Cardiopulmonary Interactions After Fontan Operations

Augmentation of Cardiac Output Using Negative Pressure Ventilation

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Background The low-output state is the chief cause of morbidity and mortality after Fontan operations. An alternative hemodynamic tool would be a welcome addition for these patients, who are typically resistant to conventional therapeutic measures.

Methods and Results The hemodynamic effects of conversion from conventional intermittent positive pressure ventilation (IPPV) to cuirass negative pressure ventilation (NPV) was investigated in nine acute postoperative Fontan patients on the pediatric intensive care unit and nine anesthetized patients undergoing cardiac catheterization in the convalescent phase after Fontan operations. Pulmonary blood flow was measured using the direct Fick method during IPPV and after a brief period of NPV. In one subgroup of patients, pulmonary blood flow was measured again after reinstitution of IPPV, and in a second subgroup, pulmonary blood flow was measured after an extended period of NPV. A brief period of NPV increased pulmonary blood flow from 2.4 to 3.5 $L \cdot min^{-1} \cdot /m^{-2}$, with a mean increase of 42%. Pulmonary blood flow continued to improve, with a total increase of 54% after an extended period of NPV. Values fell toward baseline after reinstitution of IPPV. Heart rate was unchanged during NPV, and the improvement in pulmonary blood flow was achieved by an increase in stroke volume from 25 mL/m^2 to 37 mL/m^2.

Conclusions Through improvement of the stroke volume alone, NPV brought about a marked increase in the pulmonary blood flow and, hence, cardiac output of Fontan patients. An improvement in cardiac output of this order, and by this mechanism, is currently unmatched by any therapeutic alternatives. (***Circulation*. 1997;96:3934-3942.**)

Key Words • Fontan procedure • cardiac output • ventilation

The Fontan operation and its modifications have remained an important milestone in the surgical management of selected patients with complex cyanotic congenital heart disease. In the original description of his operation in patients with tricuspid atresia, Fontan observed that the reduction in right atrial pressure that followed extubation was accompanied by a clinical improvement in all cases and concluded that spontaneous respiration should be established as early as possible in these patients.[1] We now know that in the majority of Fontan patients, pulmonary blood flow, the main determinant of cardiac output, is a largely passive diastolic phenomenon that is strongly influenced by changes in intrathoracic pressure that are present during spontaneous and mechanical ventilation.[2,3] Antegrade diastolic pulmonary arterial flow, and hence cardiac output, increases during spontaneous inspiration but is significantly lowered during positive pressure inspiration.[4]

Despite a number of modifications in surgical technique that have favorably influenced the early postoperative course of patients undergoing Fontan-like operations,[5,6] the chief cause of morbidity and mortality in this group remains a low cardiac output state. A low cardiac output is not in itself a surprising feature in the immediate postoperative period, when the important influences of mechanical ventilation are superimposed on the inevitable global effects of cardiopulmonary bypass on the heart and lungs. However, reduced cardiorespiratory function has been demonstrated both at rest and during exercise in a number of late postoperative studies of Fontan patients,[7-9] and it would appear that the pulmonary blood flow of patients in the late postoperative phase may be as sensitive to changes in the mean airway pressure as that of their acute counterparts.[2,3] NPV has previously been shown significantly to increase Doppler-derived antegrade pulmonary arterial flow in a small number of anesthetized patients with an atriopulmonary connection[10] and qualitatively in spontaneously breathing individuals after a total cavopulmonary connection.[11]

Furthermore, we previously reported a significant improvement in pulmonary blood flow during a brief period of NPV in a small number of children who were ventilated in the early postoperative period after right heart surgery.[12]

In this study, we compare the effects of IPPV and negative pressure ventilation in nine early postoperative Fontan patients and nine anesthetized patients undergoing cardiac catheterization in the late convalescent phase after Fontan-like operations so we can quantify the effects of these differing ventilatory strategies on the "Fontan" circulation.

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Selected Abbreviations and Acronyms

IPPV = intermittent positive pressure ventilation
NPV = negative pressure ventilation
Q_p = pulmonary blood flow index

Methods

Patients

The hemodynamic effects of cuirass NPV were prospectively studied on 18 separate occasions in 14 paralyzed and fully sedated patients (8 males; median age, 6.3 years) who were initially receiving IPPV after Fontan-like operations. Nine studies were carried out in the immediate postoperative period and nine were carried out in the late postoperative (convalescent) phase after elective cardiac catheterization with the patients under general anesthesia. Four patients were studied in both the acute and convalescent phases. Pulmonary blood flow was measured using the direct Fick method in all cases.

