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A pilot study on the hemodynamic effects of negative pressure ventilation in patients after cardiac surgery focussing on right ventricular function

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Right ventricular dysfunction and right ventricular failure are important complications in cardiac surgical patients and typically observed after complex surgical cases. Treatment options for optimizing the hemodynamic status in patients presenting with these complications are limited. Negative pressure ventilation has been shown to ameliorate the effects of conventional positive pressure ventilation (PPV) and to improve cardiac output in patients with Fontan circulation and patients undergoing coronary artery bypass surgery. No data are available on the effects of negative pressure ventilation on systemic hemodynamics and right heart function after complex on-pump cardiac surgery. Hypothesis of the present study is that right ventricular function improves under condition of negative pressure ventilation after complex on-pump surgery. Thirty patients after complex cardiac surgery were examined using basic hemodynamic monitoring, transesophageal ultrasound, a 3rd generation pulmonary artery catheter, cerebral oximetry and arterial and venous blood gases. The first 15 patients were ventilated for 15 min using standard PPV followed by 15 min of extrathoracal continuous negative pressure ventilation (CNPV) combined with PPV, and 15 min of extrathoracal biphasic negative pressure ventilation (BCV, biphasic cuirass ventilation) combined with an as far as possible reduced PPV. In the second 15 patients, the sequence of negative pressure ventilation was changed and BCV was performed before CNPV. Finally, every patient was ventilated for 15 min with standard PPV again. A full dataset of hemodynamics and a respiratory dataset was collected during each observation period. CNPV und BCV reduced central venous pressure and pulmonary artery occlusion pressure by 2 mmHg. During BCV cardiac index increased by + 24% (+ 0.5 l/min/m^2; 95% CI 0.2–0.8, $p = 0.001$) through an increase of stroke volume index by + 24% ($p = 0.0003$) without change of heart rate. This was accompanied by an increase of right ventricular ejection fraction (+ 18%, p = 0.008), pulmonary arterial pulsatility index (+ 30%, p = 0.0001), left ventricular ejection fraction (+ 15%, $p = 0.01$), and oxygen delivery DO_2 (+ 13%, $p = 0.0006$). Posthoc analysis in patients with reduced stroke volume index (< 27 ml/m^2 prior to the start of the study) revealed that mixed venous oxygen saturation and cerebral oxygen saturation increased by 7% ($p = 0.005$/$p = 0.006$). No adverse effects were observed. While CNPV has only moderate hemodynamic effects by reducing cardiac filling pressure, BCV improves systemic and right ventricular hemodynamics as well as global oxygen balance in patients after complex cardiac surgery. During both negative pressure ventilation modes, no immediate adverse events could be observed. These findings justify investigations if these treatment modalities may impact clinical outcomes in patients with right ventricular dysfunction or failure.

Trial registration **clinicaltrials.gov ID: NCT06088966, registered October 3rd, 2023**

Keywords Negative pressure ventilation, Right ventricular failure, Heart failure, Cardiac surgery, Hemodynamic optimization

Abbreviations

BCV	Biphasic cuirass ventilation
BSA	Body surface area
CABG	Coronary artery bypass grafting
CI	Cardiac index
CI20s	CI measured every 20 s
CNPV	Continuous negative pressure ventilation
CO	Cardiac output
CPB	Cardiopulmonary bypass
CPI	Cardiac power index
CVP	Central venous pressure
DO_2	Delivery of oxygen
EDVI	Enddiastolic volume index
LV	Left ventricle
LVEDP	Left ventricular enddiastolic pressure
LVEF	Left ventricular ejection fraction
MAPSE	Mitral annular plane systolic excursion
NIRS	Near infrared spectroscopy
NPV	Negative pressure ventilation
PAC	Pulmonary artery catheter
$paCO_2$	Partial pressure of carbon dioxide
paO_2	Partial pressure of oxygen
PAOP	Pulmonary artery occlusion pressure; wedge pressure
PAPi	Pulmonal artery pulsatility index
$PAP_{syst/diast}$	Pulmonal arterial pressure systolic/diastolic
$Paw_{insp/mean}$	Pressure airway inspiratory/mean
PEEP	Positive endexpiratory pressure
PPV	Positive pressure ventilation
PVRI	Pulmonary vascular resistance index
RV	Right ventricle
RVD	Right ventricular dysfunction
RV Ea	Right ventricular arterial elastance
RVEF	Right ventricular ejection fraction
RVF	Right ventricular failure
RV-PA	Right ventricular—pulmonary arterial coupling
RVSWI	Right ventricular stroke work index
S_cO_2	Cerebral oxygen saturation
$avDCO_2$	Difference of arterial and venous CO_2
SVI	Stroke volume index
SVI20s	SVI measured every 20 s
S_vO_2	Mixed venous oxygen saturation
SVRI	Systemic vascular resistance index
TEE	Transesophageal echocardiography

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Right ventricular dysfunction (RVD) and right ventricular failure (RVF) are important complications in patients undergoing cardiac surgery[1] and associated with increased morbidity and mortality[2]. The etiology of RVD and RVF in this setting is multifactorial and may be attributed to an already preoperatively reduced right heart function that may coincide with a reduced right ventricular (RV) function due to pericardiocentesis[3], global depression of myocardial performance after cardioplegic cardiac arrest[4,5], and low arterial perfusion pressure[2,6] due to vasodilatation following cardiopulmonary bypass (CPB)[7]. In addition, positive intrathoracic pressure induced by controlled PPV may increase right ventricular afterload due to an increase in pulmonary vascular resistance because of intraalveolar vessel compression during inflation above the functional residual capacity[8] and may thus present an additional burden for the right heart[9,10].

Therapeutic options for treating RVD and RVF are limited to reducing pulmonary vascular resistance by optimizing ventilation and applying inhaled pulmonary arterial vasodilators, optimizing systemic arterial pressure and thereby right ventricular myocardial perfusion and left ventricular filling pressure, as well as treatment with inotropic drugs[6,11]. However, especially in severe RVF these measures are often not sufficient[12].

Negative pressure ventilation (NPV) has been shown to improve hemodynamics and renal function in children and adults after congenital heart surgery and in ventilated patients without surgical intervention[13]. Continuous negative pressure ventilation (CNPV) during spontaneous ventilation increased cardiac output (CO) in adults and children[5,14–16] predominantly by increasing cardiac stroke volume[17]. This was accompanied by an increase in urine output[18]. An increase in CO determined by uncalibrated arterial pressure contour analysis was also shown, if NPV was used with undulating external negative pressure (BCV, biphasic cuirass ventilation) during spontaneous ventilation in healthy volunteers, and instead of PPV in patients after coronary

artery bypass grafting surgery (CABG)[19,20]. Improvements of oxygenation and a reduction of pulmonary arterial pressure were also observed during NPV[21]. No data are available on the effects of NPV on hemodynamics and right ventricular function in adult patients after complex cardiac surgery outside the condition of congenital heart defects.

