Airway pressure release ventilation improves pulmonary blood flow in infants after cardiac surgery*

Mark A. Walsh, MD; Michele Merat, MD; Gustavo La Rotta, MD; Pretha Joshi, MD; Vinay Joshi, MD;
Tuyen Tran, RT; Steve Jarvis, RT; Christopher A. Caldarone, MD; Glen S. Van Arsdell, MD;
Andrew N. Redington, MD; Brian P. Kavanagh, MD

Objective: We hypothesized that spontaneous inspiratory effort transmitted to the pleural space during airway pressure release ventilation would result in increased lung perfusion after surgery for tetralogy of Fallot or following a cavopulmonary shunt as a consequence of transient decreases in intrapleural pressure.

Design: Prospective crossover cohort study.

Setting: A tertiary care cardiac pediatric intensive care unit.

Patients: Children after tetralogy of Fallot repair, cavopulmonary shunt, or Fontan operation.

Interventions: Lung perfusion and cardiac output were measured during airway pressure release ventilation and pressure control ventilation with pressure support, both with and without spontaneous ventilation. Oxygen consumption was measured (mass spectrometer) and lung perfusion/cardiac output calculated (Fick equation). Constant levels of CO_2 and mean airway pressure were targeted in all study phases.

Measurements and Main Results: Twenty patients were enrolled in the study, nine after repair of tetralogy of Fallot and 11 after a cavopulmonary shunt. In the absence of spontaneous ventilation, there were no differences in lung perfusion or any of the measured gas exchange or hemodynamic parameters. In the presence of spontaneous ventilation for all patients, mean pulmonary blood flow increased from 2.4 to 2.9 L·min^{-1}M^{-2} ($p = $ .02). Oxygen delivery increased from 594 to 774 mL/min/m^2 ($p = $ .05) in the patients with tetralogy of Fallot patients and from 473 to 518 L·min^{-1}M^{-2} ($p = $ .07) in the cavopulmonary shunt group.

Conclusion: Ventilation with airway pressure release ventilation (at comparable mean airway pressure) improves lung perfusion compared with pressure control ventilation in children after tetralogy of Fallot repair and cavopulmonary shunt operations. Although this study focused on tetralogy of Fallot and cavopulmonary shunt operations, the improved cardiopulmonary interactions may be beneficial in other situations in which hemodynamics are impaired by positive pressure ventilation. (Crit Care Med 2011; 39:2599–2604)

KEY WORDS: APRV; ventilation; cardiac surgery; tetralogy of Fallot; Fontan operation

Airway pressure release ventilation (APRV) may improve oxygenation and reduce barotrauma in acute respiratory distress syndrome (1–3). There are potentially beneficial cardiopulmonary interactions such as increased cardiac output, decreased inotropic requirement, and increased splanchnic blood flow (4, 5).

APRV operates at a constant airway pressure with intermittent time-cycled pressure releases to allow exhalation and facilitate gas exchange (6); it also permits spontaneous respiration, without pressure support, throughout the ventilator cycle. The beneficial cardiopulmonary interactions are likely related to spontaneous ventilatory effort transmitted to the pleural space resulting in transient decreases in intrathoracic pressure (7). In this respect, it is similar to either negative-pressure ventilation or spontaneous ventilation (8–10).

Tetralogy of Fallot (TOF) is often characterized by low cardiac output in the postoperative period as a consequence of restrictive right ventricular physiology (11, 12). Positive pressure ventilation has been shown to further decrease cardiac output by limiting forward flow in the pulmonary artery during diastole. Fontan operations or any type of cavopulmonary shunts (CPS) are also very sensitive to the effects of positive pressure ventilation (10). Increased intrathoracic pressure

from the ventilator negates the effect of spontaneous respiration that augments venous return to the heart, thereby reducing preload and decreasing cardiac output (13–15).

The hypothesis of this study was that spontaneous ventilation during APRV would increase pulmonary perfusion compared with pressure control ventilation (PCV, used with the same level of pressure support) in children after a CPS or TOF repair.

