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Original Article

High Versus Normal Blood Pressure Targets in Relation to Right Ventricular Dysfunction After Cardiac Surgery: A Randomized Controlled Trial

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Objective: Management of right ventricular (RV) dysfunction is challenging. Current practice predominantly is based on data from experimental and small uncontrolled studies and includes augmentation of blood pressure. However, whether such intervention is effective in the clinical setting of cardiac surgery is unknown.
Design: Randomized controlled trial.
Setting: Single-center study in a tertiary teaching hospital.
Participants: The study comprised 78 patients equipped with a pulmonary artery catheter (PAC), classified according to PAC-derived RV ejection fraction (RVEF); 44 patients had an RVEF of <20%, and 34 patients had an RVEF between ≥20% and <30%.
Interventions: Patients randomly were assigned to either a normal target group (mean arterial pressure 65 mmHg) or a high target group [mean arterial pressure 85 mmHg]). The primary end- point was the change in RVEF over a one-hour study period.
Measurements and Main Results: There was no significant between-group difference in change of RVEF <20% (−1% [−3.3 to 1.8] in the normal-target group *v* 0.5% [−1 to 4] in the high-target group; p = 0.159). There was no significant between-group difference in change in RVEF 20%-to-30% (−1% [−3 to 0] in the normal-target group *v* 1% [−1 to 3] in the high-target group; p = 0.074). These results were in line with the simultaneous observation that echocardiographic variables of RV and left ventricular function also remained unaltered over time, irrespective of either baseline RVEF or treatment protocol.
Conclusion: In a mixed cardiac surgery population with RV dysfunction, norepinephrine-mediated high blood pressure targets did not result in an increase in PAC-derived RVEF compared with normal blood pressure targets.

Key Words: bloodpressure targets; right ventricular dysfunction; pulmonary artery catheter; transesophageal echocardiography; cardiac surgery

RIGHT VENTRICULAR (RV) impairment has been an underestimated clinical entity. Recent studies have shown that RV dysfunction is associated with low-cardiac-output syndrome[1,2] and increased mortality in a variety of clinical settings, including sepsis,[3] cardiac arrest,[4] and after cardiac surgery,[5] thus highlighting its importance. Because RV dysfunction generally responds poorly to treatment, managing these patients is challenging.

The right and left ventricles share the interventricular septum, muscle fibers, and the pericardium.[6] In combination with a high pericardial resistance to distention, this results in a substantial ventricular interdependence. Volume or pressure loading of the right ventricle can cause a septal shift leftwards into the left ventricle, resulting in diminished left ventricular (LV)

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filling.[7-12] Commonly, this septal shift is caused by the dilated right ventricle with a supranormal RV systolic pressure, in combination with a decreased LV systolic pressure, which alters the transseptal gradient (TSG) and, hence, movement of the septum to the left.[13] In addition, high RV pressures result in a diminished RV coronary perfusion because of altered filling, high RV wall tension, and low systemic blood pressure.[14,15] Alternatively, volume overload in the absence of elevated RV pressures may cause a diastolic septal shift toward the left ventricle, but the septal shape normalizes in systole.

One of the cornerstones of the treatment of acute RV dysfunction or failure is the reestablishment of the TSG by increasing systemic aortic pressure and, thus, the subsequent LV pressure.[13,16-19] Animal experiments have shown that vasoconstriction by banding of the aorta can be helpful in order to shift the septum back into place and to restore flow in the right coronary artery.[20,21] Because aortic banding is not feasible in the clinical setting, stimulation of α-receptors by vasoactive drugs seems to be a clinically applicable alternative.[20,22] In addition, higher blood pressures will increase RV coronary perfusion, and this might be beneficial if compromised. Furthermore, a direct inotropic effect of norepinephrine (NE) on the right ventricle is conceivable.

This current practice predominantly is based on data from small, often uncontrolled, experimental studies. However, whether such intervention is effective in the clinical setting of cardiac surgery is unknown. In the present randomized controlled trial, NE-mediated effect of high versus normal blood pressure targets on RV function in post-cardiac surgery patients with a low (<20%) or moderate (20%-30%) RV ejection fraction (RVEF) was studied. The authors hypothesized that a higher blood pressure would improve RV function in this setting.

Material and Methods

Study Design

The study was performed between April 2019 and June 2020 and was designed as a single-center, single-blinded, randomized controlled trial. Written informed consent was obtained from all eligible patients before surgery. The study complied with the Declaration of Helsinki and was approved by a local ethical and scientific committee (Regionale Toetsingscommissie Patiëntgebonden Onderzoek Leeuwarden, WMO 1051). The study was registered with ClinicalTrials.gov (NCT03806582).

Study Population

According to local protocol, all patients scheduled for heart valve surgery were equipped with a pulmonary artery catheter (PAC) after induction of anesthesia. Patients ≥18 years old with a PAC in place after full sternotomy cardiac surgery were eligible and included in the study within the first postoperative hour in the intensive care unit (ICU) in case of a postoperative RVEF <30% in combination with a mean arterial pressure (MAP) of ≤65 mmHg. Exclusion criteria were emergency surgery, off-pump surgery, allergy to (an ingredient of) NE, chronic use of α-blocking medication, severe tricuspid insufficiency (preoperative or postoperative), severe hypertrophic left ventricle with (a high risk of) systolic anterior movement of the mitral valve, absence of a regular rhythm, or surgical reasons to maintain normal blood pressure targets.

After arrival in the ICU, eligible patients were classified into the following two groups: patients with a low RVEF (<20%) and patients with moderate RVEF (between 20% and 30%). This classification was based on the RVEF as measured by the PAC in the first hour after arrival in the ICU. Such classification was based on the authors' previous work in the postoperative cardiac surgery setting, in which an RVEF >30% was considered normal.[5] In each group, patients were assigned randomly to either a normal-target blood pressure (MAP 65 mmHg) group or a high-target blood pressure (MAP 85 mmHg) group (Fig 1). Allocation concealment was executed in blocks of six patients.

