Pediatr Cardiol (2016) 37:1064–1071
DOI 10.1007/s00246-016-1392-9

ORIGINAL ARTICLE

Mechanical Ventilation After Bidirectional Superior Cavopulmonary Anastomosis for Single-Ventricle Physiology: A Comparison of Pressure Support Ventilation and Neurally Adjusted Ventilatory Assist

Limin Zhu[1] · Zhuoming Xu[1] · Xiaolei Gong[1] · Jinghao Zheng[1] · Yanjun Sun[1] · Liping Liu[1] · Lu Han[1] · Haibo Zhang[1] · Zhiwei Xu[1] · Jinfen Liu[1] · Peter C. Rimensberger[2]

Received: 3 October 2015 / Accepted: 5 April 2016 / Published online: 18 April 2016

Abstract We evaluated the effects of different respiratory assist modes on cerebral blood flow (CBF) and arterial oxygenation in single-ventricle patients after bidirectional superior cavopulmonary anastomosis (BCPA). We hypothesized that preserved auto-regulation of respiration during neurally adjusted ventilatory assist (NAVA) may have potential advantages for CBF and pulmonary blood flow regulation after the BCPA procedure. We enrolled 23 patients scheduled for BCPA, who underwent pressure-controlled ventilation (PCV), pressure support ventilation (PSV), and NAVA at two assist levels for all modes in a randomized order. PCV targeting large V_T (15 mL × kg^{-1}) resulted in lower CBF and oxygenation compared to targeting low V_T (10 mL × kg^{-1}). During PSV and NAVA, ventilation assist levels were titrated to reduce EAdi from baseline by 75 % (high assist) and 50 % (low assist). High assist levels during PSV (PSV_{high}) were associated with lower $PaCO_2$, PaO_2, and O_2SAT, lower CBF, and higher pulsatility index compared with those during $NAVA_{high}$. There were no differences in parameters when using low assist levels, except for slightly greater oxygenation in the $NAVA_{low}$ group. Modifying assist levels during NAVA did not influence hemodynamics, cerebral perfusion, or gas exchange. Targeting the larger V_T during PCV resulted in hyperventilation, did not improve oxygenation, and was accompanied by reduced CBF. Similarly, high assist levels during PSV led to mild hyperventilation, resulting in reduced CBF. NAVA's results were independent of the assist level chosen, causing normalized $PaCO_2$, improved oxygenation, and better CBF than did any other mode, with the exception of PSV at low assist levels.

Keywords Heart defect · Congenital · Bidirectional superior cavopulmonary anastomosis · Cerebrovascular circulation · Mechanical ventilation · Neurally adjusted ventilatory assist

Introduction

In the staged surgical reconstruction of a single functional ventricle resulting in a total cavopulmonary connection (modified Fontan operation), the intermediate stage is a bidirectional superior cavopulmonary anastomosis (BCPA). The intervention is aimed at increasing effective pulmonary blood flow (PBF) [1–3]. This operation routes blood flow from the superior vena cava directly into the pulmonary arteries, whereas blood flow from the inferior vena cava and coronary veins enters the single ventricle directly.

After BCPA, PBF is derived only from the upper body venous return, which, in the infant, largely reflects cerebral blood flow (CBF). Under these circumstances, the cerebral and pulmonary auto-regulatory mechanisms are in direct competition with each other, and the net result on organ perfusion will be different from that in individuals with normal ventricle physiology [2–4]. A unique consequence of BCPA [2, 3] circulation is that systemic arterial oxygenation is the weighted average of deoxygenated blood

✉ Limin Zhu
zhulimin121@hotmail.com

[1] Cardiac Intensive Care Unit, Department of Cardiovascular and Thoracic Surgery, Shanghai Children's Medical Center, Medical School of Shanghai Jiaotong University, Shanghai 200127, China

[2] Pediatric and Neonatal Intensive Care Unit, Department of Pediatrics, University Hospital of Geneva, Geneva, Switzerland

coming from the inferior vena cava and oxygenated blood from the pulmonary veins. CBF and its auto-regulation may have important clinical implications for the postoperative management and early and late neurodevelopmental outcomes after BCPA [5–8]. Hypercapnia with acidosis increases CBF [9–12] and reduces PBF by increasing pulmonary vascular resistance (PVR) in normal circulation, after cardiopulmonary bypass (CPB), and during anesthesia [13–15]. A unique aspect of PBF physiology after BCPA is the interaction of two highly autonomically regulated vascular beds—cerebral and pulmonary circulation—that have opposite responses to changes in CO_2 and acid–base status.

Neurally adjusted ventilatory assist (NAVA) delivers ventilation in proportion to neural inspiratory effort, thus taking advantage of the respiratory control feedback loop [16–18]. Electrical activity of the diaphragm (EAdi) is a measure of the patient's neural drive, auto-regulated by the patient's neuroventilatory coupling. During NAVA, the EAdi signal determines both timing and amplitude of the ventilatory assist, resulting in a proportional respiratory assist determined by an operator-set proportionality factor (NAVA level).

Therefore, we hypothesized that preserved auto-regulation of respiration during NAVA may have potential advantages for CBF and PBF regulation after the BCPA procedure and that this would result in an optimal balance between adequate pulmonary perfusion and CBF post-BCPA. Hence, this report concentrates on middle cerebral artery blood flow (MCABF) and gas exchange effects induced by different levels of ventilator assist during pressure-controlled ventilation (PCV), pressure support ventilation (PSV), and NAVA.