The present study thus aimed to determine, if NPV improves hemodynamics and right ventricular function in patients after complex cardiac surgery. Primary objectives were the effects of different modes of NPV (CNPV in addition to PPV, and BCV in addition to or instead of PPV) on cardiac stroke volume. As secondary objectives we investigated the effects of NPV on right ventricular function assessed by a third-generation pulmonary artery catheter and transesophageal echocardiography as well as the effect of CNPV and BCV on oxygenation.

Methods

Design

This prospective, sequential interventional trial was registered (clinicaltrials.gov ID: NCT06088966, registered October 3rd, 2023), approved by the local ethics committee (Ethikkommission der Universität Greifswald), and conducted in accordance with the principles of the declaration of Helsinki. Written informed consent to participate was obtained prior to the surgical procedure. Patients scheduled for on-pump cardiac surgery were considered eligible to participate if the routine monitoring included a transesophageal ultrasound (TEE) and a pulmonary artery catheter (PAC) in addition to standard hemodynamic monitoring: patients with severely reduced left ventricular ejection fraction (LVEF) (< 35%), reduced right heart function, pulmonary arterial hypertension (especially when coming along with reduced right heart function), combined CABG/valve surgery or major surgery of the thoracic aorta, especially in cases of planned deep hypothermic cardiac arrest. Exclusion criteria were: age below 18 years, inability to give written informed consent. Additionally, patients presenting with hemodynamic instability due to postoperative bleeding or impossible fitting of the cuirass were excluded from the study.

General anesthesia was induced with sufentanil and propofol and maintained by remifentanil, propofol, and a continuous infusion of dexmedetomidine. Intubation was facilitated by a single dose of rocuroniumbromid. No further muscle relaxation was performed. Anesthetic monitoring included an arterial line, a central venous catheter, and a PAC for continuous monitoring of mixed venous oxygen saturation and almost continuous monitoring of CO and stroke volume (Ccombo V, Edwards Lifesciences, Irvine CA, USA) connected to the Hemosphere® platfom, software version K.9.1).

After completion of the surgical procedure the patients were transferred into the recovery room or the intensive care unit. Patients were quickly assessed for hemodynamic stability or ongoing bleeding. Patients with hemodynamic instability not responding to fluid optimization and patients presenting with more than 200 ml/h drainage loss were excluded from the study (Fig. 1: Consort chart). The maintenance of moderate doses of inotropes and vasopressors that had been necessary for weaning from cardiopulmonary bypass was not regarded as hemodynamic instability. Thereafter, the study was started as soon as possible to minimize postoperative ventilation time.

Experimental setup

Thirty patients were included and analyzed. Two series of experiments using different modes of NPV were sequentially performed (Fig. 2). After obtaining a baseline data set after surgery under standard condition (PPV) for comparison with CNPV and BCV in every patient (presented as mean/median PPV, Tables 3, 4, and 5), CNPV in addition to PPV and BCV instead of PPV were sequentially applied. The first 15 patients received CNPV for 15 min with collection of a full data set at the end and subsequent to this BCV for 15 min with collection of a full data set at the end. In patients 16 to 30 BCV and CNPV were applied the other way around (first BCV, afterwards CNPV). Due to the alternating sequence of BCV after CNPV in patient 1 to 15 and CNPV after BCV in patient 16 to 30 and inclusion of all suitable patients as well as every patient representing his own "control group" we considered a randomization as not necessary. Finally, the patients were ventilated with standard PPV for 15 min again and the last data set was collected (final examination, abbreviated as "E").

During CNPV a pressure of − 20 cmH_2O was applied while PPV was maintained with unaltered respirator settings. During BCV the maximum negative pressure was set to − 30 cmH_2O during inspiration and a positive pressure during expiration with an intended ratio of inspiration/expiration of 1:1 to 1:3. If an air leakage occurred (due to wound dressings or the inserted chest drains) the positive pressure during expiration was reduced in an amount that no major air leak was detectable. A PEEP of 5 cmH_2O was kept during NPV to avoid the risk of atelecttrauma in all patients.

Measurements:

Each data set included basic hemodynamic and ventilatory data, an arterial (art), a central-venous (cv), and a mixed-venous (v) blood gas sample, a TEE examination (GE—VIVID S70N, etc.) and a full right heart catheter assessment with a 3. Generation PAC[22]. This monitoring technology uses the conventional continuous cardiac output method by semicontinuous thermodilution (representing an average value over an analysis time of three to six minutes) and additionally incorporates pulmonary artery pressure curve analysis to recalibrate the semicontinuous thermodilution measurements and presents these data every 20 s. PAC-derived data were recorded continuously during the measurements. Additionally cerebral oxygen saturation (ScO_2) by near-infrared spectroscopy was measured on the right forehead. In case of bifrontal measurements we calculated the mean between right and left cortex.

Statistical analysis

There were no similar studies conducted before the present study for calculation of a power analysis. So, the sample size of 30 patients was on the one hand conveniently determined based on the significant effect of NPV