METHODS

This was a prospective study performed in a tertiary pediatric cardiac surgery center between June 2007 and June 2009. Consent for undertaking the study was obtained from the Research Ethics Board at the Hospital for Sick Children. All patients undergoing primary repair of TOF or any type of CPS, either a bidirectional Glenn, stage II hybrid operation or Fontan operation, were eligible for inclusion in the study. Parents of children were approached by any of three investigators (M.W., M.M., P.J.) in the weeks before surgery to

obtain consent. Potential benefits and possible adverse events were discussed in full before obtaining informed consent from either parent or guardian. Exclusion criteria included the presence of significant parenchymal lung disease, hemodynamic instability, or significant hypoxemia (arterial saturation <70%). In the critical care unit, baseline hemodynamics and biochemistry were performed in all patients before starting the study. Chest radiography was performed to ensure correct positioning of the endotracheal tube as well as the central vascular catheters. We allowed at least 1 hr for stabilization using PCV before starting the study.

Hemodynamic and Airway Measurements. All patients had continuous invasive monitoring of systemic and superior vena cava pressures. For any type of CPS where possible, we inserted a pulmonary venous catheter to accurately determine pulmonary venous oxygen content. The pulmonary venous catheters were inserted in the operating room for study purposes. Where it was not possible to insert a pulmonary venous catheter, we assumed pulmonary venous saturations to be 99% and oxygen partial pressure to be 250 mm Hg. For any patients with TOF with significant residual left-to-right shunting, we inserted a pulmonary artery catheter. All patients were intubated with a cuffed endotracheal tube. Continuous oxygen consumption was measured using an AIMS2000 respiratory mass spectrometer (Innovision A/S, Odense, Denmark) as described previously (16). This machine measures instantaneous oxygen consumption by analysis of inhaled and exhaled gases. It updates every 30 secs and gases were taken at the same time. We also measured end-tidal CO_2. For two patients, we measured esophageal pressure during the study as a surrogate of intrapleural pressure and graphed it simultaneously with endotracheal pressure.

Study Protocol. The study had four phases (Fig. 1); the first two measured the effect of APRV and PCV in the paralyzed state, whereas the next two phases measured the effect of APRV and PCV during spontaneous respiration (Fig. 1). The measurements were made in the same order to best allow equivalent airway pressures between the groups. In cases in which there was spontaneous respiration on arrival to the critical care unit, we administered a small dose of short-acting muscle relaxant (0.3 mg/kg rocuronium) to perform the first and second phase. We then waited until there was a strong respiratory effort to begin the third and fourth phases of the study. Sedation during the third and fourth phases was titrated with lorazapam (0.1 mg/kg) and a morphine infusion (20 μg/kg/hr) so as to achieve adequate sedation while preserving respiratory effort. Study phases lasted 20–30 mins with blood sampling after each phase (Fig. 1). Pulmonary blood flow and cardiac output were determined by the Fick method (17). During all four phases, we attempted to maintain constant mean airway pressure as well as end-tidal CO_2. If intravascular fluids were given at any stage, we waited for stability before restarting the study. Stability was defined as not requiring any interventions to correct either cardiovascular or respiratory compromise for 30 mins.

Ventilator Protocol. Patients were placed on 50% inspired oxygen for the entire study. We began with APRV for 30 mins without spontaneous effort with a high pressure (P_{High}) of 13–20 cm H_2O and a low pressure (P_{Low}) of 0 cm H_2O for 2.5–3.0 and 0.3–0.5 secs, respectively, aiming for a $Paco_2$ of between 40 and 45 mm Hg. If CO_2 trended higher, we increased the amplitude and decreased the duration of P_{High} within the aforementioned limits to achieve constant levels. Once sampling was performed, we switched to PCV (second phase) targeting matched tidal volume, mean airway pressure, and end-tidal CO_2. The peak inspiratory pressure was set to a similar value before starting APRV, positive-end expiratory pressure was adjusted to between 5 and 10 cm H_2O, and inspiratory/expiratory ratio was set to 1:2.5 decreasing to 1:1 where necessary. Once a strong respiratory effort was observed, we repeated these measurements for both PCV (with pressure support) and APRV (third and fourth phases) giving a total of four sets of hemodynamics. PCV was used with identical levels of concomitant pressure support.