Materials and Methods

Patients

The study protocol was approved by the research and ethics review board at Shanghai Children's Medical Center, China. Informed and signed consent were obtained from the parents of all patients. Twenty-three patients with a median age of 10.0 months (range 4–39 months) and a median weight of 7.5 kg (range 5–11.5 kg) scheduled for BCPA were enrolled preoperatively. The demographic, diagnostic, and surgical characteristics analyzed are described in Table 1.

Surgical Procedures and Postoperative Strategy

All patients were intubated with a cuffed endotracheal tube (Mallinckrodt Medical, Westmeath, Ireland). General anesthesia was maintained with inhaled sevoflurane, intravenous fentanyl, and pancuronium bromide. CPB with modified ultrafiltration was performed for 56–120 min (median 98 min) without aortic cross-clamping in 22 patients (Table 1) as the routine strategy in our institution, while another patient underwent the BCPA procedure without CPB. All patients were weaned from CPB when the transesophageal temperature reached 35 °C and hemodynamic stability was achieved. On return to the cardiac intensive care unit, patients were mechanically ventilated with a Servo-i ventilator (Maquet Critical Care, Solna, Sweden) capable of delivering PCV, PSV, and NAVA. The FiO_2 was 0.40–0.60 in all patients. The aim of mechanical ventilation was to maintain $PaCO_2$ at 40 mmHg and PaO_2 ≥40 mmHg. Rectal temperature was maintained at 36–37.5 °C using a cooling or warming blanket. The patients received infusions of propofol (2 mg/kg/h) for the duration of the study. Hemoglobin concentration was maintained at or above 120 g/L. Dopamine (5 mcg/kg/min) and milrinone (0.5 mcg/kg/min) were infused to maintain hemodynamic stability. Superior vena cava pressure was monitored and maintained between 10–20 mmHg by infusion of 5 % albumin (5 mL/kg) before the start of the study. After stabilization, the insertion and correct positioning of the EAdi catheter were assured by means of a specific function in the ventilator ("EAdi catheter positioning"). Inotropes, vasodilators, PEEP, and FiO_2 were not adjusted after study initiation.

Measurements

Patient Monitoring

All patients underwent continuous invasive monitoring of systemic arterial and superior vena cava pressure, which was considered central venous pressure (CVP). Heart rate (HR), arterial blood pressure (BP), respiratory rate (RR), airway pressure [such as positive inspiratory pressure (PIP) and mean airway pressure (MAP)], tidal volumes (V_T) delivered by the ventilator, and rectal temperature were monitored continuously. Before the beginning of the study, the endotracheal tube cuff was checked and inflated to eliminate gas leaks. EAdi and respiratory variables were monitored from the Servo-i ventilator.

Arterial Blood Gases (ABGs)

Arterial blood samples were obtained from the peripheral arterial catheter and analyzed for $PaCO_2$, PaO_2, SaO_2, and pH using a blood gas analyzer (ABL 850, Radiometer Copenhagen, Copenhagen, Denmark).

Table 1 Patient characteristics at enrollment

Case no.	Sex	Age, mos	Weight, kg	Diagnosis	Previous operations	Operation	CPB time, min
1	F	16	7.5	D-TGA, VSD, TA, PS	None	Right BCPA	50
2	F	7	5.3	Dextrocardia, DORV, remote VSD, PS	None	Right BCPA	42
3	M	39	11.5	Dextrocardia, L-TGA, remote VSD, PS	None	Right BCPA	39
4	***F***	***10***	***7.5***	***DORV, remote VSD, PS, bilateral SVC***	***PAB***	***Bilateral BCPA***	***74***
5	M	24	11.5	TA, PH, bilateral SVC	PAB	Bilateral BCPA	Off pump
6	F	11	6.3	SV, PH	PAB	Right BCPA	38
7	F	6	7.8	DORV, remote VSD, PS, bilateral SVC	None	Bilateral BCPA	106
8	M	8	6	D-TGA, VSD, PS, bilateral SVC	None	Bilateral BCPA	49
9	M	16	10.5	DORV, remote VSD, PS	None	Right BCPA	52
10	F	5	6	Dextrocardia, DORV, UAVSD, PS	None	Left BCPA	59
11	M	6	8	Dextrocardia, SV, MGA, PS	None	Right BCPA	29
12	F	6	5	HRV	None	Right BCPA	72
13	M	6	6	Dextrocardia, SV, SA, PS, bilateral SVC	None	Bilateral BCPA	127
14	M	25	10.5	DORV, UAVSD, PS	None	Right BCPA	39
15	F	17	9.5	Dextrocardia, DORV, remote VSD, PS, bilateral SVC	None	Bilateral BCPA	55
16	M	18	10	DORV, UAVSD, PS, bilateral SVC	None	Bilateral BCPA	67
17	M	4	5	Dextrocardia, SV, MGA, PS, TAPVC, bilateral SVC	None	Bilateral BCPA + TAPVC repair	110
18	F	8	7	DORV, remote VSD, PS, bilateral SVC	None	Bilateral BCPA	55
19	M	8	10	DORV, VSD, ASD, PS,	None	Right BCPA	56
20	M	7	5.7	SV, SA, UAVSD, PA, bilateral SVC	None	Bilateral BCPA	75
21	***M***	***9***	***7***	***DORV, UAVSD, ASD, PS, bilateral SVC***	***None***	***Bilateral BCPA***	***73***
22	M	10	8	PA, VSD, bilateral SVC	None	Bilateral BCPA	72
23	F	14	10	SV, SA, PA, bilateral SVC	None	Bilateral BCPA	68