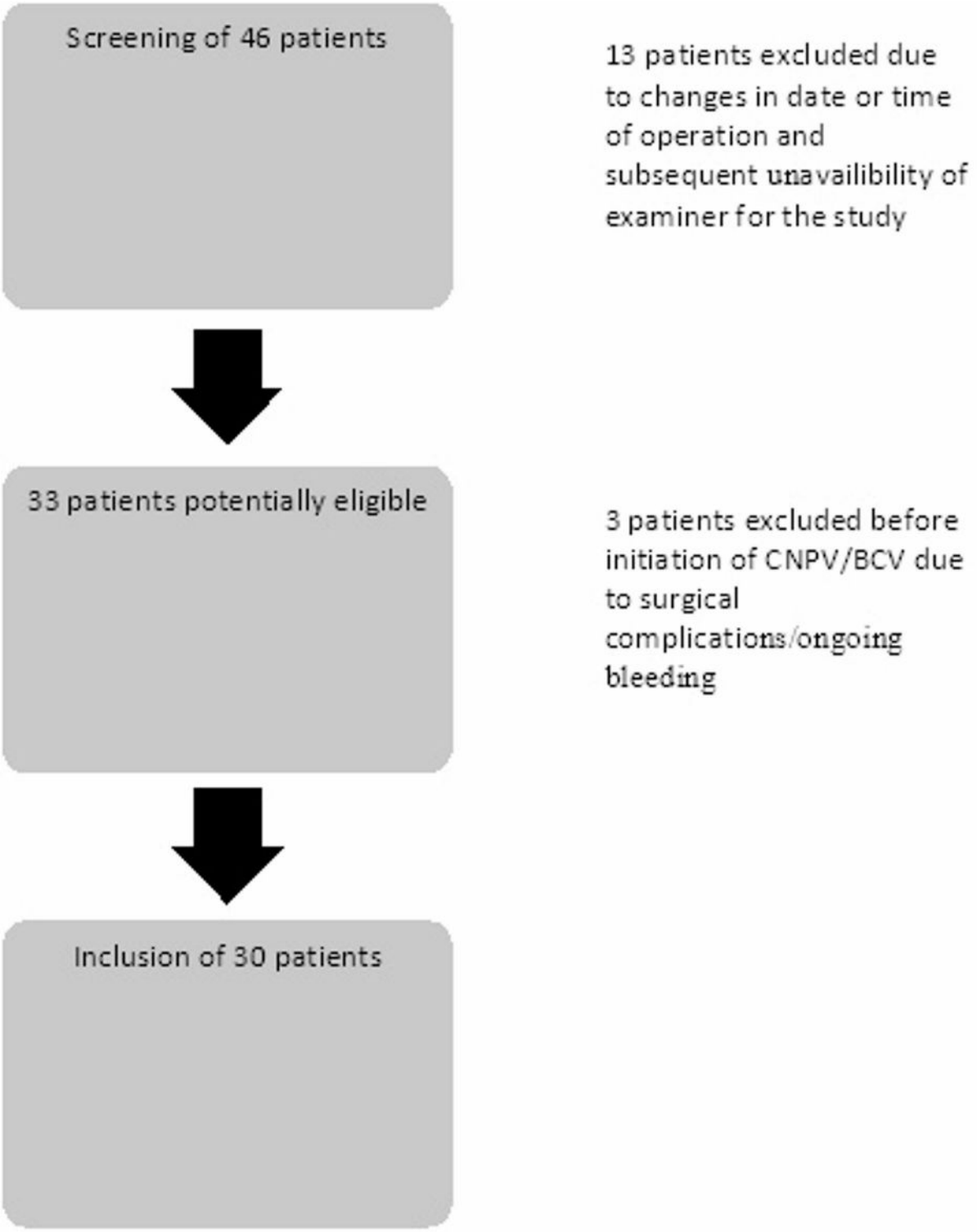

Fig. 1. Consort chart.

on hemodynamics observed in different papers by Shekerdemian et al. in 9, 11 and 16 patients depending on the paper. On the other hand, we calculated a power analysis based on the observed effect of NPV in healthy and operated children[14,15]. A calculated Cohen`s d of – 0.6 combined with an alpha-niveau of 0.05 and a power of 0.8 resulted in a sample size of 24 patients. We added an amount of 5–10 potentially dropout cases and planned the inclusion of 30 patients. There was no preplanned subgroup analysis. Due to the clinical observation of larger effects of NPV in patients with reduced cardiac function at the start of the experiments, a subgroup analysis following dichotomization based on stroke volume index (SVI) at baseline in a low and high baseline SVI group

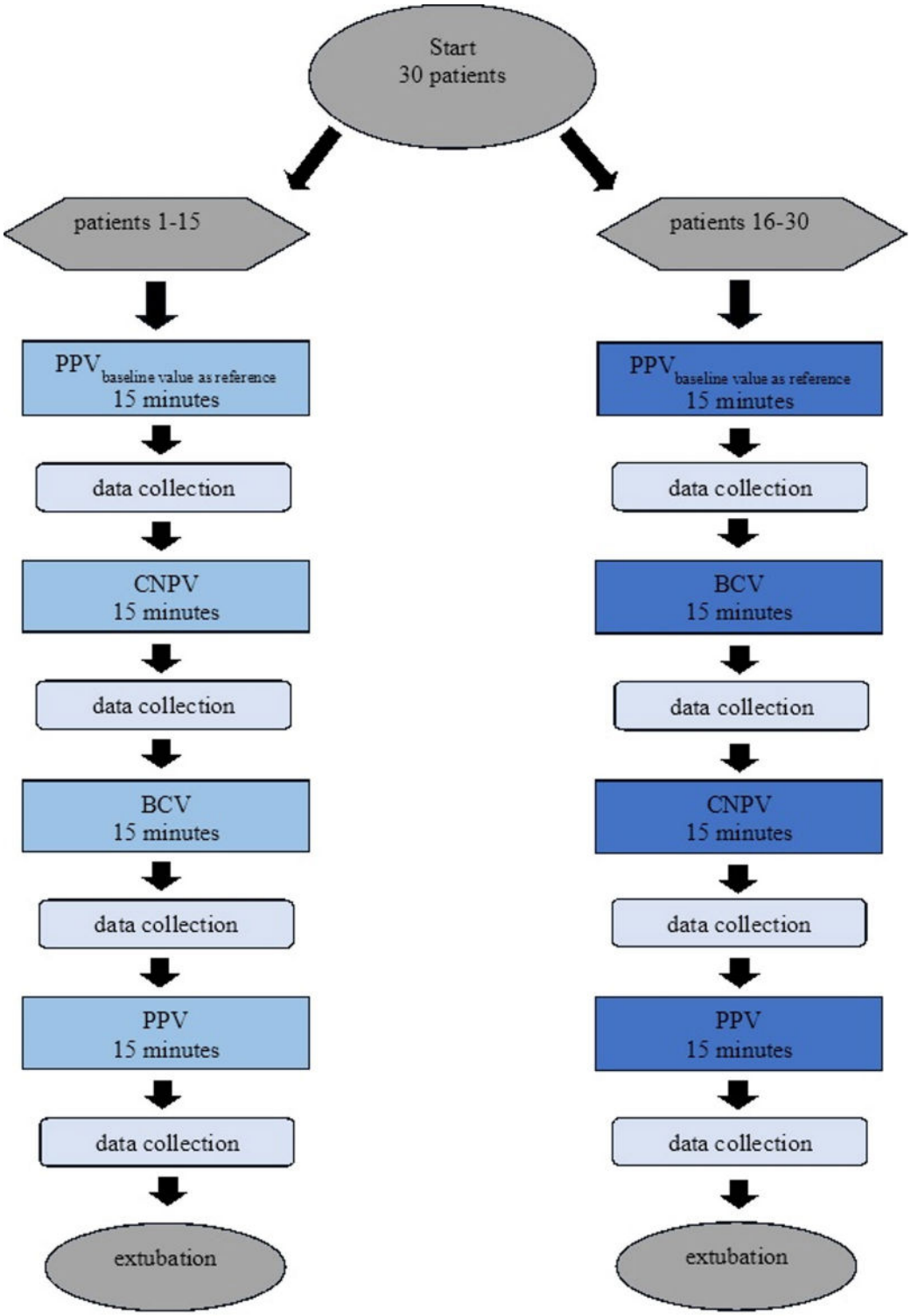

Fig. 2. sequence of protocol steps.

was performed. Additionally, to rule out an effect of NPV on heart rate, a secondary analysis of patients with and without the need of epicardial pacing was performed.