Statistical Analysis. All results are expressed as means and SD. Hemodynamic variables between the first and second phases were compared with the third and fourth phases. The data were analyzed using a randomized block design and a general linear model (PROC GLM); CONTRAST statements were used to compare phases 1 to 2 and 3 to 4. Data were analyzed first with all patients together and then CPS and TOF groups were analyzed separately. A p valve of <.05 was considered significant. All statistical analysis was performed using SAS 9.2 (Cary, NC).
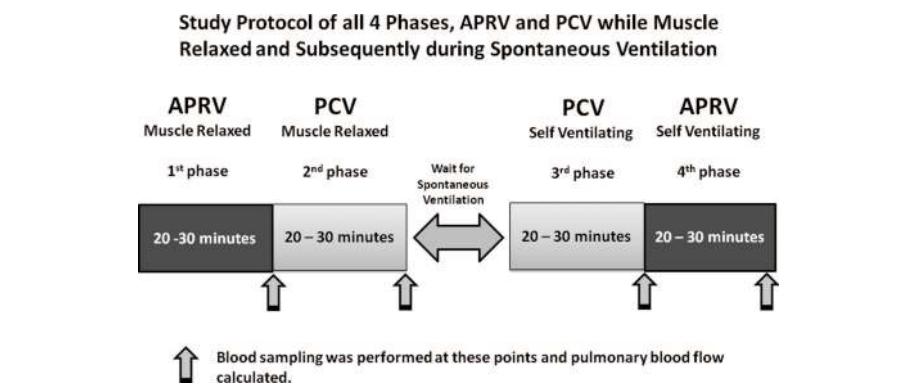

Figure 1. This shows the temporal arrangement of all four phases of the study. The first and second phases were concurrent, whereas a varying amount of time elapsed before starting the third and fourth parts of the study. Pulmonary blood flow and other hemodynamic variables were recorded at the end of each period. *PCV*, pressure control ventilation; *APRV*, airway pressure release ventilation.

RESULTS

A total of 20 patients were recruited to be in the study, nine after repair of TOF and 11 after a CPS (two stage II hybrids, five CPS, four Fontan operations). During the study period, 234 patients were eligible to be in the study; 45 patients were approached and 23 consented. Baseline demographics and anatomic details are shown in Table 1. The mean age for the TOF and CPS groups was 6 months. Mean cardiopulmonary bypass times for TOF and CPS groups were 108 and 90 mins, respectively, and the mean cross-clamp time for the TOF group was 82 mins. The initial mean airway pressure was 9 cm H_2O for both TOF and CPS. Before starting the study, mean mixed venous (and arterial) hemoglobin saturations were 76% (99%) and 54% (82%) for the TOF and CPS groups, respectively. Direct measurement of pulmonary venous oxygen content was possible in three of nine of the CPS group and was assumed in the other six patients.

All studies were started within 4 hrs of return to the critical care unit. All patients survived the surgery, no patients were withdrawn from the study, and there was no study-associated morbidity. The median interval between the second and third periods (awaiting spontaneous respiration) was 40 mins.

Pulmonary Blood Flow and Cardiac Output. In the absence of spontaneous ventilation, there was no significant difference in pulmonary blood flow (Table 2) between APRV and PCV for all patients ($p = .43$) for the TOF group ($p = .56$) or for the CPS group ($p = .75$). During spontaneous ventilation (third and fourth phase), pulmonary blood flow was signif-

Table 1. Demographics, cardiopulmonary bypass, cross-clamp times (hours'minutes), anatomic details, operation details, initial mean airway pressures, initial arterial saturations, and mixed venous saturations on arrival to the critical care unit