Entries in bold text indicate patients who were excluded from analysis

ASD atrial septal defect; *BCPA* bidirectional superior cavopulmonary anastomosis; *CPB* cardiopulmonary bypass; *D-TGA* d-transposition of the great arteries; *DORV* double-outlet right ventricle; *HRV* hypoplastic right ventricle; *L-TGA* left transposition of the great arteries; *MGA* malposition of the great arteries; *PA* pulmonary atresia; *PAB* pulmonary artery banding; *PH* pulmonary hypertension; *PS* pulmonary stenosis; *SA* single atrium; *SV* single ventricle; *SVC* superior vena cava; *TA* tricuspid atresia; *TAPVC* total anomalous pulmonary venous connection; *UAVSD* unbalanced atrioventricular septal defect; and *VSD* ventricular septal defect

Transcranial Doppler (TCD)

The flow velocity through the middle cerebral artery (MCA) was measured with a 2-MHz pulse-wave ultrasound transducer (EMS-9UA), fixed above the zygomatic arch with a soft rubber holder (Delica Electronics Co., Ltd. Shenzhen, China). The transducer interrogated the portion of the MCA near its junction to the ipsilateral anterior cerebral artery.

Study Protocol

The study protocol was started within 2 h of discontinuation of CPB and as soon as a cardiorespiratory steady state was achieved. The protocol consisted of two periods, which were defined as control ventilation and assist ventilation. FiO_2 was fixed at 0.4 for all patients after study initiation. PEEP, routinely set at 3–4 cmH_2O, was maintained constant throughout the study period. During the first period of the study, all subjects were ventilated with PCV titrated to achieve a tidal volume (V_T) of 10 mL/kg (PCV_{low}) or 15 mL/kg (PCV_{high}) at the same respiratory frequency for 30 min with a close monitor of ventilator pressure and hemodynamic in a random order before awake from anesthesia. If hemodynamic instability of patient or the peak inspiratory pressure was more than 20 cmH_2O, he will be withdrawn from the study immediately. When the first period was finished and signs of EAdi recovery were registered, the second study period was initiated. EAdi level after 2 min of continuous positive airway pressure was considered $EAdi_{base}$. After establishing $EAdi_{base}$, administration of two levels of PSV and NAVA was

initiated, following a predefined computer-generated random sequence, defined as $level_{low}$ and $level_{high}$. Respiratory assist was delivered to achieve a reduction in peak EAdi by 50 % of $EAdi_{base}$ (PSV_{low}) and ($NAVA_{low}$). During $level_{high}$, respiratory assist was administered to achieve a reduction in peak EAdi by 75 % of $EAdi_{base}$ (PSV_{high}) and ($NAVA_{high}$). Each patient underwent four 30-min trials during the second period. The last 5 min of each trial was recorded and stored on a dedicated personal computer for data analysis. The systolic peak velocity (V_s) and the end diastolic velocity (V_d) of MCABF measured by TCD were recorded during the last 2 min of each trial. The mean velocity (V_m) of MCABF was calculated as "$V_m = (V_s - V_d)/3 + V_d$." The pulsatility index (PI) was calculated as "$PI = (V_s - V_d)/V_m$." At the end of each test period, an arterial blood sample was collected for blood gas analysis.

Data Analysis

Data are expressed as mean ± standard deviation using SAS 9.2 statistical software (SAS Institute, Cary, NC). PCV_{low} and PCV_{high} from the first period and data from the four registrations in the second period were compared using a repeated-measures ANOVA. The comparison of different levels of assistance within each mode (PSV_{low} vs. PSV_{high} and $NAVA_{low}$ vs. $NAVA_{high}$) and equivalent levels of assistance (PSV_{low} vs. $NAVA_{low}$ and PSV_{high} vs. $NAVA_{high}$) was assessed by the least significant difference (LSD) methods post hoc test. A p value of <0.05 was considered significant.

Results

Twenty-three patients were enrolled in this study; two patients did not complete the study and were not included in the data analysis. Both excluded patients, marked in Table 1, did not complete the study protocol due to failure to obtain a consistent EAdi signal. Ultrasound examination revealed bilateral diaphragmatic paralysis in both subjects.

PCV with Low and High Tidal Volume Targets

In the first study period, PCV_{low} versus PCV_{high}, patients were hyperventilated during the PCV_{high} but not during the PCV_{low} period, with pH values of 7.47 ± 0.05 versus 7.42 ± 0.05 ($P < 0.001$), and $PaCO_2$ values of 33.5 ± 5.5 versus 39.3 ± 7.2 mmHg ($P < 0.001$), respectively. Resulting ventilator pressure and oxygenation data for both groups are given in Table 2. The PCV_{high} group had higher CVP compared to the PCV_{low} group (16 ± 4 vs. 15 ± 4 mmHg; $P = 0.001$). MCABF velocity values were lower in the PCV_{high} group compared to the PCV_{low} group (V_s, 96.6 ± 28.3 vs. 101.8 ± 24.9 m s^{-1}; $P = 0.029$; V_m, 50.1 ± 16.5 vs. 53.8 ± 16.3 m s^{-1}; $P = 0.042$; and V_d, 26.7 ± 9.7 vs. 32.2 ± 11.3 m s^{-1}; $P < 0.001$). PI was higher during PCV_{high} than during PCV_{low} (1.5 ± 0.2 vs. 1.3 ± 0.3, $P < 0.001$) (Table 2).