All analyses were performed with MedCalc (version 22.009, Ostend, Belgium). The primary endpoint was SVI measured by PAC every 20 s (SVI20s); all other measurements were analyzed as secondary outcomes and should therefore be regarded as hypothesis generating. Hemodynamic data are given as the mean ± 95% confidence intervals (95% CI) of the four different ventilations modes (PPV only; CNPV with PPV; BCV; PPV

	mean	SD	SEM	95% CI
Age (years)	65	8	2	62–68
High (cm)	177	9	2	173–180
Weight (kg)	89	16	3	85–100
BSA (m^2)	2	0.3	0.05	1.9–2.1
BMI (kg/m^2)	28	5	0.8	27–30
HR (beats/min)	69	13	2.6	64–70
MABP (mmHg)	80	13	2	76–85
ASA classification	3.6	0.6	0.1	3.4–3.8
Euroscore additiv	6.9	6.2	1.1	4.6–9.3
Euroscore 2	6.2	14	3	0.9–11.5
STS score	2.1	1.7	0.3	1.5–2.8
NTproBNP (pg/ml)	1167	1487	272	612–1722
Creatinine (µmol/l)	86	25	5	76–95
Creatinine clearance (ml/min)*	79	18	3	72–85
Hemoglobine (mmol/l)	8.3	1.7	0.3	7.6–8.9
Haematocrit (%)	0.4	0.05	0.008	0.4–0.4

Table 1. Patient demographics and surgical risk factors. n = 30 patients undergoing negative pressure ventilation (NPV); BSA (body surface area), BMI (body mass index), HR (heart rate), MABP (mean arterial blood pressure determined before induction of general anesthesia), ASA (American Society of Anesthesiology), STS (Society of Thoracic Surgeons), NTproBNP (N-terminal pro B-type natriuretic peptide), *: estimated creatinine clearance according to Cockcroft-Gault method.

Surgical procedure	n	%		
CABG	2	7		
AV-replacement	11	37		
AV-replacement + CABG	6	20		
AV-replacement + replacement of ascending aorta	2	7		
AV-replacement + replacement of aortic arch	1	3		
AV-replacement + MV-replacement/repair	2	7		
AV-replacement + MV-replacement/repair + CABG	1	3		
MV-replacement/repair + CABG	2	7		
AV-replacement + MV-replacement/repair + TV replacement/repair	1	3		
Replacement of ascending aorta	1	3		
Replacement of aortic arch	1	3		
	Mean	SD	Sem	95% CI
Duration of general anaesthesia [min]	324	95	17	289–360
Duration of surgery [min]	272	84	16	240–304
Duration of cardiopulmonal bypass [min]	159	70	13	132–185
Duration of aortic clamping [min]	116	48	9	98–134

Table 2. Surgical procedures and core data. n = 30 patients undergoing negative pressure ventilation (NPV); CABG (coronary artery bypass grafting), AV (aortic valve), MV (mitral valve).

only). Normally distributed data were analyzed by a paired Student's t-test, otherwise a Wilcoxon matched pairs test was conducted. A p-value of < 0.05 was regarded as statistically significant.

Results

As planned, 30 patients were included in our study and were available for analyses. No patient had to be excluded during the experiments due to hemodynamic instability or complications of the negative pressure ventilation. Patient demographics and surgical/anesthesiological risk factors are presented in Table 1. The surgical procedures as well as surgical core data are presented in Table 2.

	Mean/*median* PPV	Mean/*median* CNPV	mean/*median* of difference	95% CI of difference	*p*
Hemodynamics					
HR (beats/min)	*80*	*80*	*0*	−2 to 0	0.11
SABP (mmHg)	111	114	3	−5 to 12	0.47
MABP (mmHg)	80	80	− 0.2	−4 to 4	0.93
DABP (mmHg)	66	66	− 0.9	−4 to 2	0.64
CVP (mmHg)	*13*	*12*	*− 1*	−2 to −1	< 0.001
PAP syst. (mmHg)	31	32	1	−1 to 3	0.48
PAP med. (mmHg)	*22*	*22*	*− 1*	−1 to 0	0.17
PAP diast. (mmHg)	18	17	− 1	−1 to −0.04	0.04
PAOP (mmHg)	*9*	*6*	*− 2*	−3 to −1	< 0.001
SVI (ml/m^2)	*26*	*28*	*0.5*	−1 to 2.5	0.44
SVI20s (ml/m^2)	26	28	1.8	−4 to 6	0.13
CI (l/min/m^2)	*2.1*	*2.3*	*0.05*	−0.1 to 0.2	0.37
CI20s (l/min/m^2)	*2.1*	*2.3*	*0.15*	−0.1 to 0.4	0.14
EDVI (ml/m^2)	*106*	*99*	*− 10*	−24 to 4	0.12
EDVI20s (ml/m^2)	113	99	- 14	−25 to −2	0.02
RVEF (%)	24	27	3	−0,0006 to 5	0.05
RVEF20s (%)	23	27	3	0,5 to 6	0.02
RVSWI (gm/m^2/beat)	*3.5*	*4*	*0.5*	0 to 1	0.02
LVSWI (gm/m^2/beat)	20.8	22.7	1.9	−0.6 to 4.4	0.13
SVRI (dyn*s/cm^5/m^2)	2754	2764	10	−240 to 261	0.93
PVRI (dyn*s/cm^5/m^2)	267	315	47	−25 to 119	0.19
DO_2 (ml/min)	562	586	24	−9 to 57	0.14
avDifCO_2 (mmHg)	−7.6	−7.5	0.09	−1 to −1.2	0.86
NIRS (%)	59.5	61	1.5	−0.7 to 3.6	0.17
PAPi	*0.9*	*1.2*	*0.3*	0.1 to 0.5	< 0.001
CPI RV (W/m^2)	*0.1*	*0.1*	*0.001*	−0.007 to 0.009	0.75
CPI LV (W/m^2)	*0.4*	*0.4*	*0.01*	−0.02 to 0.04	0.4
RV Ea (mmHg/ml)	0.64	0.64	− 0.0021	−0.08 to 0.07	0.48
RV-PA	0.24	0.27	− 0.025	−0.05 to −0.0009	0.03
Ventilation parameters and blood gas analyses					
SpO_2 (%)	*99*	*99*	*0*	−0.5 to 0.5	1
pO_2 art. (mmHg)	125	133	7	−5 to 20	0.2
pCO_2 art. (mmHg)	43	46	2	0.4 to 4	0.02
pH art	7	7	− 0.01	−0.03 to 0.0001	0.05
SO_2 art. (%)	*99*	*99*	*0.05*	−0.3 to 0.55	0.78
SvO_2 (%)	62	63	1	−1 to 4	0.3
MV (l/min)	6.9	6.5	− 0.3	−0.9 to 0.3	0.29
Echocardiographical variables					
RV FAC (%)	*32*	*30*	*3*	−3 to 10	0.21
RV TAPSE (cm)	*1.3*	*1.3*	*− 0.03*	−0.3 to 0.3	0.88
LVEF (%)	28	31	3	−1 to 7	0.16
LV MAPSE (mm)	9.9	10.5	0.6	−0.3 to 1.6	0.19
LEI-Index	1.1	1.1	0.01	−0.05 to 0.07	0.73
Continued					