Patient No.	Diagnosis	Age, Months	Weight	Operation	Cardiopulmonary Bypass Time	Cross-Clamp	Initial Mean Arterial Pressure	Initial Saturation	Initial Mixed Venous Saturation
1	HLHS	6	7.5 kg	Hybrid stage II	3'19	'15	9	76%	46%
2	DILV	6	7.0 kg	Hybrid stage II	3'36	'15	11	81%	54%
3	TOF	7	8.4 kg	Repair TOF	1'35	1'11	15	97%	77%
4	TA	31	12 kg	Fontan	'33	—	12	87%	47%
5	TOF	48	18 kg	Repair TOF	1'48	'57	9	99%	60%
6	TOF/atrioventricular septal defect	8	11 kg	Repair TOF	3'05	2'22	8	100%	79%
7	Unbalanced atrioventricular septal defect	38	12 kg	Fontan	1'46	'08	9	86%	62%
8	TOF	6	10 kg	Repair TOF	1'38	1'22	10	99%	86%
9	TOF	8	8.8 kg	Repair TOF	1'46	1'25	9	99%	86%
10	TOF	6	6.0 kg	Repair TOF	1'18	1'07	8	99%	66%
11	HLHS	36	13 kg	Fontan	1'30	—	12	95%	67%
12	DILV	38	13 kg	Fontan	2'30	—	7	89%	53%
13	TOF	6	8.5 kg	Repair TOF	3'02	1'31	8	97%	70%
14	TA	4	6.5 kg	BCPS	1'25	'50	9	82%	55%
15	HLHS	4	6.5 kg	BCPS	1'15	'42	7	77%	53%
16	Pulmonary atresia intact ventricular septum	4	6.3 kg	BCPS	1'07	'06	9	81%	47%
17	TA	6	6.8 kg	BCPS	1'31	'20	9	81%	55%
18	TOF	6	5.6 kg	Repair TOF	2'42	2'05	11	98%	74%
19	TA	6	6.8 kg	BCPS	'58	'16	13	82%	54%
20	TOF	6	6.3 kg	Repair TOF	2'52	1'09	8	99%	76%

HLHS, hypoplastic left heart syndrome; TOF, tetralogy of Fallot; TA, tricuspid atresia; DILV, double inlet left ventricle; BCPS, bidirectional cavopulmonary shunt.

Table 2. Summary of our main outcome variables separated into two groups showing mean and SD: those who had repair of tetralogy of Fallot and those who had single ventricle palliation