Protocol and Study Treatment

After induction of anesthesia in the operating room, but before sternal opening, deep transgastric measurements of the right ventricle were obtained from every patient by the attending cardiac anesthesiologist (tricuspid annular systolic plane excursion [TAPSE] by M-mode and pulsed-wave tissue Doppler imaging [PW TDI]). Postoperative transesophageal echocardiography (TEE) image acquisition in the ICU was obtained by a single dedicated echocardiographer using the Philips IE33 transesophageal echocardiography system (Philips Medical Systems; Amsterdam, The Netherlands) with an X7-2t TEE probe (Philips Medical Systems). Images were recorded, and offline analysis was performed by an observer who was unaware of treatment allocation or hemodynamic status. All images were analyzed using Philips IntelliSpace Cardiovascular 2.3 software. Measurements were obtained in the midesophageal two- and four-chamber, transgastric, and modified deep transgastric views. RV parameters were measured in the modified deep transgastric position (0 degrees) and included TAPSE by M-mode and PW TDI as follows: peak systolic annular velocity (S'), early diastolic myocardial relaxation (E'), and active atrial contraction in late diastole (A'). The myocardial performance index, as a global index of myocardial function, was measured with PW TDI. LV parameters included LV ejection fraction by Simpson's method; TDI mitral annulus motion (ie, S', E', and A'); and transmitral PW Doppler flow (E and A waves).

After surgery, all patients were admitted to the ICU and remained on mechanical ventilation during the direct postoperative phase. Patients were sedated with propofol and fentanyl. Settings of mechanical ventilation were standardized, with a respiratory frequency of 20-to-25 times per minute, tidal volumes limited up to 6 mL/kg ideal bodyweight, and a postoperative end-expiratory pressure of 10 cmH_2O. Patients were extubated within three hours of ICU admission if

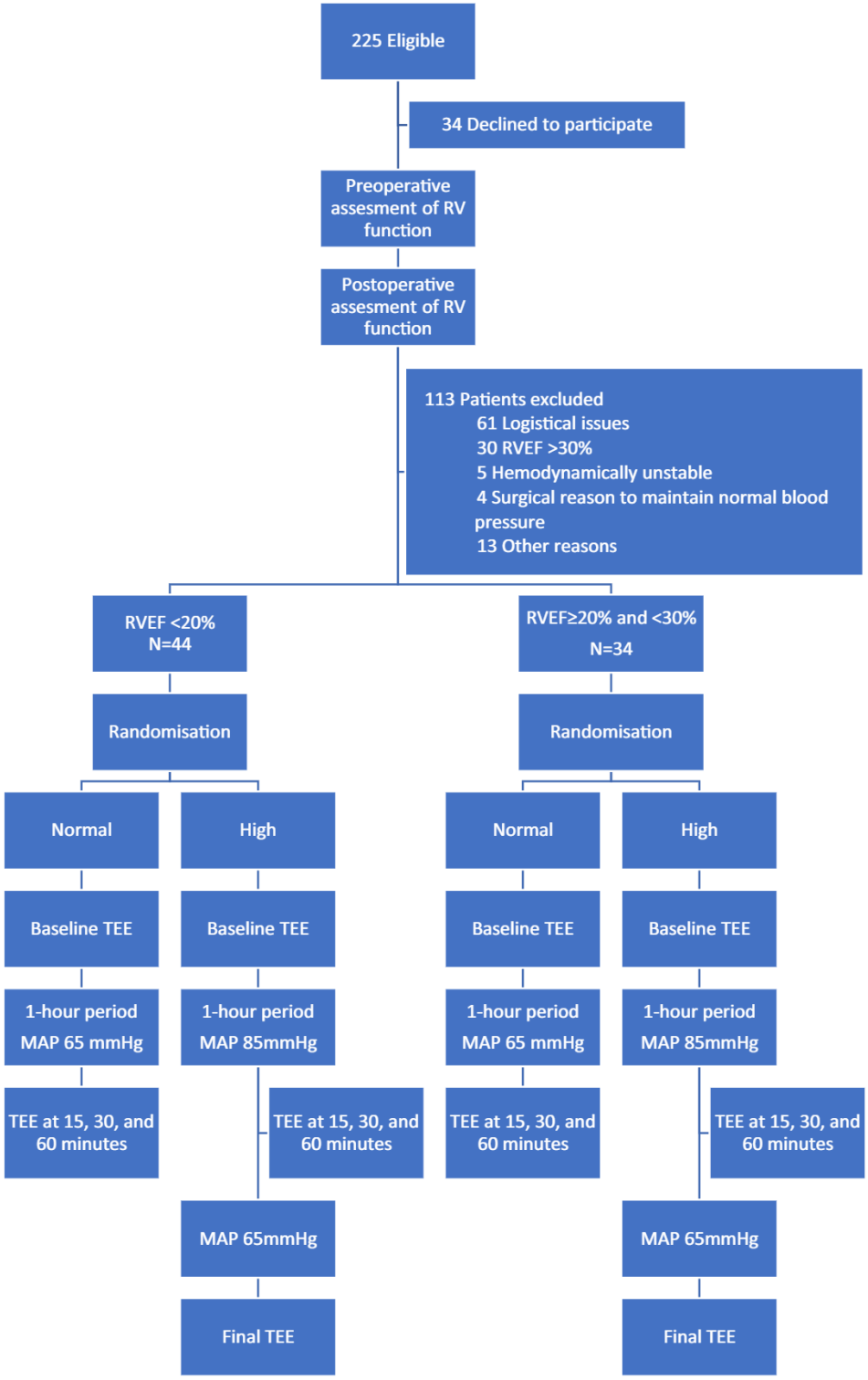

Fig 1. Study protocol. MAP, mean arterial pressure; RV, right ventricular; RVEF right ventricular ejection fraction; TEE, transesophageal echocardiography.

hemodynamically stable and in an absence of complications (bleeding, infarction). In the ICU, the following data were recorded as baseline: general characteristics, systemic hemodynamic variables, TEE measurements, midesophageal two- and four-chamber views for Simpson left ventricular ejection fraction, and modified deep transgastric (0 degree) view for TAPSE and PW TDI of the right ventricle. Results of standard laboratory tests included blood gas analysis, arterial lactate concentration, cardiac biomarkers (creatine kinase and creatine kinase-myoglobin binding), fluid balance, ventilator settings, and surgery characteristics.