Table 2 Results of the first study period

Major indicator	Ventilation mode		P value
	PCV_{low}	PCV_{high}	
Hemodynamics			
HR (beats/min)	146 ± 19[a]	146 ± 18	0.258
SBP (mmHg)	93 ± 16	94 ± 15	0.703
CVP (mmHg)	15 ± 4	16 ± 4	0.001
Breathing pattern			
RR (breaths/min)	20 ± 1	20 ± 1	–
V_T (mL × kg^{-1})	9.7 ± 0.4	14.2 ± 0.6	<0.001
PIP (cmH_2O)	11.3 ± 3.7	15.9 ± 3.9	<0.001
MAP (cmH_2O)	4.2 ± 1.8	6.4 ± 2.1	<0.001
MCA blood flow			
V_s (m × s^{-1})	101.8 ± 24.9	96.6 ± 28.3	0.029
V_m (m × s^{-1})	53.8 ± 16.3	50.1 ± 16.5	0.042
V_d (m × s^{-1})	32.2 ± 11.3	26.7 ± 9.7	<0.001
PI	1.3 ± 0.31	1.5 ± 0.2	0.001
Arterial blood analysis			
pH	7.42 ± 0.05	7.47 ± 0.05	<0.001
$PaCO_2$ (mmHg)	39.3 ± 7.2	33.5 ± 5.5	<0.001
PaO_2 (mmHg)	47.5 ± 7.7	42.3 ± 7.9	<0.001
SaO_2 (%)	82.0 ± 5.3	77.6 ± 7.4	<0.001

CVP central venous pressure; *HR* heart rate; *MAP* mean airway pressure; *MCA* middle cerebral artery; *$PaCO_2$* arterial carbon dioxide tension; *PaO_2* arterial oxygen tension; *PCV* pressure-controlled ventilation; *PI* pulsatility index of middle cerebral artery blood flow; *PIP* peak inspiratory pressure; *RR* respiratory rate; *SaO_2* systemic arterial oxygen saturation; *SBP* systolic arterial pressure; *V_d* end diastolic velocity of middle cerebral artery blood flow; *V_m* mean velocity of middle cerebral artery blood flow; *V_s* systolic velocity of middle cerebral artery flow; and *V_T* tidal volume

[a] Data are expressed as mean ± standard deviation

PSV Versus NAVA

Among the four groups on a ventilatory assist mode, either PSV or NAVA at low or high levels of assist resulted in several differences in ventilation parameters (e.g., airway pressures and V_T), blood gases, and cerebral blood flow (see Table 3). Post hoc analysis showed the following main differences between various combinations of ventilator modes and assist levels:

1. PSV_{high} versus PSV_{low} and $NAVA_{high}$ versus $NAVA_{low}$, respectively

Table 3 Results of the second study period

Ventilation mode							
Major indicator	PSV_{low}	PSV_{high}	*P* value, PSV_{low} versus PSV_{high}	$NAVA_{low}$	$NAVA_{high}$	*P* value, $NAVA_{low}$ versus $NAVA_{high}$	*P* value
Hemodynamics							
HR (beats/min)	143 ± 16[a]	141 ± 20	0.27	142 ± 15	140 ± 15	0.452	0.598
SBP (mmHg)	96 ± 17	94 ± 14	0.451	97 ± 14	97 ± 14	0.979	0.631
CVP (mmHg)	14 ± 4	14 ± 4	0.779	13 ± 3	13 ± 3	0.485	0.134
Breathing pattern							
RR (breaths/min)	29 ± 8	26 ± 8	0.034	30 ± 9	28 ± 9	0.081	0.012
V_T (mL × kg^{-1})	10.2 ± 2.5	12.2 ± 3.8	0.001	10.0 ± 3.1	10.6 ± 2.9**	0.264	0.001
PIP (cmH_2O)	8.5 ± 3.0	11.5 ± 3.5	<0.001	8.5 ± 3.1	9.7 ± 5.2**	0.100	<0.001
MAP (cmH_2O)	3.5 ± 1.2	4.5 ± 1.7	<0.001	3.4 ± 1.2	3.7 ± 1.6**	0.215	<0.001
$EAdi_{peak}$ (μV)	7.0 ± 4.0	4.1 ± 2.3	<0.001	6.7 ± 3.6	4.1 ± 2.1	<0.001	<0.001
$EAdi_{mini}$ (μV)	0.7 ± 0.7	0.6 ± 0.6	0.505	0.5 ± 0.4*	0.5 ± 0.4*	0.780	0.007
MCA blood flow							
V_s (m × s^{-1})	99.6 ± 28.3	97.5 ± 27.7	0.431	99.0 ± 23.9	98.0 ± 27.7	0.705	0.860
V_m (m × s^{-1})	57.0 ± 17.5	53.4 ± 16.0	0.030	58.7 ± 16.1	55.4 ± 16.0	0.051	0.017
V_d (m × s^{-1})	35.7 ± 14.0	34.7 ± 12.8	0.019	33.6 ± 13.6	35.2 ± 13.1**	0.159	0.001
PI	1.2 ± 0.3	1.3 ± 0.4	0.264	1.1 ± 0.3**	1.2 ± 0.3**	0.246	0.001
Arterial blood analysis							
pH	7.41 ± 0.03	7.45 ± 0.06	0.002	7.43 ± 0.05	7.42 ± 0.03**	0.385	0.008
$PaCO_2$ (mmHg)	39.9 ± 6.8	34.5 ± 6.6	<0.001	37.6 ± 6.4**	38.1 ± 6.0**	0.593	<0.001
PaO_2 (mmHg)	45.7 ± 8.9	43.7 ± 8.6	0.013	46.6 ± 8.9	46.7 ± 8.0**	0.918	0.001
SaO_2 (%)	79.6 ± 10.3	79.0 ± 9.1	0.424	81.9 ± 8.6**	82. 0 ± 7.5**	0.959	<0.001