Parameter	Airway Pressure Release Ventilation (Muscle Relaxed)	Pressure Control Ventilation (Muscle Relaxed)	p	Airway Pressure Release Ventilation (Spontaneous Ventilation)	Pressure Control Ventilation (Spontaneous Ventilation)	p
All patients (n = 20)						
Pulmonary blood flow, L/min/m²	2.6 ± 1.37	2.5 ± 1.22	.43	2.9 ± 1.51	2.4 ± 1.11	.02
Oxygen delivery, mL/min/m²	627 ± 279	581 ± 223	.34	620 ± 285	528 ± 208	.03
Airway pressure, cm H_2O	13.5 ± 2.3	12.0 ± 2.3	.1	12.3 ± 2.6	11.3 ± 2.3	.09
Tetralogy of Fallot (n = 9)						
Pulmonary blood flow, L/min/m²	3.28 ± 1.5	2.87 ± 1.5	.56	3.59 ± 1.4	2.96 ± 1.2	.07
Cardiac index, L/min/m²	3.44 ± 1.6	3.01 ± 1.2	.53	3.71 ± 1.3	3.05 ± 1.3	.08
Oxygen delivery, mLs/min/m²	685 ± 293	588 ± 227	.49	774 ± 293	594 ± 213	.05[a]
Airway pressure	13 ± 1.6	12 ± 1.3	.37	12 ± 1.5	12 ± 1.3	1
Central venous pressure, mm Hg	10.4 ± 1.9	10 ± 1.5	.58	10 ± 2.0	10 ± 1.7	.34
Mean blood pressure, mm Hg	63 ± 8.5	64 ± 8.2	.86	62 ± 7.4	61 ± 8.1	.86
Heart rate, beats/min	153 ± 15	154 ± 13	.92	155 ± 17	155 ± 19	.83
CO_2, mm Hg	45 ± 9.1	44 ± 8.5	.76	48 ± 7.6	46 ± 8.2	.23
Mixed venous saturation taken from superior vena cava	65 ± 11.3	66 ± 13.2	.83	72 ± 12.4	74 ± 11.2	.15
Cavopulmonary shunts (n = 11)						
Pulmonary blood flow, L/min/m²	1.81 ± 1.4	1.87 ± 1.3	.75	2.18 ± 1.5	1.94 ± 1.3	.03[a]
Oxygen delivery, mL/min/m²	554 ± 281	571 ± 167	.87	518 ± 295	473 ± 205	.07
Mean airway	14 ± 1.5	11 ± 1.8	.03[a]	13 ± 1.7	11 ± 1.9	.03[a]
Pressure, cm H_2O						
Central venous pressure, mm Hg	17 ± 1.8	16 ± 1.6	.48	17 ± 1.9	16 ± 2.1	.65
Mean blood pressure, mm Hg	66 ± 7.7	66 ± 8.2	.93	69 ± 8.7	66 ± 7.8	.26
Heart rate, beats/min	135 ± 12	134 ± 11.7	.89	139 ± 12.3	140 ± 11.4	.59
CO_2, mm Hg	48 ± 8.7	45 ± 9.2	.44	48 ± 9.7	46 ± 10.1	.15
Mixed venous saturation taken from superior vena cava	57 ± 10.4	56 ± 11.1	.96	59 ± 10.8	58 ± 10.2	.95

[a]Significant $p \leq .05$.