Patients were equipped with both an arterial line and a PAC (7.5-F continuous cardiac output/mixed venous oxygen saturation [SvO_2]/continuous end-diastolic volume PAC, model

774F75; Edwards Lifesciences, Irvine, CA), which interfaced with a computerized monitoring system (Vigilance continuous cardiac output/SvO_2/continuous end-diastolic volume monitor; Edwards Lifesciences). This PAC enables near-continuous data on cardiac output/index (CCO/CCI), oxygen supply-and-demand balance (SvO_2), RV end-diastolic volume, and RVEF. The correct position of the PAC was confirmed with waveform analysis and a chest x-ray upon arrival in the ICU and before the start of the study. Zeroing of the pressure systems was done directly after ICU admittance. Leveling of the pressure systems was checked after every reposition of either the patient or the bed. Details on PAC measurements are provided elsewhere.[23] During the study period, PAC-derived data continuously were registered After enrollment in the ICU, TEE was performed every 15 minutes, starting 15 minutes before the start of the study. The final TEE measurement was performed after 60 minutes in the normal-target group or in case MAP returned to 65 mmHg for the high-target group. Hemodynamic data were collected every minute and were averaged over 15 minutes, starting 30 minutes before the study start. Final measurements were performed over a 30-minute period after the study stop. In line with previous literature, the TSG measurements at baseline and at the end of the study were estimated according to the following formula[13]:

$$\text{TSG} = \text{systolic blood pressure} - \text{systolic pulmonary artery pressure}$$

Before the start of the study protocol, adequate filling status was obtained. In the high-target group, NE was titrated to achieve an MAP of 85 mmHg. Dosage was increased every two minutes until the target was reached, with a maximum increase in NE administration of 0.24 μg/kg/min relative to the starting dose or a maximum systolic pressure of 140 mmHg. After the one-hour study period, NE was tapered to an MAP of 65 mmHg.

In the normal-target group, MAP was titrated to 65 mmHg according to local protocol. In case vasopressors were deemed necessary to maintain this level of MAP, the choice of vasopressors was made before the start of the study period by the attending physician and remained unaltered during the entirety

Table 1
Baseline Characteristics of Patients With an RVEF <20% and Patients With an RVEF Between ≥20% and <30%

	RVEF <20%			RVEF 20%-30%		
	Normal Target (n = 22)	High Target (n = 22)	p Value	Normal Target (n = 17)	High target (n = 17)	p Value
Demographics						
Age (y)	70 [65-78]	73.5 [69-78]	0.180	68 [57-78]	71 [65-77]	0.558
Male (%)	77	90	0.216	65	77	0.452
Body mass index	27 [25-31]	29 [27-31]	0.398	31 [25-32]	27 [25-30]	0.221
Preoperative comorbidities (%)						
DM type 1	0	0		0	0	
DM type 2	23	9	0.216	29	18	0.419
Peripheral vessel disease	9	5	0.550	12	18	0.628
TIA/CVA	14	9	0.635	18	24	0.671
Neurologic dysfunction*	0	0		0	0	
COPD†	9	5	0.550	0	6	0.310
Pulmonary hypertension‡	41	38	0.852	24	19	0.817
Serum creatinine (μmol/L)	96 [79-123]	93 [77-115]	0.581	84 [72-89]	85 [81-108]	0.241
Cardiac status (%)						
NYHA class III or IV	64	50	0.361	59	47	0.492
Preoperative myocardial infarction	14	9	0.635	18	0	0.287
Previous cardiac surgery	0	5	0.312	0	0	
Previous PCI	5	9	0.550	6	18	0.287
Stenosis RCA	50	50	1.000	18	24	0.671
History with PCI RCA	0	9	0.148	6	18	0.287
Medication before surgery (%)						
Beta blocker	55	64	0.226	47	41	0.730
ACE-inhibitor	41	55	0.365	35	18	0.244
Angiotensin-1 antagonist	27	14	0.262	18	18	1.000
Calcium antagonist	27	14	0.262	29	24	0.697
Diuretics	41	41	1.000	41	30	0.473
Psychiatric drugs	5	5	1.000	6	18	0.287

NOTE. Data are presented as median [interquartile range]. Normaltarget: mean arterial pressure 65 mmHg. High target: mean arterial pressure 85 mmHg.
Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RCA, right coronary artery; RVEF, right ventricular ejection fraction; TIA, transient ischemic attack.

* Disease severely affecting ambulation or day-to-day functioning.

† Long-term use of bronchodilators or steroids for lung disease.

‡ Pulmonary hypertension (mean pulmonary artery pressure ≥25 mmHg) measured with pulmonary artery catheter in the operation room before surgery.

Table 2
Perioperative Details of Patients With an RVEF <20% and Patients With an RVEF Between ≥20% and <30%