CVP central venous pressure; *$EAdi_{mini}$* minimal electrical activity of the diaphragm; *$EAdi_{peak}$* maximal electrical activity of the diaphragm; *HR* heart rate; *MAP* mean airway pressure; *MCA* middle cerebral artery; *NAVA* neutrally adjusted ventilatory assist; *$PaCO_2$* arterial carbon dioxide tension; *PaO_2* arterial oxygen tension; *PCV* pressure-controlled ventilation; *PI* pulsatility index of middle cerebral artery blood flow; *PIP* peak inspiratory pressure; *PSV* pressure support ventilation; *RR* respiratory rate; *SaO_2* systemic arterial oxygen saturation; *SBP* systolic arterial pressure; *V_d* end diastolic velocity of middle cerebral artery blood flow; *V_m* mean velocity of middle cerebral artery blood flow; *V_s* systolic velocity of middle cerebral artery flow; and *V_T* tidal volume

* $P < 0.05$ NAVA versus PSV at an equivalent level of assistance

** $P < 0.01$ NAVA versus PSV at an equivalent level of assistance

[a] Data are expressed as mean ± standard deviation

The four episodes of assisted ventilation ventilator parameters are given in Table 3. For the two assist levels during PSV, we observed a lower $EAdi_{peak}$ (4.1 ± 2.3 vs. 7.0 ± 3.9; $P < 0.001$) during PSV_{high} when compared to PSV_{low}. pH values were higher (7.45 ± 0.06 vs. 7.41 ± 0.03; $P = 0.002$), $PaCO_2$ was lower (34.5 ± 6.6 vs. 39.9 ± 6.8 mmHg, $P < 0.001$), and PaO_2 was lower (43.7 ± 8.58 vs. 45.7 ± 8.9 mmHg; $P = 0.013$) during PSV_{high} when compared to PSV_{low}. MCABF velocities were significantly lower ($P = 0.03$) during PSV_{high} compared to PSV_{low}. Detailed MCABF velocity results are given in Table 3.

During NAVA, there were no differences in RR, V_T, PIP, and MAP between $NAVA_{high}$ and $NAVA_{low}$. There was a lower $EAdi_{peak}$ (4.1 ± 2.1 vs. 6.7 ± 3.6 μV; $P < 0.001$) but no difference in $EAdi_{min}$ (0.5 ± 0.4 vs. 0.5 ± 0.4 μV, $P = 0.780$) in $NAVA_{low}$ compared to $NAVA_{high}$. No difference in arterial blood gas between the two assist levels could be observed. Also, there was no difference in MCABF velocities between the two NAVA assist levels (Table 3).

2. PSV_{high} versus $NAVA_{high}$ and PSV_{low} versus $NAVA_{low}$, respectively

Comparing the breathing patterns and resulting ventilator pressures at similar assist levels during PSV and NAVA, respectively, there were no differences between PSV_{low} and $NAVA_{low}$, whereas there were differences between PSV_{high} and $NAVA_{high}$. V_T, PIP, and MAP were significantly higher during PSV_{high} than during $NAVA_{high}$ (Table 3). Comparing the arterial blood gases between the two modes (NAVA and PSV) at the same level of assist,

SaO_2 (81.9 ± 8.6 vs. 79.6 ± 10.3 %; $P < 0.01$) was higher and $PaCO_2$ (37.6 ± 6.4 vs. 39.9 ± 6.8 mmHg; $P < 0.01$) was lower during $NAVA_{low}$ than during PSV_{low}. At the higher level of assist, a lower pH (7.42 ± 0.03 vs. 7.45 ± 0.06; $P < 0.01$), a higher $PaCO_2$ (38.1 ± 6.0 vs. 34.5 ± 6.6 mmHg; $P < 0.01$), and a higher SaO_2 (82.0 ± 7.5 vs. 79.0 ± 9.1 %; $P < 0.01$) were observed during $NAVA_{high}$ compared to PSV_{high}. The PI of MCABF was lower in NAVA than in PSV at both assist levels [1.1 ± 0.3 vs. 1.2 ± 0.3 at the lower assist level ($P < 0.01$) and 1.2 ± 0.3 vs. 1.3 ± 0.4 at the high assist level ($P < 0.01$)]. V_d, but not V_s or V_m, of MCABF (35.2 ± 13.1 vs. 34.7 ± 12.8 m/s; $P < 0.01$) was higher during $NAVA_{high}$ than during PSV_{high}.