icantly increased during APRV for all patients ($p = .02$) and for the CPS group ($p = .03$); it approached statistical significance for the TOF group ($p = .07$) (Table 2). Although we waited for obvious respiratory effort before starting phases III and IV of the study, in two cases, measurements were performed in the setting of modest spontaneous ventilator effort (in
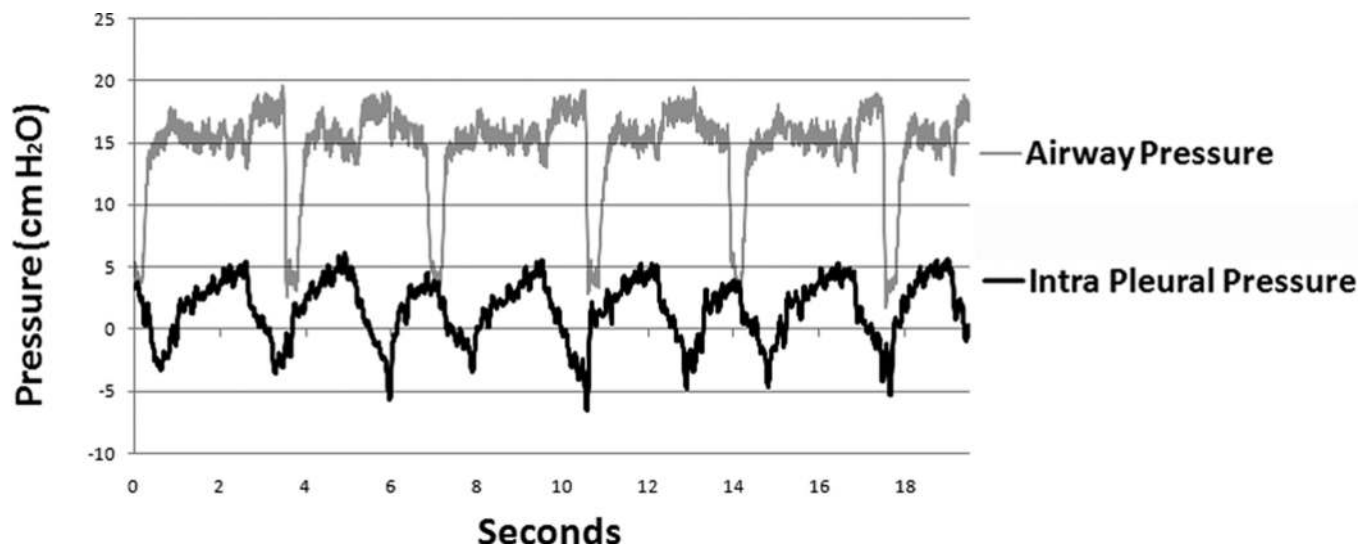
Figure 2. This graph shows concurrent intrapleural (esophageal) and intraendotracheal pressure for a patient during airway pressure release ventilation with spontaneous ventilation. The effect of spontaneous ventilation causing periodic decreases in intraendotracheal pressure can be seen.
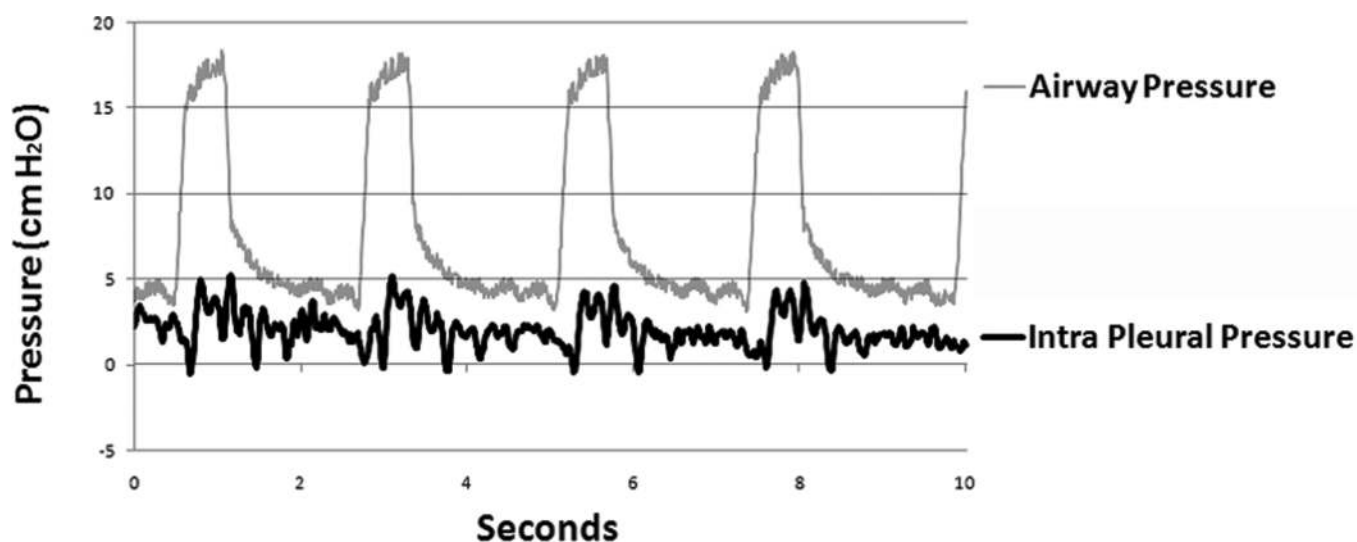

Figure 3. This graph shows concurrent intrapleural (esophageal) and intraendotracheal pressure for a patient during pressure control ventilation with spontaneous ventilation. The effect of synchronized pressure control ventilation causing increases in intraendotracheal pressure can be seen.

these cases, the inspiration-associated increases in pulmonary blood flow were marginal; data not shown). Cardiac output was measured in the TOF group only because there was no inferior vena cava catheter in the CPS group. Like with pulmonary blood flow, there was a trend toward increased cardiac output in the TOF group ($p = .08$) (Table 2).