Acute Patients

Nine children (4 boys; median age, 5.8 years) were studied on the pediatric intensive care unit at the Royal Brompton Hospital between 4 and 14 hours after a fenestrated total cavopulmonary connection. This is our procedure of choice, with the inclusion of a fenestration in the lateral tunnel being independent of preoperative hemodynamics. All patients had indwelling peripheral arterial catheters and pulmonary arterial and pulmonary venous catheters that were inserted intraoperatively.

Anthropometric data, diagnoses, details of previous palliative procedures, and inotropic support at the time of study are given in Table 1.

Convalescent Patients

Nine paralyzed and fully sedated patients (4 males; median age, 6.7 years) were studied under while general anesthesia after elective cardiac catheterization between 5 months and 15 years after an atriopulmonary connection (3 patients) or total cavopulmonary connection (6 patients). Details of surgery, interval since surgery, and indications for cardiac catheterization are given in Table 2.

TABLE 1. Clinical Details for Acute Patients Studied in the Early Postoperative Period

Patient	Diagnosis	Palliation	Support
1	DILV, VA conc, VSD	PAB+PDA lig	DA 10
2	DILV, VA disc, sub-PS	Left BT	DA 6
3	DILV, VA disc, VSD	PAB	DA 10
4	TA, VA conc, VSD, ASD	None	DA 7
5	AVSD, DORV, left-side anterior aorta, PS	None	DA 6
6	PA IVS	Left BT, BDG	DA 6
7	DORV, acquired PAtr, multiple VSD	Left BT, right BT	DB 4
8	PA IVS, acquired TA	Right BT, left BT, BDG	DA 8
9*	DILV, CoA, bilateral SVC	CoA repair+PAB, VSD enlargement	DA 6, EP 0.15 PD

DILV indicates double-inlet left ventricle; VA conc, concordant ventriculoarterial connection; VSD, ventricular septal defect; PDA, patent arterial duct; PAB, pulmonary artery band; AVSD, atrioventricular septal defect; DORV, double-outlet right ventricle; PS, pulmonary stenosis; VA disc, discordant ventriculoarterial connection; BT, Blalock-Taussig shunt; PA IVS, pulmonary atresia with intact ventricular septum; DB, dobutamine; BDG, bidirectional Glenn; TA, tricuspid atresia; CoA, coarctation aorta; *, study not completed; Ep, epinephrine; and PD, peritoneal dialysis.

Patients 1 through 4 were studied in both the acute and convalescent phase.

Patients 1* through 4* and 14 were studied after successful transcatheter closure of a surgical fenestration using a 17-mm umbrella device (Bard). Complete occlusion was confirmed with angiography at the end of the procedure in all cases. Patient 10 did not have evidence of baffle obstruction either angiographically or in terms of directly measured pressure gradients under anesthesia and so fulfilled the criteria for inclusion in the study. Patient 13 had a right-to-left shunt through a inferior baffle leak, and it was not possible to occlude this with a transcatheter technique.

Criteria for Inclusion

All patients were in sinus rhythm at the time of study, and no patient had evidence of anatomic obstruction to the "Fontan pathway" or overt systemic ventricular dysfunction. All convalescent patients were in New York Heart Association functional class I or II.

Ventilation

All patients were intubated with a cuffed endotracheal tube (Mallinckrodt Medical). IPPV was delivered using a Servo ventilator 900C (Siemens), and NPV was delivered using the Hayek external high-frequency oscillator. This consists of an appropriately sized flexible Perspex cuirass that fits over the patient's chest and upper abdomen from the level of the clavicles to the level of the umbilicus. Ventilatory adjustments are made from a bedside power unit, to which the cuirass is attached. In this study, the Servo ventilator was used to deliver oxygen and a small amount of additional pressure support (3 to 5 cm H_2O) during NPV to overcome the inevitable resistance to gas flow presented by the endotracheal tube. Ventilatory parameters during IPPV and NPV are summarized in Table 3.

Hemodynamic Monitoring

All patients had continuous surface ECG monitoring and noninvasive monitoring of peripheral oxygen saturation, oxygen consumption, and end-tidal carbon dioxide. Systemic blood pressure, pulmonary arterial pressure, and (in patients with a right-to-left shunt) pulmonary venous pressure were monitored invasively.

Hemodynamic Measurements

Pulmonary blood flow was measured using the direct Fick method. Oxygen consumption was directly measured using respiratory mass spectrometry as previously described.[12,13] The mass spectrometer inlets and argon (indicator gas) flow were calibrated before each period of patient monitoring. Before commencement of steady state monitoring, the cuff of the endotracheal tube was inflated to eliminate any leak of respired gases; the oropharynx was then checked for leaks by sampling for carbon dioxide with one of the mass spectrometer sampling probes.