Discussion

In patients with a BCPA for single-ventricle physiology, venous return from the brain as well as from the upper extremities is directed into the lungs via the superior vena cava, whereas venous return from the inferior vena cava drains into the right atrium and via the single functional ventricle directly into the arterial circulation. In consequence, systemic arterial oxygenation is the weighted average of the deoxygenated blood coming from the inferior vena cava and the oxygenated blood from the pulmonary veins.

Hypoxemia in the early postoperative period is therefore often considered to be a consequence of transiently elevated PVR that occurs after CPB, which may limit the age at which BCPA can be performed safely. Conventionally, postoperative hypoxemia is refractory to conventional treatment aimed at decreasing PVR, especially in young infants. Hyperventilation and inhaled nitric oxide have been shown ineffective and do not improve oxygenation in the absence of an intrapulmonary shunt [15, 19].

The determinants of systemic oxygenation after the BCPA are multifactorial and depend upon PBF, CBF, cardiac output, and intrapulmonary shunting [20–22]. A unique aspect of the physiology of PBF after BCPA is the interaction of two highly autonomically regulated vascular beds—the cerebral and the pulmonary circulation—that have opposite responses to changes in CO_2 and acid–base status [23–25]. It has been reported that hyperventilation to achieve lower PVR impairs oxygenation, while hypoventilation improves oxygenation in patients after BCPA [12, 14, 15, 20, 21]. Li et al. [12] reported that moderate hypercapnia with respiratory acidosis improved arterial oxygenation and reduced oxygen consumption and arterial lactate levels, thus improving overall oxygen transport in children after BCPA. Fogel et al. [13] reported that $PaCO_2$ had a major influence on CBF and PBF distribution, whereas changes in PO_2 had only a minor impact. They concluded that increased CO_2 tension in patients after BCPA results in increased blood flow to the brain and lungs, improved PaO_2, increased cerebral O_2 transport, and increased cardiac index, which accounted for the increased CBF. Hoskote et al. [14] demonstrated that increasing $PaCO_2$ from 35 to 55 mmHg improved systemic oxygenation, systemic blood flow, CBF, and PBF. It also decreased systemic vascular resistance without increasing PVR after BCPA. The improvement in oxygenation with hypercapnic acidosis suggests that an increase in cerebral and systemic blood flow overrides the vasoconstrictive effect of hypercapnic acidosis on PVR after BCPA [12–14, 20, 21]. In the first period of our study, we confirmed that hyperventilation due to an excessively high V_T did not improve the systemic oxygenation in BCPA circulation; instead, it tended to accentuate hypoxemia. PVR, which depends on the balance in the vascular tone of its two components: the alveolar vessels and the extra-alveolar or parenchymal vessels, is directly affected by changes in lung volume. When the lung is inflated above functional residual capacity, PVR is elevated because the alveolar vessels become compressed as a result of alveolar distension. Meanwhile, the blood flow from the SVC returning to the lung is reduced because of the elevated intrathoracic pressure as a result of high ventilation pressure. These help to explain the effect of lower saturation when the patients after BCPA were hyperventilated, although the cardiovascular effects of mechanical ventilation are complex. The decrease in MCA flow velocity is a major issue as it decreased PBF and the delivery of oxygenated blood into the systemic circulation.

However, most of the methods to increase PBF described above, with the exception of hypoventilation, relied on extrinsically administered CO_2, which is not practical for clinical use. Hypercapnia with respiratory acidosis will stimulate the respiratory centers, often resulting in deep sedation or paralysis to inhibit spontaneous inspiratory efforts in these strategies. This would work against the aim of early extubation after BCPA. NAVA, a new method to ventilate patients where auto-regulation of the patient's neuroventilatory efforts determines ventilation, seems much closer to normal physiology and may be ideal for patients after BCPA.

In the second part of our study, we demonstrated that NAVA with a high support level avoided hyperventilation, in contrast to the high level of PSV. All other settings, except PSV_{high}, maintained $PaCO_2$ within the normal range. As a result, there was a tendency toward decreased V_d and increased PI of the MCABF during PSV_{high}, while this phenomenon did not occur during NAVA, even when a high level of assist was applied. These potential advantages are probably linked to the basic concept of NAVA, which

delivers respiratory assist throughout inspiration in proportion to the EAdi signal, reflecting the patient's neural respiratory drive. Hence, ventilator function and cycling are controlled by the patient's respiratory drive and rhythm. By optimizing the respiratory control feedback loop, NAVA has the potential to enhance patient–ventilator interaction, ensuring synchrony and minimizing the risk of over-assistance. Sinderby [26] reported that in healthy subjects, NAVA can safely and efficiently unload the respiratory muscles during a maximal inspiratory maneuver, without failing to cycle-off ventilatory assist and without causing excessive lung distention, even when a high level of support was administered. Colombo et al. [27] showed that, in contrast to PSV, NAVA resulted in auto-regulation of the respiratory efforts at different assist levels, avoiding over-assistance and patient–ventilator asynchrony. Terzi et al. [28] reported that, compared to PSV, NAVA in patients with acute respiratory distress syndrome holds promise for limiting the risk of over-assistance, preventing patient–ventilator asynchrony and improving overall patient–ventilator interaction.