	Mean/*median* PPV	Mean/*median* CNPV	mean/*median* of difference	95% CI of difference	*p*
E (m/s)	0.7	0.7	0.04	− 0.04 to 0.1	0.35
A (m/s)	*0.45*	*0.43*	*-0.005*	− 0.075 to 0.045	0.79
e′ (m/s)	*0.07*	*0.07*	*0*	− 0.02 to 0.01	0.9
E/A	1.6	1.7	0.07	− 0.2 to 0.4	0.6
E/e′	*8.2*	*7.4*	*− 0.4*	− 1.7 to 0.7	0.36

Table 3. Comparison between positive pressure ventilation (PPV) and the combination of continuous negative pressure ventilation (CNPV) and PPV. *HR* heart rate, *SABP, MABP, DABP* systolic, mean, and diastolic arterial blood pressure, *CVP* central venous blood pressure, *PAP* pulmonary artery blood pressure, *PAOP* wedge pressure, *SVI* stroke volume index, *CI* cardiac index, *EDVI* enddiastolic volume index, *RVEF* right ventricular ejection fraction, *RVSWI* right ventricular stroke work index, *LVSWI* left ventricular stroke work index, *SVRI* systemic vascular resistance index, *PVRI* pulmonary vascular resistence index, DO_2 delivery of oxygen, $avDifCO_2$ arteriovenous difference of CO_2, art arterial, SvO_2 mixed venous saturation, *MV* minute volume, *RVFAC* right ventricular fractional area change, *RVTAPSE* right ventricular tricuspid anular plane systolic excursion, *PAPi* pulmonary artery pulsatility index, *CPI* cardiac power index left ventricle/right ventricle, *RV* Ea right ventricular arterial elastance, *RV-PA* right ventricular-pulmonary arterial coupling; n = 30.

Effects of CNPV combined with PPV

Application of CNPV was possible in all patients with a mean negative extrathoracic pressure of -20 cmH_2O (95% CI − 20 to − 20). While SVI and SVI20s did not change during the combination of CNPV (− 20 cmH_2O) and PPV, this ventilatory strategy lead to a reduction of central venous pressure (CVP), pulmonary artery diastolic (PAP_{diast}) and occlusion pressure (PAOP), and right ventricular enddiastolic volume index (RVEDVI) and an increase in right ventricular ejection fraction (RVEF), right ventricular stroke work index (RVSWI), right ventricular—pulmonal arterial coupling (RV-PA) and pulmonal artery pulsatility index (PAPi) (Table 3 and Fig. 3). The systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) remained constant during NPV and there was no significant change in right ventricular arterial elastance (RV Ea) (Table 3). Tidal volume and minute volume as well as partial pressure of oxygen (paO_2) and arterial oxygen saturation (SaO_2) remained unchanged during CNPV while a slight increase of partial pressure of carbon dioxide ($paCO_2$) was observed (Table 3). All TEE-derived variables remained unchanged during CNPV + PPV (Table 3).

Effects of BCV

The intended negative pressure of − 30 cmH_2O during inspiration and of + 3 cmH_2O during expiration could be applied in 21 patients with a mean negative extrathoracic pressure of -9 cmH_2O (95% CI − 10 to − 8). In 8 of the left 9 patients the negative pressure during inspiration was between − 20 and − 30 cmH_2O. In one patient an air leakage occurred that limited the negative pressure to − 12 cmH_2O but BCV still resulted in changes of hemodynamics. BCV resulted in markedly decreased airway pressures (Table 4), but to keep a sufficient tidal volume positive pressure support ventilation was still necessary in some patients. 2 patients still needed a positive pressure support of > 10 cmH_2O and 9 patients needed a positive pressure support of > 5 to ≤ 10 cm H_2O during BCV.

No significant changes in tidal or minute volume were observed during BCV. To keep the minute volume and endtidal carbon dioxide (CO_2) stable we had to increase the respiratory rate in some patients slightly during BCV. A slight but significant increase in $paCO_2$ was observed during BCV, but this did not lead to changes in arterial pH. Neither paO_2 nor SaO_2 changed in a statistically significant manner (Table 5).

BCV led to a decrease in CVP and PAOP. Arterial blood pressure and heart rate remained unchanged. Application of BCV led to an increase of PAPi, cardiac power index (CPI) of right ventricle, SVI and SVI20s, RVEF20s, RVSWI, LVEF, Mitral annular plane systolic excursion (MAPSE), RV-PA and delivery of oxygen (DO_2) while CVP and PAOP decreased (Table 5 and Fig. 2). No significant changes were observed in SvO_2, ScO_2, SVRI, PVRI, RV Ea and the difference of arterial and venous CO_2 ($avDCO_2$) (Table 5). We did not observe any changes in tricuspid valve function, i.e. an onset or an increase in tricuspid valve regurgitation.

Subgroup analyses

Dichotomization along the baseline SVI revealed a cut-off value of 27. Isolated analysis of patients showing an SVI20s < 27 ml/min/m^2BSA at beginning of the study (under usual PPV) revealed a more pronounced effect of BCV. Despite of comparable effects on cardiac function patients with an impaired SVI at beginning of the study showed clear signs of improved global balance of oxygen delivery and -consumption, shown by an increase of ScO_2 (+ 4; $p = 0.006$) and SvO_2 (+ 4%; $p = 0.005$). There were small differences of $paCO_2$ compared to the analysis of all patients (Table 6).

Subgroup analyses of hemodynamic changes in patients with or without active epicardial pacing revealed no relevant differences. Patients without stimulation by a pacemaker showed no decrease of heartrate during BCV. Externally paced patients showed comparable DO_2 and SvO_2 when compared to those without active pacemaker (data not shown).