Oxygen delivery was increased in both TOF ($p = .05$) and CPS ($p = .07$) groups during spontaneous ventilation; there was no difference in oxygen delivery in the absence of spontaneous ventilation (Table 2). The mean airway pressure was not significantly different between any phases in the TOF group; it was, however,

higher in both APRV phases of the CPS group ($p = .03$). Arterial CO_2 was comparable in both groups in all phases as was central venous pressure, mean blood pressure, heart rate, and mixed venous hemoglobin saturation.

Effects on Pleural Pressure. We monitored esophageal (intrapleural) and endotracheal (airway) pressures during spontaneous ventilation on two patients (patients 19 and 20), and representative traces are shown (Figs. 2 and 3). During APRV (Fig. 2), there is a decrease in intraendotracheal pressure during spontaneous inspiration that is accompanied by a decrease in intrapleural pressure. In contrast, during PCV with

pressure support (Fig. 3), the intrapleural pressure is less variable; it is persistently >0 cm H_2O and there are positive (as opposed to negative in APRV) deflections during the synchronized positive pressure inspirations.

In one patient who was spontaneously ventilating on returning to the critical care unit, the third (PCV) and fourth (APRV) phases were performed twice. This provided two direct comparisons between PCV and APRV for the same patient during spontaneous ventilation (Table 3). For this patient, pulmonary blood flow was 1.86 L/min/m² on APRV, decreased to 1.53 L/min/m² with PCV (and pressure support), increased to 1.8 L/min/m² with

Table 3. Summary of patient 11 comparing APRV and PCV twice during spontaneous ventilation (pulmonary blood flow was higher during APRV on both occasions)

Parameter	First Hour		Second Hour	
	APRV (SV)	PCV (SV)	APRV (SV)	PCV (SV)
Pulmonary blood flow, L/min/m^2	1.86	1.53	1.8	1.3
Oxygen delivery, mL/min/m^2	411	336	373	278
Airway pressure, cm H_2O	12	11	11	10
Central venous pressure, mm Hg	15	18	15	15
Mean blood pressure, mm Hg	65	64	55	62
Heart rate, beats/min	150	155	155	155
CO_2, mm Hg	47	44	43	41
PaO_2, mm Hg	83	75	92	80
Mixed venous saturation taken from superior vena cava	67	67.5	70	66

APRV, airway pressure release ventilation; PCV, pressure control ventilation; SV, spontaneous ventilation.
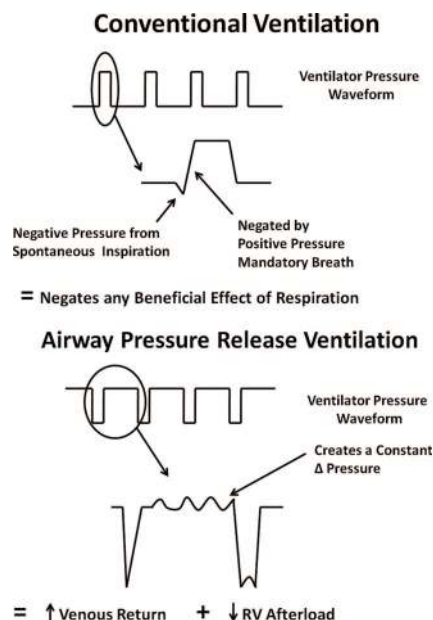

Figure 4. This schematic shows how synchronized ventilation can negate any beneficial effect of spontaneous respiration. We can see how airway pressure release ventilation benefits pulmonary blood flow by creating a constant oscillation of pressure in the chest. *RV*, right ventricle.

repeat APRV, and decreased to 1.3 L/min/m^2 on return to PCV (with pressure support). A similar trend was observed with oxygen delivery, which was higher with APRV.

DISCUSSION

Our study shows that pulmonary blood flow is increased during APRV compared with PCV and that this effect is a result of spontaneous ventilatory effort. Oxygen delivery was also increased in APRV in parallel with pulmonary blood flow. Representative pressure tracings indicate that the spontaneous respirations associated with APRV caused intermittent reductions in intrathoracic pressure as opposed to PCV, which resulted in only positive deflections.