In the second period of our study, we confirmed our hypothesis that ventilating patients after BCPA with an auto-regulated ventilation mode, NAVA, avoids over-assistance and hyperventilation and achieves better oxygenation by CBF auto-regulation. We also found that the correlation between $PaCO_2$ and MCABF was not exactly linear, especially when comparing PSV_{low} and $NAVA_{low}$. This finding indicates that lung perfusion is not the only reason for improved oxygenation in patients after BCPA. The variable breathing pattern and assistance of sighs seen during NAVA, which are proportional to the patients' supported effort, may improve ventilation/perfusion matching and are probably another important effect. $EAdi_{min}$ in NAVA was significantly lower than that in PSV, indicating that end expiratory lung volume was more easily maintained during NAVA.

Our results suggest that NAVA could be the preferred ventilation strategy for patients after the BCPA procedure for single-ventricle physiology. In the past decades, there are some studies that mentioned the cardiovascular effects with different ventilatory techniques [29]. Walsh et al. [30] reported that ventilation with airway pressure release ventilation, when the spontaneous inspiratory effort transmitted to the pleural space results in a consequence of decreased intrapleural pressure, improves lung perfusion compared with pressure control ventilation in children after tetralogy of Fallot repair and cavopulmonary shunt operations. In some cases with high risk of pulmonary venous obstruction before BCPA procedure, such as the patients with single-ventricle physiology combined with total anomalous pulmonary venous connection or obvious systemic atrioventricular valve insufficiency, positive pressure ventilation should be helpful for them to keep functional residual capacity. Moreover, the patients after BCPA procedure with systemic ventricular dysfunction or acute lung injury may not be extubated rapidly postoperatively.

Limitations of the Study

We did not distinguish between the effects of hypercarbia and intrathoracic pressure on CBF and PBF. These two factors are difficult to separate and represent the combined influence of the factors of oxygenation in BCPA circulation. Time considerations did not allow this project to separate the differences related to hypercarbia and intrathoracic pressure, and our results are not objective. We only compared NAVA and PSV in our study, without involving other ventilation strategies. And 30 min of ventilation might be limited in patients with other interfering factors to reach steady state. Further research needs to be done in the future. Some authors reported that CBF was influenced by a high concentration of sedatives [31, 32]. However, the dose of propofol maintained in our study was small and identical in all patients. Thus, the influence of sedatives on MCABF velocity in our study was probably limited.

Conclusion

In the early postoperative period of BCPA in patients with single-ventricle physiology, large V_Ts, leading to a slightly increased pH and lower $PaCO_2$, will result in lower CBF and higher resistance of the cerebral vascular bed during controlled mechanical ventilation. Allowing for spontaneous ventilation should therefore be beneficial in BCPA circulation. However, over-assistance can also occur during PSV, whereas during NAVA, with its closed loop concept on the ventilatory drive, this does not occur independently of the assist level. Therefore, NAVA does allow for better oxygenation in BCPA circulation and, through lower cerebral vascular resistance, improved CBF. This suggests that NAVA may play an important role in the postoperative care of patients with single-ventricle physiology.

Compliance with Ethical Standards

Conflicts of Interest The authors have no conflicts of interests to declare.

Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research com-

mittee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Glenn WW (1984) Superior vena cava-pulmonary artery anastomosis. Ann Thorac Surg 37:9–11
2. Seliem MA, Baffa JM, Vetter JM, Chen SL, Chin AJ, Norwood WI Jr (1993) Changes in right ventricular geometry and heart rate early after hemi-Fontan procedure. Ann Thorac Surg 55: 1508–1512
3. Fogel MA, Weinberg PM, Chin AJ, Fellows KE, Hoffman EA (1996) Late ventricular geometry and performance changes of functional single ventricle throughout staged Fontan reconstruction assessed by magnetic resonance imaging. J Am Coll Cardiol 28:212–221
4. Hopkins RA, Armstrong BE, Serwer GA, Peterson RJ, Oldham HN Jr (1985) Physiological rationale for a bidirectional cavopulmonary shunt a versatile complement to the Fontan principle. J Thorac Cardiovasc Surg 90:391–398
5. Tideman E, Marsál K, Ley D (2007) Cognitive function in young adults following intrauterine growth restriction with abnormal fetal aortic blood flow. Ultrasound Obstet Gynecol 29:614–618
6. Rosenbaum JL, Almli CR, Yundt KD, Altman DI, Powers WJ (1997) Higher neonatal cerebral blood flow correlates with worse childhood neurologic outcome. Neurology 49:1035–1041
7. Chang L, Anderson T, Migneco OA, Boone K, Mehringer CM, Villanueva-Meyer J, Berman N, Mena I (1993) Cerebral abnormalities in myotonic dystrophy. Cerebral blood flow, magnetic resonance imaging, and neuropsychological tests. Arch Neurol 50:917–923
8. Koide H, Kobayashi S, Kitani M, Tsunematsu T, Nakazawa Y (1994) Improvement of cerebral blood flow and cognitive function following pacemaker implantation in patients with bradycardia. Gerontology 40:279–285
9. Li J, Hoskote A, Hickey C, Stephens D, Bohn D, Holtby H, Van Arsdell G, Redington AN, Adatia I (2005) Effect of carbon dioxide on systemic oxygenation, oxygen consumption, and blood lactate levels after bidirectional superior cavopulmonary anastomosis. Crit Care Med 33:984–989
10. Fogel MA, Durning S, Wernovsky G, Pollock AN, Gaynor JW, Nicolson S (2004) Brain versus lung: hierarchy of feedback loops in single-ventricle patients with superior cavopulmonary connection. Circulation 110((11 Suppl 1)):II147–II152
11. Hoskote A, Li J, Hickey C, Erickson S, Van Arsdell G, Stephens D, Holtby H, Bohn D, Adatia I (2004) The effects of carbon dioxide on oxygenation and systemic, cerebral, and pulmonary vascular hemodynamics after the bidirectional superior cavopulmonary anastomosis. J Am Coll Cardiol 44:1501–1509
12. Bradley SM, Simsic JM, Mulvihill DM (1998) Hyperventilation impairs oxygenation after bidirectional superior cavopulmonary connection. Circulation 98(19 Suppl):II372–II376; discussion, II376–II377
13. Chang AC, Zucker HA, Hickey PR, Wessel DL (1995) Pulmonary vascular resistance in infants after cardiac surgery: role of carbon dioxide and hydrogen ion. Crit Care Med 23:568–574
14. Karsli C, Luginbuehl I, Farrar M, Bissonnette B (2003) Cerebrovascular carbon dioxide reactivity in children anaesthetized with propofol. Paediatr Anaesth 13:26–31
15. McNeill BR, Murkin JM, Farrar JK, Gelb AW (1990) Autoregulation and the CO_2 responsiveness of cerebral blood flow after cardiopulmonary bypass. Can J Anaesth 37:313–317
16. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, Gottfried SB, Lindström L (1999) Neural control of mechanical ventilation in respiratory failure. Nat Med 5:1433–1436
17. Piquilloud L, Vignaux L, Bialais E, Roeseler J, Sottiaux T, Laterre PF, Jolliet P, Tassaux D (2011) Neurally adjusted ventilatory assist improves patient-ventilator interaction. Intensive Care Med 37:263–271
18. Grasselli G, Beck J, Mirabella L, Pesenti A, Slutsky AS, Sinderby C (2012) Assessment of patient-ventilator breath contribution during neurally adjusted ventilatory assist. Intensive Care Med 38:1224–1232
19. Adatia I, Atz AM, Wessel DL (2005) Inhaled nitric oxide does not improve systemic oxygenation after the bidirectional superior cavopulmonary anastomosis. J Thorac Cardiovasc Surg 129:217–219
20. Aeba R, Katogi T, Kashima I, Omoto T, Kawada S, Omae K (2000) Factors influencing arterial oxygenation after bidirectional cavopulmonary shunt without additional sources of pulmonary blood flow. J Thorac Cardiovasc Surg 120:589–595
21. Bradley SM, Simsic JM, Mulvihill DM (2003) Hypoventilation improves oxygenation after bidirectional superior cavopulmonary connection. J Thorac Cardiovasc Surg 126:1033–1039
22. Salim MA, Case CL, Sade RM, Watson DC, Alpert BS, DiSessa TG (1995) Pulmonary/systemic flow ratio in children after cavopulmonary anastomosis. J Am Coll Cardiol 25:735–738
23. Kety SS, Schmidt CR (1946) The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men. J Clin Invest 25:107–119
24. Lakshminrusimha S, Steinhorn RH, Wedgwood S, Savorgnan F, Nair J, Mathew B, Gugino SF, Russell JA, Swartz DD (2011) Pulmonary hemodynamics and vascular reactivity in asphyxiated term lambs resuscitated with 21 and 100 % oxygen. J Appl Physiol 111:1441–1447
25. Fullerton DA, Kirson LE, St Cyr JA, Kinnard T, Whitman GJ (1993) Influence of hydrogen ion concentration versus carbon dioxide tension on pulmonary vascular resistance after cardiac operation. J Thorac Cardiovasc Surg 106:528–536
26. Sinderby C, Beck J, Spahija J, de Marchie M, Lacroix J, Navalesi P, Slutsky AS (2007) Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest 131:711–717
27. Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P (2008) Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med 34:2010–2018
28. Terzi N, Pelieu I, Guittet L, Ramakers M, Seguin A, Daubin C, Charbonneau P, du Cheyron D, Lofaso F (2010) Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: physiological evaluation. Crit Care Med 38:1830–1837
29. Lellouche F, Brochard L (2009) Advanced closed loops during mechanical ventilation (PAV, NAVA, ASV, SmartCare). Best Pract Res Clin Anaesthesiol 23:81–93
30. Walsh MA, Merat M, La Rotta G, Joshi P, Joshi V, Tran T, Jarvis S, Caldarone CA, Van Arsdell GS, Redington AN, Kavanagh BP (2011) Airway pressure release ventilation improves pulmonary blood flow in infants after cardiac surgery. Crit Care Med 39:2599–2604
31. Ogawa Y, Iwasaki K, Aoki K, Gokan D, Hirose N, Kato J, Ogawa S (2010) The different effects of midazolam and propofol sedation on dynamic cerebral autoregulation. Anesth Analg 111:1279–1284
32. Karsli C, Luginbuehl I, Farrar M, Bissonnette B (2002) Propofol decreases cerebral blood flow velocity in anesthetized children. Can J Anaesth 49:830–834