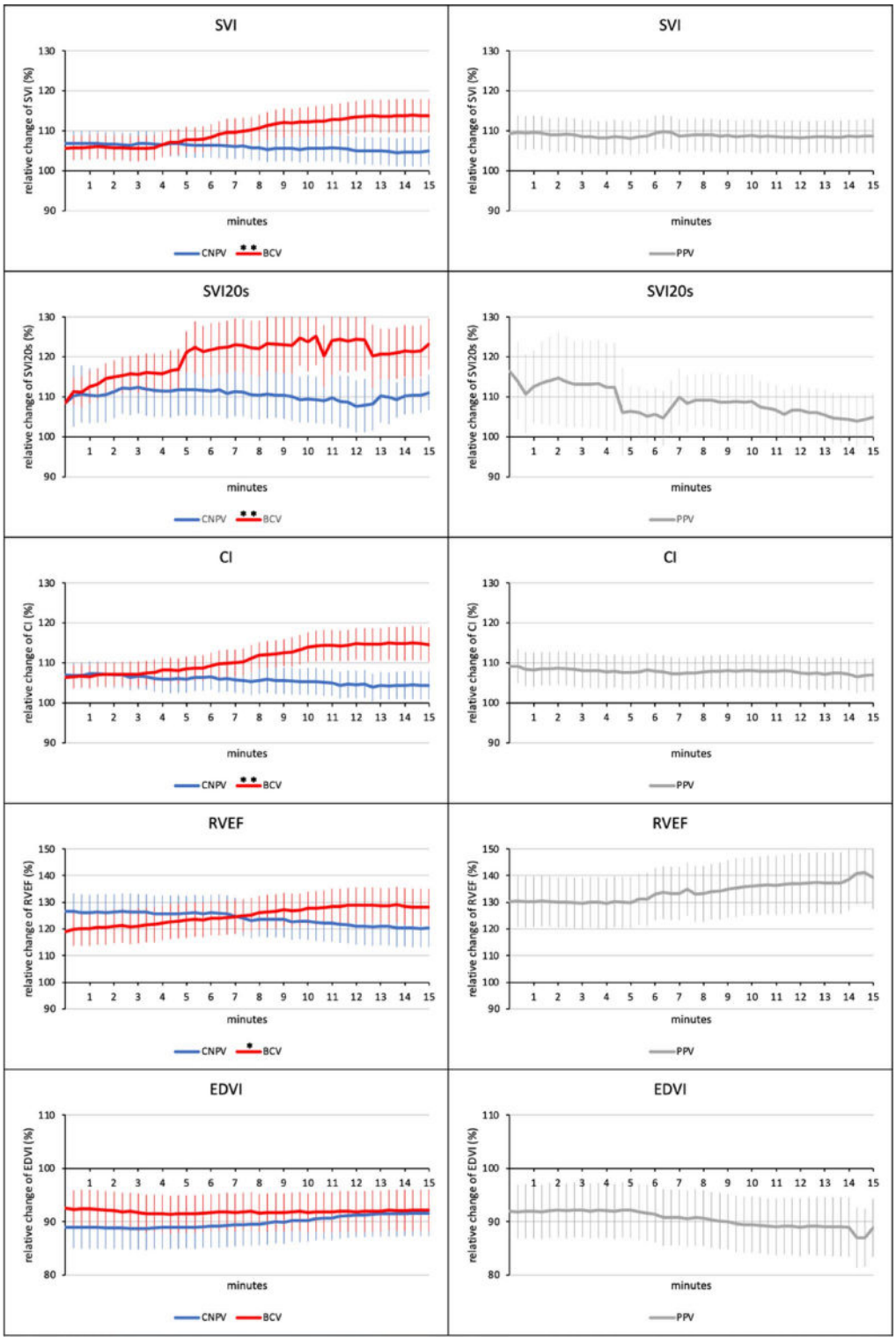

Fig. 3. Changes of measurements via PAC over the time under condition of CNPV and BCV on the left and 15 min of conventional PPV as final treatment of every study on the right. All data is presented as relative changes referring to initial measurement before any treatment. Depicted are measurements of pulmonary artery catheter as percent of initial measurement under conditions of PPV (%) over the time. Different coloured curves show different ventilation modes. Ventilation modes are 15 min of continous negativ pressure ventilation and PPV (CNPV), 15 min of biphasic cuirass ventilation with reduced positive pressure ventilation (BCV) and 15 min of usual positive pressure ventilation as ending of treatment in every single patient (PPV); error bars show ± SEM; n = 30; compared to initial measurement under PPV: * = $p < 0.05$; ** = $p < 0.005$.

	Median PPV	Median BCV ± PPV	Median of difference	95% CI of difference	*p*
Paw peak (cmH_2O)	18	10	− 7	− 9 to − 6	< 0.001
Paw mean (cmH_2O)	10	7	− 3	− 4 to − 2	< 0.001
PEEP (cmH_2O)	7	5	− 0.5	− 2 to 0	0.002

Table 4. Comparison between positive pressure ventilation settings during positive pressure ventilation (PPV) and the combination of biphasic cuirass ventilation (BCV) with reduced PPV. Paw (pressure airway); n = 30.

Discussion

Since the introduction of continuous and undulating negative pressure ventilation by means of a cuirass into clinical practice, several studies in children and adults[13–20] have revealed that these ventilation modes may improve hemodynamics, primarily by increasing stroke volume. The findings of the present study—employing monitoring by a 3rd generation PAC and transesophageal ultrasound—extend these findings by showing that in adult patients after complex cardiac surgery both NPV modalities reduce left and right ventricular filling pressures and that BCV improves not only left but also right ventricular function, at least based on right heart catheter data. In contrast to previous work[23] the improvement in RV-function was not accompanied by a decrease in right ventricular afterload (no changes in PVRI, right ventricular resistance index or right ventricular arterial Elastance (RV Ea)).

The hemodynamic effects of CNPV with a continuous negative extrathoracic pressure of − 20 cm H_2O were less pronounced than the respective changes observed during BCV. In line with our findings, prior studies showed that BCV and CNPV lead to a comparable reduction of CVP and PAOP and an increase in SVI[19] and SvO_2[17] with a superior effect of BCV when compared to CNPV regarding the increase of SVI[24] in spontaneously breathing patients.

Both, CNPV and BCV, seem to improve the relationship of RV contractility and afterload indicated by an improvement of RV-PA during CNPV and BCV. This could explain the improvement of RVEF and PAPi under both conditions. However, due to a lack of changes in right ventricular resistance index, PVRI and right ventricular arterial Elastance (RV Ea) as variables of right ventricular afterload, the underlying mechanism by which NPV improves hemodynamics in this study remains speculative and is not likely to depend on a reduction of right ventricular afterload.

One could speculate that LVEF could worse under condition of NPV because of the often-reported beneficial hemodynamics of the LV under condition of PPV. In reality the impact of PPV on LV-hemodynamics is difficult to predict, because it depends on whether zone 1, 2 or 3 condition predominates in the lung and whether the LV is preload or afterload sensitive[8]. The effect of PPV on LVEF has to be analyzed on a beat-to-beat basis because PPV can lead to a short-term increase of LV preload by applying pressure onto pulmonary vasculature. Nevertheless, the long lasting and dominant effect of PPV seems to be a decrease of LV preload as consequence of a reduction of RV preload in combination with a decrease in LV afterload[9,25].

Whatever the cause, during BCV the presented data show an improved CO around 24% in cardiac index measured every 20 s (CI20s) mainly due to increased stroke volume of + 24% during BCV. Regarding the increase of LVEF around + 15% and LVMAPSE around + 19% combined with an increase in RVEF of + 16% the increased stroke volume seems to appear in right and left heart. This seems not to be due to increased preload because of unchanged EDVI or decreased afterload due to constant PVRI, RV Ea and SVRI. This effect is not influenced by an increased amount of infused volume because this was avoided during the study what is demonstrated by the unchanged EDVI (Table 5).

This could indicate that patients with reduced stroke-volume and therefore patients with an afterload sensitive RV and/or LV could benefit most from the use of NPV. This needs further investigation in upcoming studies.

Due to the possible (short term) increase in LV preload during PPV[8] and—as shown in this and in former studies[21]—one may speculate that NPV has more pronounced hemodynamic effects in patients with an already increased left ventricular enddiastolic pressure (LVEDP) and/or reduced left heart function[14]. Interestingly, when analyzing the total cohort of patients, an increase in CI and improved DO_2 but no signs of improved oxygen balance like an increase of ScO_2 and SvO_2 were observed. Focussing only on patients with preexisting cardiac dysfunction (SVI < 27 ml/min/m^2 BSA at the beginning of the study during PPV) ScO_2 and SvO_2 increased. This suggests that BCV is able to increase CI in all patients but that an improved oxygen balance may only occurs in patients with impaired cardiac performance.