	RVEF <20%			RVEF 20%-30%		
	Normal Target (n = 22)	High Target (n = 22)	p Value	Normal Target (n = 17)	High Target (n = 17)	p Value
Hemodynamic characteristics after induction of anesthesia						
CVP (mmHg)	12 [8-13]	10 [8-13]	0.532	11 [8-14]	13 [9-14]	0.279
MAP (mmHg)	65 [63-68]	65 [61-75]	0.842	68 [67-75]	68 [62-75]	0.822
sABP (mmHg)	98 [91-106]	95 [88-104]	0.614	98 [93-106]	94 [89-98]	0.129
dABP (mmHg)	50 [44-56]	53 [46-61]	0.259	56 [52-58]	56 [50-63]	0.654
sPAP (mmHg)	29 [25-36]	32 [25-38]	0.504	28 [23-34]	29 [26-33]	0.504
dPAP (mmHg)	17 [13-21]	15 [13-24]	0.807	17 [14-22]	18 [15-20]	0.828
mPAP (mmHg)	21 [18-26]	21 [17-28]	0.584	21 [18-26]	22 [19-24]	0.651
HR (beats/min)	62 [55-69]	63 [52-79]	0.698	64 [54-76]	63 [55-79]	0.666
CCI (L/min/m^2)	1.9 [1.4-2.5]	1.9 [1.6-2.1]	0.803	1.8 [1.6-2.2]	1.9 [1.5-2.4]	0.787
EDVi (mL/m^2)	137 [119-157]	149 [121-170]	0.611	106 [101-119]	124 [96-132]	0.419
RVEF (%)	20 [16-33]	18 [13-24]	0.592	29 [22-32]	25 [20-32]	0.336
SvO_2 (%)	72 [67-76]	73 [68-78]	0.635	71 [68-75]	72 [67-77]	0.724
SV (mL)	62 [49-77]	57 [44-73]	0.579	61 [52-68]	57 [50-64]	0.430
TEE parameters after induction of anesthesia						
TAPSE (mm)	16.5 [11.2-21.2]	14.2 [8.4-18]	0.241	17 [12-21]	14 [12-20]	0.467
S' (cm/s)	7.2 [5.6-8.5]	7.2 [5.3-8.8]	0.850	8.1 [7.1-9.7]	7.3 [5.5-8.6]	0.273
MPI	0.71 [0.48-0.86]	0.66 [0.42-1.13]	0.988	0.54 [0.43-0.60]	0.62 [0.47-0.76]	0.396
LVEF (%)	52 [36-58]	50 [36-64]	0.325	53 [47-65]	58 [45-63]	0.532
Intraoperative characteristics						
AoX (min)	108 [73-158]	91 [63-118]	0.162	100 [82-152]	78 [64-96]	0.039*
ECC (min)	146 [98-190]	118 [84-154]	0.127	132 [100-180]	112 [93-131]	0.139
RCA graft (%)	41	36	0.757	35	12	0.106
Type of procedure (%)						
CABG + AVR	45	45	0.049*	59	24	0.093
CABG + MVR/MVP	18	5		0	6	
AVR	5	32		17	41	
MVR/MVP	14	5		17	6	
Other	18	13		6	24	
Postoperative eyeballing RV function by TEE (%)						
Good	68	77		88	81	
Moderate	23	18	0.752	6	19	0.347
Poor	9	5		6	0	
Postoperative eyeballing LV function by TEE (%)						
Good	68	68		76	75	
Moderate	27	23	0.809	18	13	0.762
Poor	5	9		6	13	
Postoperative characteristics						
Bleeding (%)	14	5	0.294	6	6	1.000
MI (%)	14	0	0.073	0	0	
Resubmission (%)	5	0	0.312	0	0	
CVVHD (%)	5	0	0.312	6	0	0.310
Creatinine (μmol/L)†	122 [82-167]	96.5 [75-134]	0.064	87 [77-103]	91 [80-127]	0.717
CK (U/L)†	957 [406-1613]	615 [454-1273]	0.760	617 [538-977]	450 [289-705]	0.060
CK-MB (U/L)†	69 [40-128]	63 [38-80]	0.379	48 [44-74]	42 [26-54]	0.102
Lactate (mmol/L)†	2.1 [1.8-3.7]	2.1 [1.5-2.7]	0.254	2.2 [1.7-3]	2.1 [1.7-3.3]	0.822
Fluid balance (mL)	1,802 (1,050)	1,600 [1,125-2,000]	0.191	1,500 [1,050-2,100]	1,800 [1,350-2,600]	0.406

NOTE. Data are presented as median [interquartile range]. Normal target: mean arterial pressure 65 mmHg. High target: mean arterial pressure 85 mmHg. Hemodynamic data were obtained with an arterial line and a pulmonary artery catheter. Transesophageal echocardiographic right ventricular measurements were obtained in the modified deep transgastric position (0 degrees). The left ventricular ejection fraction was obtained with Simpson's method. Hemodynamic characteristics and transesophageal echocardiography parameters were measured after the induction of anesthesia in the operating room, but before sternal opening.

Abbreviations: AoX, aortic cross-clamp; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CCI, continuous cardiac index; CK, creatine kinase; CK-MB creatine kinase myoglobin binding; CVP, central venous pressure; CVVHD, continuous venovenous hemodialysis; dABP, diastolic arterial pressure; dPAP, diastolic pulmonary arterial pressure; ECC, extracorporeal circulation; EDVi, end diastolic volume index; HR heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MI, myocardial insufficiency; mPAP, mean pulmonary arterial pressure; MPI, myocardial performance index; MVP, mitral valve repair; MVR, mitral valve replacement; RCA, right coronary artery; RV, right ventricular; RVEF, right ventricular ejection fraction; S', systolic myocardial contraction; sABP, systolic arterial pressure; sPAP, systolic pulmonary arterial pressure; SV, stroke volume; SvO_2, mixed venous saturation; TAPSE, tricuspid annular systolic plane excursion; TEE, transesophageal echocardiography.

* Indicates a significant difference across intervention and control groups ($p < 0.05$).

† Peak value.

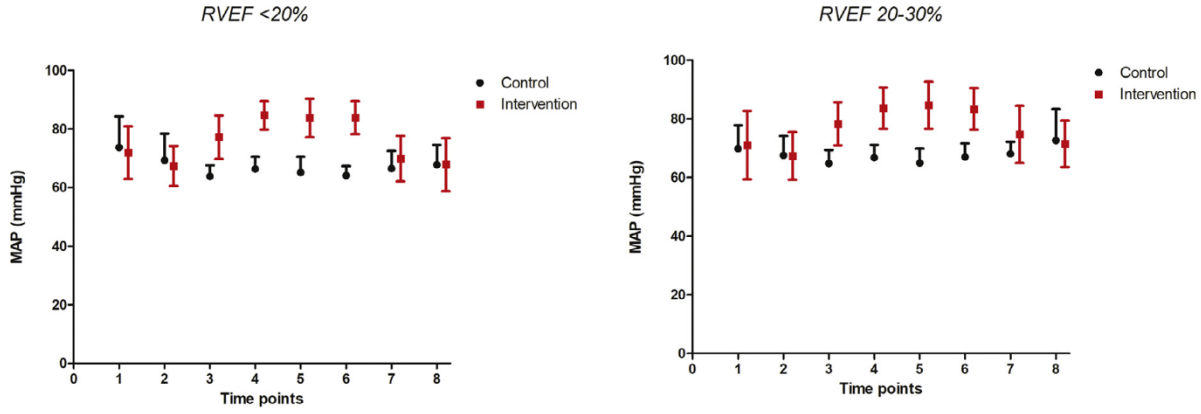

Fig 2. Change of mean arterial pressure over time. Mean arterial pressures were collected every minute and were averaged over a period of 15 minutes, starting 30 minutes before study start (timepoints 1 and 2). Timepoints 3-to-6 indicate the study period. Final measurements were performed over a 30-minute period after study stop (timepoints 7 and 8); *indicates a p value of < 0.001 between groups. MAP, mean arterial pressure; RVEF, right ventricular ejection fraction.