Many studies have shown beneficial effects of APRV for oxygenation in acute respiratory distress syndrome (3, 18, 19). Spontaneous respiration during APRV may divert ventilation toward areas of increased perfusion, and contraction of the diaphragm causes more posterior and dorsal lung segments, which have more dependent blood supply, to expand. Conventional ventilation often preferentially ventilates underperfused areas, especially at the higher peak pressures used in acute respiratory distress syndrome. Hence, much of the accrued benefit of APRV in acute respiratory distress syndrome comes from improving the ventilation–perfusion mismatch (20, 21). In children after cardiac surgery, the presence of spontaneous ventilation promotes venous return to the heart and reduces right ventricular afterload (14). However, this is of particular importance after a CPS in which pulmonary blood flow is passive and highly influenced by pleural pressure. The negative dips in intrathoracic pressure with APRV may help in negating some of the adverse effects of positive pressure ventilation on flow-dependent circulation.

The difference between the pressure–time waveform for PCV and APRV can be seen in Figure 4. In conventional synchronized mandatory ventilation (PCV with pressure support), a spontaneous inspiratory breath immediately triggers a positive breath from the ventilator thereby cancelling out any beneficial effect of spontaneous breathing. During APRV, these synchronized mandatory breaths do not occur; rather, the patient's breaths set up oscillations in the intrathoracic cavity as seen in Figure 2.

There is marked variation in the intrathoracic pressure during spontaneous ventilation, decreasing to below zero during inspiration. The presence of this constant oscillation between positive and negative intrathoracic pressure is likely the main driving force behind increasing pulmonary blood flow during APRV. It is also interesting to note from the graph that transitioning from high pressure to low pressure was not associated with any significant change in intrathoracic pressure; instead, changes in intrathoracic pressure occurred solely with spontaneous breaths. During PCV, synchronized mandatory breaths are associated with a very brief decrease in intrathoracic pressure (required to cycle the ventilator); this is then rapidly replaced by a positive deflection as the ventilator attempts to supply synchronized (but positive) breaths, which elevate intrathoracic pressure.

Pulmonary blood flow, oxygen delivery, and cardiac output (TOF group) were all significantly improved with APRV. There was no difference in arterial lactate, which probably reflects stable hemodynamics and adequate oxygen delivery in all patients during all phases of the study. Appropriate sedation appears to be important for APRV; it should be titrated so as to avoid unnecessary agitation while also maintaining a strong respiratory effort.

A pulmonary venous catheter was placed in three of nine patients from the CPS group; pulmonary venous oxygen content was assumed for the remainder of the patients. The assumed values of 250 mm Hg and 99% saturations may overestimate pulmonary venous oxygen content in the patients with CPS. Nevertheless, these differences were small (median difference of 18 mm Hg in PaO_2 and median saturation difference of 1.75) and were present for both APRV and PCV phases of the study and did not significantly impact the overall results.

Performing phases III and IV in the same sequence in each patient may have resulted in bias attributable to the residual effects of muscle relaxants, although randomization is always a better option where practical. As a result of the variable time lag between phases I and II (muscle relaxed) and phases III and IV (spontane-

ous ventilation), we did not compare phase I vs. III or II vs. IV, etc. Although we attempted to maintain equivocal mean airway pressures, in the CPS group, mean airway pressure was marginally higher during APRV. This higher mean airway pressure during APRV would tend to decrease pulmonary blood flow and hence the increased pulmonary blood flow seen during APRV is all the more significant. It is also noteworthy that by matching mean airway pressure between PCV and APRV, there was a higher mean airway pressure (5–10 cm H_2O) than would normally be used in such patients (in the absence of parenchymal lung disease). Nevertheless, we felt it more important that the different modes of ventilation be compared without the confounding bias of mean airway pressure.

In conclusion, we have shown in a prospective crossover study that pulmonary blood flow is increased during APRV compared with PCV (with pressure support) and that the effect is dependent on spontaneous ventilatory effort. This illustrates a physiological principle associated with this mode of ventilation that may be applicable in cases in which pulmonary blood flow is limited by cardiopulmonary interactions.

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