Data dealing with the effects of BCV on heart rate are conflicting showing improved SVI with unchanged heart rate[19] or unchanged cardiac index (CI) despite a decrease in heart rate[20], both situations reflecting improved cardiac performance. To exclude influences of active pacemakers in several patients the difference between paced and non-paced patients was analyzed. Heart rate in both groups remained unchanged during BCV and there was no difference in increase of cardiac performance.

The findings justify investigations if these treatment modalities may impact clinical outcomes in patients with right ventricular dysfunction or failure. Future studies could focus onto the hypothesis that NPV is safe for ventilation in patients on intensive care units after cardiac surgery for an extended period of time or onto the confirmation of improved organ function (for example kidney function) due to enhanced hemodynamics during NPV.

	Mean/*median* PPV	Mean/*median* BCV ± PPV	Mean/*median* of difference	95% CI of difference	*p*
Hemodynamics					
HF (beats/min)	*80*	*80*	*0*	0 to 0	0.86
SABP (mmHg)	111	111	0.1	− 11 to 11	0.99
MABP (mmHg)	81	80	− 0.9	− 9 to 7	0.82
DABP (mmHg)	67	65	− 2	− 8 to 4	0.49
CVP (mmHg)	*13*	*11*	*− 1*	− 2 to 1	0.004
PAP syst. (mmHg)	31	33	1	− 1 to 3	0.17
PAP med. (mmHg)	*22*	*23*	*0*	− 1 to 2	0.89
PAP diast. (mmHg)	18	18	− 1	− 2 to 0.2	0.1
PAOP (mmHg)	*16*	*14*	*− 2*	− 3 to − 0.5	0.007
SVI (ml/m^2)	26	28	3	1 to 5	0.003
SVI20s (ml/m^2)	26	33	6	3 to 9	< 0.001
CI (l/min/m^2)	2	2.3	02	0.1 to 0.4	0.002
CI20s (l/min/m^2)	2.1	2.5	0.5	0.2 to 0.8	0.001
EDVI (ml/m^2)	*106*	*95*	*− 8*	− 23 to 2	0.15
EDVI20s (ml/m^2)	*109*	*96*	*− 9*	− 23 to 3	0.14
RVEF (%)	*24*	*27*	*5*	2 to 7	0.008
RVEF20s (%)	24	28	4	1 to 7	0.008
RVSWI (gm/m^2/beat)	*3.5*	*4*	*0.5*	0 to 1	0.008
LVSWI (gm/m^2/beat)	20.8	25.4	4.6	1.7 to 7.4	0.003
SVRI (dyn*s/cm^5/m^2)	*2754*	*2565*	*− 189*	976 to 987	0.17
PVRI (dyn*s/cm^5/m^2)	*263*	*327*	*36*	− 30 to 102	0.27
DO_2 (ml/min)	562	634	72	34 to 110	< 0.001
avDifCO_2 (mmHg)	− 7.6	− 6.8	0.8	− 0.3 to 2	0.16
NIRS (%)	60	51	2	− 0.04 to 4	0.05
PAPi (mmHg)	*0.9*	*1.3*	*0.3*	0.2 to 0.5	< 0.001
CPI RV (W/m^2)	0.11	0.12	0.01	0.003 to 0.02	*0.01*
CPI LV (W/m^2)	*0.36*	*0.4*	*0.04*	*− 0.01 to 0.09*	0.13
RV Ea (mmHg/ml)	0.64	0.62	0.03	− 0.03 to 0.08	0.19
RV-PA	0.24	0.28	− 0.45	− 0.07 to − 0.02	0.002
Respiratory and blood gases					
SpO2 (%)	*99*	*98.5*	*− 0.5*	− 1.5 to 0	0.05
pO_2 art. (mmHg)	*115*	*100*	*− 1.5*	− 12 to 12	0.81
pCO_2 art. (mmHg)	43	45	2	0.1 to 4	0.04
pH art	7.4	7.4	− 0.009	− 0.02 to 0.007	0.28
SO_2 art. (%)	99	98	− 0.15	1.2 to 0.3	0.47
SvO_2 (%)	61.5	63.1	1.6	− 0.9 to 4.1	0.21
Ppeak (cmH_2O)	*18*	*10*	*− 7*	− 9 to − 6	< 0.001
Pmean (cmH_2O)	*10*	*7*	*− 3*	− 4 to − 2	< 0.001
PEEP (cmH_2O)	*7*	*5*	*− 0.5*	− 2 to 0	0.002
Resp. Rate (breaths/min)	*14*	*15*	*0*	0 to 2	002
Tidal volume (ml)	522	490	− 33	− 68 to 3	0.07
MV (l/min)	6.9	6.7	− 0.2	− 0.7 to 0.3	0.48
Ultrasound					
RV FAC (%)	*32*	*31*	*1.4*	− 5 to 9	0.65
RV TAPSE (cm)	*1.3*	*1.4*	*− 0.05*	− 0.3 to 0.2	0.66
LVEF (%)	*31*	*31*	*5*	1 to 9	0.01
LV MAPSE (mm)	9.9	11.8	1.9	0.7 to 3	0.003
LEI	1.1	1.1	− 0.01	− 0.09 to 0.06	0.73
Continued					

	Mean/*median* PPV	Mean/*median* BCV ± PPV	Mean/*median* of difference	95% CI of difference	*p*
E (m/s)	*0.6*	*0.7*	*0.07*	0.01 to 0.1	0.02
A (m/s)	*0.5*	*0.4*	*− 0.005*	− 0.06 to 0.04	0.7
e′ (m/s)	*0.07*	*0.07*	*0*	− 0.01 to 0.02	0.74
E/A	1.6	1.7	0.08	− 0.2 to 0.4	0.55
E/e′	*8.3*	*8.2*	*1*	− 0.4 to 3.1	0.18

Table 5. Comparison between positive pressure ventilation (PPV) and biphasic cuirass ventilation (BCV) with or without PPV. *HF* heart frequency, *SABP, MABP, DABP* systolic, mean, and diastolic arterial blood pressure, *CVP* central venous blood pressure, *PAP* pulmonary artery blood pressure, *PAOP* wedge pressure, *SVI* stroke volume index, *CI* cardiac index, *EDVI* enddiastolic volume index, *RVEF* right ventricular ejection fraction, *RVSWI* right ventricular stroke work index, *LVSWI* left ventricular stroke work index, *SVRI* systemic vascular resistance index, *PVRI* pulmonary vascular resistence index, DO_2 delivery of oxygen, $avDifCO_2$ arteriovenous difference of CO_2, art arterial, SvO_2 mixed venous saturation, *MV* minute volume, *RVFAC* right ventricular fractional area change, *RVTAPSE* right ventricular tricuspid anular plane systolic excursion, *PAPi* pulmonary artery pulsatility index, *CPI* cardiac power index left ventricle/right ventricle, *RV* Ea right ventricular arterial elastance, *RV-PA* right ventricular-pulmonary arterial coupling; n = 30.