of the process. During the study period, other interventions, including fluid administration, alterations in ventilatory settings, and pacemaker adjustments, were not allowed unless the patient's situation was considered critical. The primary endpoint was the change in PAC-derived RVEF over a one-hour study period. Secondary endpoints were the change over time in echocardiographic parameters of the left and right ventricles, cardiac index, and TSG.

Analysis

A separate power calculation was performed for each RVEF group. For the RVEF <20% group a mean RVEF of 17%, with a standard deviation of 2% based on earlier observations, was anticipated.[5] A sample size of 44 patients to detect a relative difference of 10% in a 2-sided test with a 0.05 type 1 error and an 80% probability was calculated. A relative difference of 10% in this group is just outside the coefficient of variation of RVEF measurements.

For the RVEF 20%-to-30% group, a mean RVEF of 25% with a standard deviation of 2.6% was anticipated.[5] A sample size of 34 patients to detect a relative difference of 10% in a two-sided test with a 0.05 type 1 error and an 80% probability was calculated.

SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY) was used for statistical analysis. Data are described as median with interquartile range unless stated otherwise. Non-parametric tests were applicable because of the sample size. Comparison between groups was performed using a Mann-Whitney test. For paired data, the Wilcoxon signed rank test was applicable. For nominal or ordinal data, the chi-square test was used. A two-sided p value of < 0.05 was considered to be statistically significant.

Results

Between April 2019 and May 2020, 225 patients were screened before surgery, and a total of 191 patients signed informed consent. After cardiac surgery, 78 patients matched the inclusion criteria. Forty-four patients were assigned to the group with an RVEF of <20%, and 34 patients were assigned to the group with an RVEF between 20% and 30%.

Baseline and Perioperative Characteristics

RVEF <20%

There were no differences in baseline and perioperative characteristics between the normal-target and high- arget groups, with the exception of a difference in type of procedures (p = 0.049) (Tables 1 and 2).

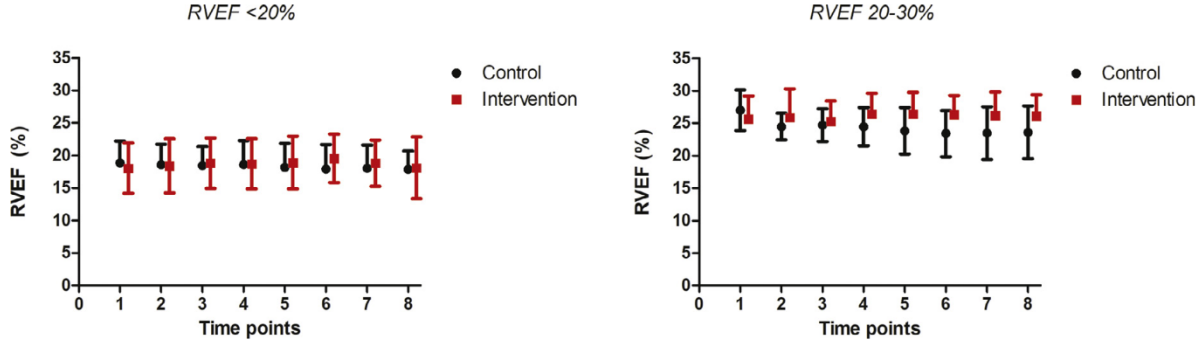

Fig 3. Change of right ventricular ejection fraction over time. Pulmonary artery catheter–derived right ventricular ejection fraction measurements were collected every minute and were averaged over a period of 15 minutes, starting 30 minutes before the study start (timepoints 1 and 2). Timepoints 3-to-6 indicate the study period. Final measurements were performed over a 30-minute period after study stop (timepoints 7 and 8). RVEF, right ventricular ejection fraction.