A prerequisite for the accurate and meaningful measurement of pulmonary blood flow using the direct Fick method is a cardiorespiratory steady state. Acute postoperative studies were not carried out within 4 hours of a patient's return from the operating theater. This delay ensured central rewarming in all cases and allowed sufficient time for adequate sedation, analgesia, and paralysis to be induced through continuous intravenous infusions. In addition, patients were not suctioned or moved during the entire study period, and doses of intravenous inotropes in the early postoperative patients were not altered. A cardiorespiratory steady state was defined as a 15-minute period during IPPV and before measurement of pulmonary blood flow during which patients were not spontaneously breathing or moving and did not display any changes in heart rate or blood pressure that might suggest insufficient sedation or analgesia. During this period, blood pressure, heart rate, oxygen consumption, and end-tidal carbon dioxide were required to not fluctuate by >5%.

TABLE 2. Clinical Detail of Convalescent Patients

Patient	Age, y	Year Postoperative	Operation	Indication for CC
1*	5.7	0.8	Fenestrated TCPC	Closure of fenestration
2*	6	0.4	Fenestrated TCPC	Closure of fenestration
3*	4.4	0.6	Fenestrated TCPC	Closure of fenestration
4*	3	0.6	Fenestrated TCPC	Closure of fenestration
10	9.3	6.0	APC	? Baffle obstruction
11	16	7.2	APC	Arrhythmia
12	16.7	15	APC	Arrhythmia
13	6.7	3.3	TCPC	Decreased exercise tolerance
14	16.5	1.3	Fenestrated TCPC	Closure of fenestration

TCPC indicates total cavopulmonary connection; APC, atriopulmonary connection; and *, patients who were also studied in the acute phase.

In all cases, the mixed venous oxygen content was calculated from pulmonary arterial blood samples. All of the acute patients and patient 13 had a right-to-left shunt through a surgically created fenestration (patients 1 through 9) or an angiographically evident baffle leak (patient 13). In these patients, for the calculation of pulmonary blood flow, "arterial" oxygen content was calculated from pulmonary venous samples. Systemic arterial oxygen content was also measured to calculate the systemic blood flow and assess the right-to-left shunt fraction. In patients without a shunt (patients 10, 11, 12, and 14), arterial oxygen content was calculated from aortic samples. The pulmonary-to-systemic flow ratio was assumed to equal 1.0 in these patients.

Study Protocol

Standard Studies

The term "standard study" was used to define the comparative, brief study protocol designed to assess the hemodynamic effects of conversion from IPPV to NPV; the outline for a standard study is shown in Fig 1A. In brief, at the end of a 15-minute steady state period during IPPV ($IPPV_1$), pulmonary blood flow, and (in patients with a right-to-left shunt) systemic blood flow were measured. NPV was then commenced using an appropriate sized cuirass, and a second pulmonary blood flow measurement was made after 15 minutes of NPV (NPV_1). Seventeen standard studies were completed.

Extended Studies

Patients in whom the study period was extended beyond the above standard protocol outlined above constituted two subgroups:

Subgroup 1 (7 Patients, 3 Acute Patients). In patients in subgroup 1, a third measurement of pulmonary blood flow was made after IPPV was reinstituted at the end of a standard study ($IPPV_2$) to ensure that no bias was introduced by the standard protocol that involved conversion from IPPV to NPV, in that order. The outline for subgroup 1 patients is given in Fig 1B.

TABLE 3. Ventilatory Parameters During $IPPV_1$ and NPV_1

Parameter	$IPPV_1$	NPV_1
Minute volume, mL/kg	150 to 220	140 to 220
Frequency, breaths/min	15 to 22	20 to 50
Tidal volume, mL/kg	10 to 15	5 to 7
P_{insp}, cm H_2O	+17 to +23	−18 to −24
P_{exp}, cm H_2O	0 to 2	+1 to +4
P_{aw}, cm H_2O	+5 to +9	−6 to −9
Pressure support, cm H_2O		+3 to +5
FIO_2	0.3 to 0.6	0.3 to 0.6

P_{insp} indicates inspiratory pressure; P_{exp}, expiratory pressure; P_{aw}, mean airway pressure; and FIO_2, inspired oxygen fraction.

Subgroup 2 (6 Patients, 3 Acute Patients). In patients in subgroup 2, the period of NPV was extended after the completion of a standard study, and a third measurement of pulmonary blood flow was made after a total of 30 to 45 minutes of NPV (NPV_2). This modification was chosen to investigate the hemodynamic effects of a prolonged conversion to NPV. The study outline is given in Fig 1C.