	Mean/*median* PPV	Mean/*median* BCV ± PPV	Mean/*median* of difference	95% CI of difference	*p*
Hemodynamics					
HF (beats/min)	80	80	0	0,8 to 1,0	0.7
SABP (mmHg)	110	116	6	− 7 to 19	0.35
MABP (mmHg)	81	83	2	− 8 to 12	0.68
DABP (mmHg)	*69*	*69*	*0*	*− 8 to 8*	0.97
CVP (mmHg)	*14*	*12*	*− 1*	*− 4 to 2*	0.39
PAP syst. (mmHg)	30	33	3	− 2 to 8	0.33
PAP med. (mmHg)	22	23	1	− 3 to 5	0.47
PAP diast. (mmHg)	20	19	− 1	− 3 to 1	0.38
PAOP (mmHg)	18	15	− 2	− 5 to 0	0.06
SVI20s (ml/m^2)	*22*	*29*	*7*	*2 to 11*	0.007
CI20s (l/min/m^2)	*1.7*	*2.5*	*0.7*	*0.2 to 1.2*	0.006
EDVI20s (ml/m^2)	101	95	− 6	− 30 to 9	0.42
RVEF20s (%)	20	25	5	1 to 10	0.02
SVRI (dyn*s/cm^5/m^2)	*3167*	*2842*	*− 325*	*− 772 to 122*	0.14
PVRI (dyn*s/cm^5/m^2)	*323*	*300*	*46*	*− 75 to 182*	0.36
DO_2 (ml/min)	496	616	120	56 to 183	0.001
$avDifCO_2$ (mmHg)	− 9	− 7	2	− 0.2 to 3	0.08
NIRS (%)	*58*	*62*	*4*	*1 to 6*	0.006
Blood gases					
pO_2 art. (mmHg)	126	133	8	− 10 to 25	0.37
pCO_2 art. (mmHg)	42	45	3	0.3 to 5	0.03
SvO_2 (%)	58	62	4	1 to 6	0.005
Ultrasound					
RV FAC (%)	25	25	0	− 10 to 10	0.42
RV TAPSE (cm)	*1.3*	*1.1*	*− 0.05*	− 0.5 to 0.3	0.76
LVEF (%)	25	29	5	− 4 to 16	0.24

Table 6. Comparison between positive pressure ventilation (PPV) and the combination of biphasic cuirass ventilation (BCV) with reduced PPV in patients with initially reduced SVI (SVI < 27 ml/min/m2BSA at moment of PPV). *HF* heart frequency, *SABP, MABP, DABP* systolic, mean, and diastolic arterial blood pressure, *CVP* central venous blood pressure, *PAP* pulmonary artery blood pressure, *PAOP* wedge pressure, *SVI* stroke volume index, *CI* cardiac index, *EDVI* enddiastolic volume index, *RVEF* right ventricular ejection fraction, *SVRI* systemic vascular resistance index, *PVRI* pulmonary vascular resistence index, DO_2 delivery of oxygen, $avDifCO_2$ arteriovenous difference of CO_2, art arterial, SvO_2 mixed venous saturation, *RVFAC* right ventricular fractional area change; *RVTAPSE* right ventricular tricuspid anular plane systolic excursion; n = 14.

Limitations

The measurements were performed in the immediate postoperative period. Despite there was no change in dosing of vasopressors and inotropes during our experiments it cannot be completely ruled out that the hemodynamic status of examined patients was influenced by the specific changes in vascular tone typically observed after cardiac surgery with cardiopulmonary bypass in moderate hypothermia[26]. Thus, our findings need to be replicated in other clinical settings and ideally also outside the field of cardiac surgery.

As mentioned in the experimental setup section we considered a randomization as not absolutely necessary due to the alternating sequence of ventilation. Nevertheless, an influence of the initial ventilation mode onto the following ventilation mode cannot be completely excluded.

2 patients still needed an additional positive pressure support during BCV of > 10 cmH_2O and 9 patients of > 5 cmH_2O to ≤ 10 cm H_2O to keep sufficient tidal volumes during BCV. This could have limited the effect of BCV leading to underestimation of the hemodynamic effects of BCV. It is well known that extrathoracic negative pressure results in a variable amount of intrathoracic negative pressure in individual patients. An esophageal pressure measurement would have been helpful to determine the exact amount of transpulmonal pressure, but due to the esophageal ultrasound there was no possibility for such a measurement. Following studies should consider to include an esophageal pressure measurement as part of the experimental setup.

It is still unclear with which amount of delay data is processed and displayed by 3rd generation PAC. For this reason, it is obscure whether time delayed character of hemodynamic changes after initiation or withdrawal of negative pressure ventilation is due to retarded effect of changed ventilation or due to delayed measurement.

One dataset represents a measurement under condition of usual PPV for 15 min as last measurement in every patient (Fig. 3) to exclude a carry over effect only depending on time after surgery and improvement of cardiac function independent of ventilation mode. Here it becomes obvious that the increase of SVI20 and CI during BCV is unlikely to solely depend on passing of time because in this case the increase would proceed. Nevertheless a carry over effect between different treatments or an effect depending on time after surgery can not be ruled out completely.

The measurement of transpulmonal pressure was not possible due to concomitant use of the TEE probe. Measurement of transpulmonal pressure would maybe have enabled more negative extrathoracic pressures with increased tidal volumes and a decreased need for additional intrathoracic pressure during BCV + PPV. This would may have led to an increased improvement of hemodynamics during BCV. Future studies in this field without need of transesophageal ultrasound should consider adding intrathoracic pressure measurement during treatment.

Conclusion

While CNPV has only moderate hemodynamic effects, BCV improves systemic and right ventricular hemodynamics as well as global oxygen balance in patients after complex cardiac surgery. During both NPV modes no adverse events could be detected in the real-world setting. These findings justify investigations if these treatment modalities may impact clinical outcomes in patients with right ventricular dysfunction or failure.

Data availability

Data supporting the findings of this study are available within the paper, further data are available from the corresponding author upon reasonable request.

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Author contributions

SS: Substantial contributions to the conception, design of the work, acquisition of data, analysis of data, interpretation of data, drafted the work, substantively revised the work HG: Design of the work, acquisition of data, analysis of data, interpretation of data LS: Analysis of data, interpretation of data, drafted the work, substantively revised the work KF: Analysis of data, interpretation of data, substantively revised the work DH: Acquisition of data, revised the manuscript for important intellectual content MH: Substantial contributions to the conception, design of the work, analysis of data, interpretation of data, substantively revised the work LM: Acquisition of data, revised the manuscript for important intellectual content All authors approved the final version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was approved by the local ethics committee (reference number BB 041/23, Ethikkommission der Universität Greifswald, Felix-Hausdorff-Straße 3, 17487 Greifswald). Written consent of every patient was obtained before considering inclusion.

Additional information

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