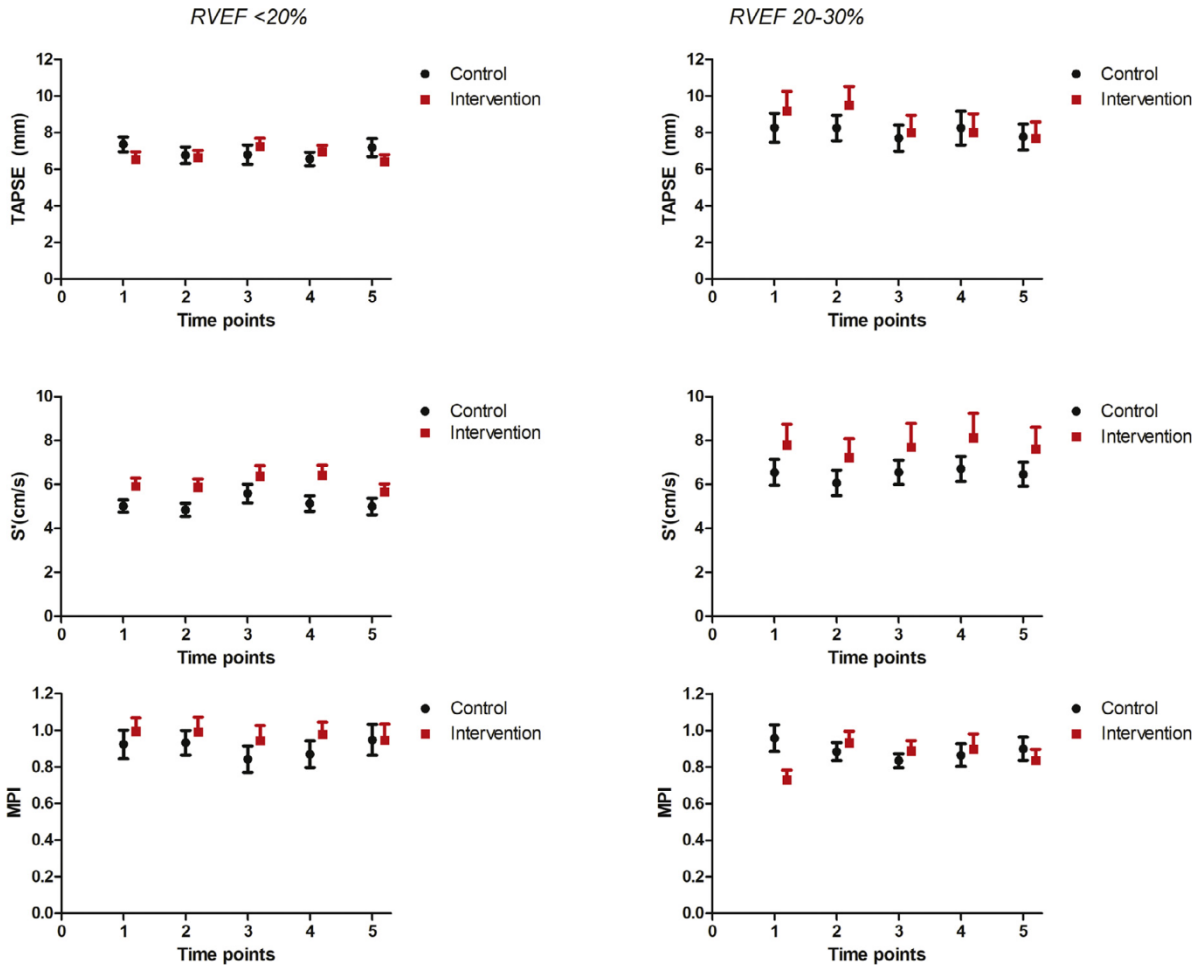

Fig 4. Change in transesophageal echocardiographic parameters over time. Right ventricular parameters were measured in the modified deep transgastric position. After admission to the intensive care unit, transesophageal echocardiography was performed every 15 minutes, starting with baseline transesophageal echocardiography 15 minutes before the study period (timepoint 1). The final transesophageal echocardiography measurement was performed after 60 minutes in the control group or in case the mean arterial pressure returned to 65 mmHg for the intervention group (timepoint 5). MPI, myocardial performance index; RVEF, right ventricular ejection fraction; S', systolic myocardial contraction; TAPSE, tricuspid annular systolic plane excursion.

RVEF 20% to 30%

There were no differences in baseline and perioperative characteristics between the normal-target and high-target groups, with the exception of aortic clamp time (100 [82-152] min *v* 78 [64-96] min, respectively, p = 0.039) (see Tables 1 and 2).

Study Target: MAP

RVEF <20%

At baseline, there were no differences in MAP. No significant increase in MAP was observed in the normal-target group during the study period. The MAP in the high-target group was significantly higher compared with the normal-target group (64 [62-67] mmHg *v* 85 [83-86] mmHg; p < 0.001) at the study stop (Fig 2).

RVEF 20% to 30%

At baseline, there were no differences in MAP. No significant increase in MAP was observed in the normal-target group during the study period. The MAP in the high-target group was significantly higher compared with that of the normal-target group (67 [66-70] mmHg *v* 82 [81-87] mmHg; p < 0.001) at the study stop (see Fig 2).

Primary Endpoint: RVEF

RVEF <20%

Baseline RVEF was not significantly different between the normal-target and high-target groups (19% [17-21.5] *v* 18% [15-20], respectively; p = 0.427). In addition, there was no significant between-group difference in the change in RVEF (−1% [−3.3 to 1.8] in the normal-target group *v* 0.5% [−1 to 4] in the high- target group; p = 0.159) (Fig 3).

RVEF 20% to 30%

Baseline RVEF was not significantly different between the control and intervention groups (25% [23-26] *v* 25% [23-27], respectively; p = 0.702). In addition, there was no significant between-group difference in the change in RVEF (−1% [−3

Table 3
Echocardiographic Transesophageal LV Parameters of Patients With an RVEF <20% and Patients With an RVEF Between ≥20% and <30%

	RVEF <20% Normal Target (n = 22)			RVEF 20%-30% Normal Target (n = 17)		
LV parameter	Baseline	End Point	p Value	Baseline	End Point	p Value
S' lateral MV (cm/s)	6.2 [5.1-8.5]	6.7 [4.9-7.2]	0.182	6.3 [5.5-9.1]	6.4 [4.9-8.6]	0.254
E' lateral MV (cm/s)	4.4 [3.9-7.5]	5.3 [4.1-5.3]	0.753	4.4 [3.6-5.1]	4.5 [3.8-5.2]	0.583
E/A	0.8 [0.7-1.0]	0.8 [0.7-0.9]	0.779	0.7 [0.6-0.8]	0.7 [0.6-0.8]	0.346
E/E'	10.5 [9-13.3]	9.7 [8.2-14.3]	0.160	10.7 [8.9-15.5]	10 [8.8-15.5]	0.529
	RVEF <20% High Target (n = 22)			RVEF 20-30% High Target (n = 17)		
	Baseline	End Point	p Value	Baseline	End Point	p Value
S' lateral MV (cm/s)	6 [5.2-8.4]	6 [4.8-6.7]	0.306	7.6 [5.6-9.6]	6.6 [5.1-8.5]	0.247
E' lateral MV (cm/s)	5.3 [4.3-6.1]	4.6 [4.0-6.1]	0.734	6.5 [4.5-11.3]	5.2 [4.3-8.0]	0.594
E/A	0.9 [0.7-1.2]	0.8 [0.6-0.9]	0.233	0.8 [0.7-1.1]	0.9 [0.7-1.0]	0.018*
E/E'	8.7 [4.8-15.2]	9 [5.6-13.9]	0.753	9.9 [8-11.9]	10.6 [8.5-17.2]	0.123

NOTE. Data are presented as median [interquartile range]. Normaltarget: mean arterial pressure 65 mmHg. High target: mean arterial pressure 85 mmHg. Baseline measurements were obtained in the intensive care unit after enrollment, 15 minutes before the study period. The final transesophageal echocardiographic measurement was performed after 60 minutes of study period in the normal target group or in case mean arterial pressure returned to 65 mmHg for the high target group. Measurements were obtained in midesophageal two-chamber view.
Abbreviations: E', early diastolic myocardial relaxation; E/A, ratio of peak velocity blood flow from left ventricular relaxation in early diastole to peak velocity flow in late diastole; E/E', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; LV, left ventricular; MV, mitral valve; RVEF, right ventricular ejection fraction; S', systolic myocardial contraction.
* Indicates a significant difference between baseline and end point ($p < 0.05$).

to 0] in the normal-target group *v* 1% [−1 to 3] in the high-target group; p = 0.074 (see Fig 3).

