 (n=1)
 - Previous participation in the study (n=1)
 - Declined participation (n=11)
 - Other reasons (n=463)
 - Inclusion omission (224)
 - Study material not available (n=112)
 - Organizational reasons (n=65)
 - Other medical priorities (n=35)
 - Participation in another study (n=25)
 - Norepinephrine double concentration infusion (n=2)

* The patients eligibility data concern only 4 of the 6 study centers

**Patients randomization †
(n=286)**

† The following data concern the 6 study centers



Variables	QC (n=95)	DPC (n=95)	AC (n=96)	p value
Age (years), mean (range)	63.9 (18-88)	63.3 (27-88)	63.8 (22-87)	0.84
Male gender, 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
NE dose at inclusion ($\mu\text{g kg}^{-1} \text{min}^{-1}$), mean (SD)	0.7 (0.8)	0.7 (0.7)	0.6 (0.5)	0.80
NE indication:				0.89
- Hemodynamic instability after cardiac arrest, n (%)	10 (10.5)	12 (12.6)	10 (10.4)	
- Hemorrhagic 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

Table 1: Patients' characteristics and ICU mortality. BMI: Body Mass Index. ICU: Intensive Care Unit. NE: norepinephrine. SAPS: Simplified Acute Physiology Score. SOFA: sequential organ failure assessment.

	QC (n=235)	DPC (n=229)	AC (n=193)	p value (Kruskal- Wallis)
Time between inclusion and first changeover (hour), mean (SD)	6.1 (6.5)	9.3 (15.2)	7.3 (7.4)	p =0,324
MAP at baseline (mm Hg), mean (SD)	74.7 (13.3)	74.1 (12.5)	75.7 (12.4)	p=0.196
NE infusion rate at the beginning of the changeovers ($\mu\text{g kg}^{-1} \text{ min}^{-1}$), mean (SD)	1.07 (1.10) ^a	1.11 (1.14)	0.73 (0.63) ^b	p=0.001
NE infusion rate at the beginning of the changeovers (mL h^{-1}), mean (SD)	1.37 (1.81) ^a	1.41 (1.45)	1.04 (2.09) ^b	p=0.001

Table 2: Changeovers characteristics. NE: norepinephrine. a: $p < 0.05$ compared to AC. b: $p < 0.05$ compared to QC. c: $p < 0.05$ compared to DPC . Differences between DPC and AC were not tested (not planned).

	QC	DPC	AC	Global p value
Primary outcome				
Changeovers associated with at least one MAP variations >15 mmHg in absolute (increase or decrease) value, n (%)	57 (25.6) ^a	89 (39.7) ^c	46 (25.4)	p=0.001
Secondary outcomes				
Changeovers associated with at least one MAP increases >15 mmHg, n (%)	24 (10.8) ^a	64 (28.6) ^c	28 (15.5)	p=0.001
Changeovers associated with at least one MAP decreases >15 mmHg, n (%)	39 (17.5)	33 (14.7)	25 (13.8)	p=0.001

Table 3: Numbers and percentages of changeovers with at least one mean arterial pressure variations > 15 mmHg in absolute value (increase or decrease), with at least one mean arterial pressure increases > 15 mmHg and with at least one mean arterial pressure decreases > 15 mmHg. QC: quick changeover, DPC: double pump changeover, AC: automated changeover. a: p<0.05 compared to DPC. b: p<0.05 compared to AC. c: p<0.05 compared to QC. Differences between DPC and AC were not tested (not planned).

Variables	Odd ratio [95% CI]	p value
Double pump changeover	2.47 [1.23;4.95]	0.011
Automated changeover	0.8 [0.38;1.60]	0.557
NE rate of infusion at the beginning of the changeover ($\mu\text{g kg}^{-1} \text{min}^{-1}$)	0.64 [0.46;0.88]	0.006
Time between randomization and the beginning of the changeover	1.00 [0.97;1.02]	0.645

Table 4: Sensitivity analysis (mixed model) to identify factors independently associated with MAP variation (increase or decrease) >15 mmHg. Reference arm is the quick changeover technique.