Secondary Endpoints

Echocardiographic parameters of the right ventricle are depicted in Figure 4. Echocardiographic parameters of the left ventricle are listed in Table 3. No improvement over time was observed in RV and LV parameters, irrespective of baseline RVEF. Hemodynamic variables are listed in Table 4.

RVEF <20%

In the high-target group, mean pulmonary artery pressure (mPAP) increased significantly over time (from 19 mmHg [18-25.5] to 25 mmHg [21.0-29.5]; $p < 0.001$). The estimated TSG increased significantly (from 66 [59-73] mmHg to 86 [79-100] mmHg; $p < 0.001$) (see Table 4). This was accompanied by an increase in RV stroke work index in the high-target group between baseline and study stop (from 4.0 g/m/beat/m^2 [3.1-5.2] to 4.7 g/m/beat/m^2 [4.2-6.9]; p = 0.001) (see Table 4).

RVEF 20% to 30%

In the high-target group, mPAP increased significantly over time (from 19 mmHg [18-21.5] to 21 mmHg [18.5-24,5]; p = 0.010). The estimated TSG increased significantly (from 79 [66-92] mmHg to 103 [90-116] mmHg; $p < 0.001$ (see Table 4).This was accompanied by an increase in RV stroke work index between baseline and study stop in the high-target group (from 4.5 g/m/beat/m^2 [3.6-5.8] to 5.4 g/m/beat/m^2 [4.5-5.9]; p = 0.049) (see Table 4).

Discussion

In this study, NE-mediated high blood pressure targets, increasing MAP from 65-to-85 mmHg, did not result in an increase in PAC-derived RVEF compared with normal blood pressure targets. These observations were in line with the simultaneous observation that there were no improvements in RV echocardiographic parameters (ie, TAPSE, S', and myocardial performance index) in the intervention group.

These results seemed to contradict the general paradigm that an increase in blood pressure is likely to improve RV performance as a result of improvement in right coronary artery blood flow and reestablishment of the TSG and, thus, of RV and LV dimensions.[13,14] Animal experiments have suggested the effectiveness of arterial vasoconstriction in the setting of RV dysfunction and failure. In rabbits and dogs, afterload-induced acute RV failure was attenuated by aortic banding as a result of subsequent restoration of LV pressures.[20,21] These observations confirmed the relevance of a previously described linear relationship between the maximal RV systolic pressure and the mean femoral artery pressure.[24] In rabbits, administration of NE resulted in similar effects.[20] In the clinical setting, the administration of epinephrine in a small group of aortic valve surgery patients resulted in a significantly higher PAC-derived RVEF compared with placebo. However, MAP was the same between groups.[25]

To understand the present study's seemingly contradictive results, it is pivotal to acknowledge the specific setting. First, the present study was performed in a mixed group of postoperative cardiac surgery patients who were not selected for well-known risk factors of RV dysfunction (ie, pulmonary artery

Table 4
Hemodynamic Variables During Study Period

	RVEF <20% Normal Target (n = 22)			RVEF 20%-30% Normal Target (n = 17)		
	Baseline	End Point	p Value	Baseline	End Point	p Value
CVP (mmHg)	8 [5-11]	7 [5-10]	0.054	9 [6-11]	8 [5-10]	0.150
MAP (mmHg)	68 [62-74]	64 [62-67]	0.008*	68 [63-72]	67 [66-70]	0.722
mPAP (mmHg)	22 [18-26]	22 [18-25]	0.069	19 [15-24]	18 [17-25]	0.541
CCI (L/min/m^2)	1.9 [1.7-2.4]	1.7 [1.6-2.2]	0.010*	2.2 [1.9-2.5]	2.0 [1.8-2.4]	0.010*
TSG (mmHg)	72 [63-80]	63 [53-73]	0.005*	76 [63-92]	72 [67-86]	0.331
EDVi (mL/m^2)	119 [101-147]	110 [102-141]	0.070	104 [98-112]	101 [93-107]	0.050
RVEF (%)	19 [17-22]	18 [15-20]	0.468	25 [23-26]	23 [21-26]	0.180
SVi (mL/m^2)	22 [19-27]	19 [17-25]	0.011*	26 [22-28]	23 [20-27]	0.002*
RVSWi (g/m/beat/m^2)	3.9 [3.2-5.1]	4.2 [3.1-4.6]	0.260	3.5 [2.8-5.6]	3.3 [2.8-4.9]	0.408
NE dose (μg/kg/min)	0.0 [0-0.5]	0.4 [0.0-1.2]	0.028*	0.0 [0.0-0.0]	0.0 [0.0-0.2]	0.144
	RVEF <20% High Target (n = 22)			RVEF 20%-30% High target (n = 17)		
	Baseline	End Point	p Value	Baseline	End Point	p Value
CVP (mmHg)	8 [6-9]	8 [6-9]	0.264	7 [5-8]	7 [5-9]	0.590
MAP (mmHg)	67 [61-71]	85 [83-86]	< 0.001*	67 [61-71]	82 [81-87]	< 0.001*
mPAP (mmHg)	19 [18-24]	25 [21-30]	< 0.001*	19 [18-22]	21 [19-25]	0.010
CCI (L/min/m^2)	2 [1.9-2.2]	2.2 [1.9-2.4]	0.534	2.3 [1.9-2.7]	2.3 [2.1-2.5]	0.751
EDVi (mL/m^2)	122 [107-152]	126 [103-154]	0.881	100 [92-127]	99 [94-117]	0.408
TSG (mmHg)	66 [59-73]	86 [79-100]	<0.001*	79 [66-92]	103 [90-116]	<0.001*
RVEF (%)	18 [15-20]	19 [17-21]	0.337	25 [23-27]	26 [24-29]	0.430
SVi (mL/m^2)	23 [21-25]	25 [21-26]	0.434	30 [22-34]	27 [24-31]	0.954
RVSWi (g/m/beat/m^2)	4.0 [3.1-5.2]	4.7 [4.2-6.9]	0.001*	4.5 [3.6-5.8]	5.4 [4.5-5.9]	0.049*
NE dose (μg/kg/min)	0.6 [0.1-0.8]	0.9 [0.6-1.6]	0.003*	0.4 [0.1-0.7]	0.9 [0.2-1.5]	0.016*

NOTE. Data are presented as median [interquartile range]. During the study period, hemodynamic data were collected with a pulmonary artery catheter which enables near-continuous data collection. Data were averaged over a period of 15 minutes, with baseline measurements starting 15 minutes before study start. The endpoint measurements were performed over the last 15 minutes of the one-hour study period. The transseptal gradient at baseline and at the end of the study were estimated according to the following formula: transseptal gradient = systolic blood pressure − systolic pulmonary artery pressure

Abbreviations: CCI, continuous cardiac index; CVP, central venous pressure; EDVi, end-diastolic volume index; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; NE, norepinephrine; RVEF, right ventricular ejection fraction; RVSWi, right ventricular stroke work index; Svi, stroke volume index; TSG, transseptal gradient.

* Indicates a significant difference between baseline and endpoint ($p < 0.05$).

hypertension and LV failure) or a specific cutoff value for the TSG. This is reflected by the fact that the median TSG only modestly was reduced at baseline and during the intervention increased by 20 and 24 mmHg, respectively, in patients with a low or moderate RVEF. Apparently, the intervention was accompanied by the anticipated increase in TGS but not to the extent of that previously described in hypotensive patients with acute RV pressure overload. In the clinical setting of cardiac surgery, the achieved increase in blood pressure always must be weighed against an additional risk of bleeding, and as such, this clinical study reflected only a small margin of the range in blood pressure augmentation that can be achieved in animal experiments.

An alternative explanation for the lack of blood pressure–induced response in RVEF may be provided by the important observation in the present study that the increase in blood pressure was accompanied by an increase of mPAP during NE administration. It is conceivable that a potential positive effect of the increase in blood pressure on RV function was counteracted by an unintended increase in RV afterload. In this scenario, the maintenance of Cardiac index may be achieved by a direct inotropic effect of NE or via enhancement of right coronary artery blood flow. In this case, PAC-derived RVEF should be combined with additional variables of RV contractility to fully appreciate the underlying mechanisms. The importance of the increase in afterload during NE administration is illustrated by two conflicting results in the setting of septic shock. Recently, a cohort of 11 septic shock patients was evaluated with the combined use of a PAC and transthoracic echocardiography. NE was used to increase MAP from 60-to-90 mmHg for a period of at least ten minutes. The authors observed improved RV function with both PAC and transthoracic echocardiography in the absence of an increase in RV afterload.[26] However, in other small uncontrolled studies, the use of NE was accompanied by a significant increase in mPAP, whereas both RVEF and RV enddiastolic volume index remained unchanged.[27,28] This increase in afterload may be equally important in the setting of cardiac surgery, which was demonstrated by an absence of increase in cardiac index during the use of NE despite a substantial increase in blood pressure.[29] Not in every clinical setting does the application of an early vasoconstricting approach intended for blood pressure

support seem to be the best course of action; in the failing heart, the optimal afterload is narrow and carefully must be tuned. [30]

The application of the findings of the present study is limited to the specific setting of cardiac surgery. Controls were well-maintained within the generally accepted MAP target for postoperative cardiac surgery patients. Although it cannot be ruled out that higher MAP targets (with a subsequent effect on the increase in TSG) may have revealed different results, the clinical setting simply did not allow for additional broadening of the chosen pressure limits. However, this does not reduce the clinical relevance of the present study because the net result in overall cardiac performance was unaltered during the NE-mediated increase in blood pressure. Clearly, the trigger to start a therapeutic intervention depends on the definition of RV dysfunction or failure, which until now remains a topic of debate.[31,32] The choice to select patients according to the postoperative RVEF clearly characterized the present study's population, but this was in line with previous publications[33] and was supported by its association with long-term survival and ICU morbidity.[5,34] In addition, the window of observation was limited to one hour. Although the response in RV performance to aortic banding or NE administration in the experimental setting was near-instantaneous,[20] unexpected effects of the increase in MAP outside the scope of this study cannot be ruled out. In addition, the limited number of patients in the present study had the potential for a type-II error (ie, the unjustified rejection of the hypothesis that NE-mediated increment of blood pressure does improve RV function). However, the study was powered to detect a relative change in RVEF of 10%, representing a small absolute difference, and the data did not suggest any tendency toward a difference in the primary endpoint between the normal- and high-target groups. Finally, the use of NE may be debated. Compared with the left ventricle, the density of β-receptors in the right ventricle is much less.[35] In an animal study, the effect of NE remained present after administration of a selective β-blocker, indicating that the stimulation of α-receptors is the main therapeutic target.[20] Experimental studies suggested that vasopressin increases systemic vascular resistance in the absence of pulmonary vasoconstriction.[36,37] Although such characteristics may have potential for the management of RV dysfunction, their effects remain controversial and might even result in a negative performance of the right ventricle.[38] Similarly, phenylephrine has been associated with negative inotropic effects.[39] In the authors' opinion, the choice for NE as a vasopressor seemed appropriate.

Conclusion

In a mixed population of patients with RV dysfunction after cardiac surgery, NE-mediated high-blood-pressure targets, increasing MAP from 65 mmHg-to-MAP 85 mmHg, did not result in an increase in PAC-derived RVEF compared with normal-blood-pressure targets.

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Conflict of Interest

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