Statistical Analysis

Group data are expressed as mean±SD. Within-group data for all patients during IPPV and NPV were compared using an ANOVA with Bonferroni's correction for multiple comparisons. Statistical comparisons between acute and convalescent

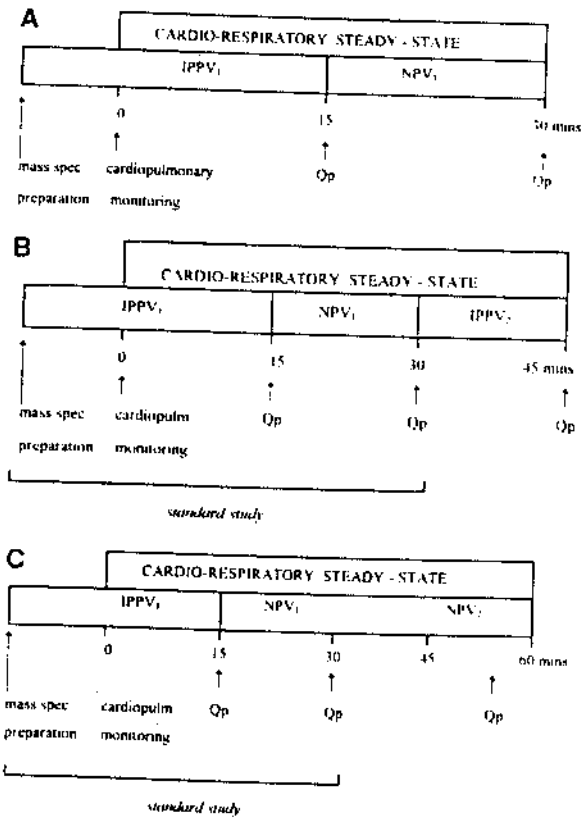

FIG 1. A, Q_p was measured in a cardiorespiratory steady state during IPPV ($IPPV_1$) and after 15 minutes of NPV (NPV_1). B, At the end of a standard study, IPPV was reinstituted, and a third measurement of Q_p was made 15 minutes later ($IPPV_2$). C, NPV was continued at the end of a standard study, and a third measurement of Q_p was made after an additional 30 to 45 minutes of NPV (NPV_2).

TABLE 4. Baseline Hemodynamics During $IPPV_1$ for Acute and Convalescent Patients

Parameter ($IPPV_1$)	Acute	Convalescent	P
Age, median y	5.8	6.7	NS
Hb, g/dL	13.1 (1.9)	13.4 (1.4)	NS
CO_2, kPa	4.8 (1.4)	4.7 (1.0)	NS
Sao_2, aorta: %	94.2 (2.8)	97.1 (2.2)*	.05
Svo_2, PA: %	56.5 (16.8)	70.2 (5.8)*	.03
Arteriovenous difference†	7.4 (2.7)	5.3 (1.3)*	.03
Arteriovenous difference‡	6.5 (3.0)	5.5 (1.4)	.07
Vo_2, mL · min^{-1} · m^2	141 (51)	129 (35)	NS
Q_p, L · min^{-1} · m^{-2}	2.3 (1.3)	2.56 (1.0)	NS
Increase in Q_p during NPV, %	35 (19)	47 (28)	NS
Base excess	−5.4 (3.1)	−0.7 (2.0)*	.003
Transpulmonary gradient, mm Hg	4.6 (2.5)	3.5 (2.5)	NS
LVEDP, mm Hg	8.9 (3.6)§	7.8 (3.6)	NS
PVRI, U/m^2	2.1 (1.2)	1.1 (1.0)*	.05
HR, bpm	138 (9)	88 (28)*	<.0001
Stroke volume	21 (9.9)	31.7 (13)*	.01
Mean arterial pressure, mm Hg	56 (7)	64 (7)*	.03

NS indicates not statistically significant (P>.05); Hb, hemoglobin; Sao_2, arterial saturation; Svo_2, mixed venous saturation; LVEDP, left ventricular end-diastolic pressure; Vo_2, oxygen consumption; Q_p, pulmonary blood flow index; PVRI, pulmonary vascular resistance index; and HR, heart rate. Values are mean±SD.

*Statistically significant difference.

†Pulmonary arteriovenous oxygen difference (ie, O_2 content [pulmonary vein minus pulmonary artery] in patients with right-to-left shunt, and O_2 content [systemic artery minus pulmonary artery] in the remainder.

‡Systemic arteriovenous difference [systemic artery minus pulmonary artery].

§Value at preoperative cardiac catheterization in acute patients.

patients were made using the Mann-Whitney U test. In all cases, the null hypothesis was rejected for values of P>.05.

Results

In patient 9, the hemodynamic study could not be completed. The cuirass was easily fitted with an adequate seal, but the patient desaturated on the start of NPV. The possible reasons for this are discussed later.

Baseline Hemodynamic Data During $IPPV_1$

Baseline data for the two groups of patients during $IPPV_1$ are given in Table 4. There was no difference in the mean oxygen consumption between acute and convalescent patients. In the presence of a patent baffle fenestration in all acute patients, the systemic arterial oxygen saturation was ≈3% lower than that in the convalescent group. The mixed venous saturation was much lower in the acute patients (56.5±16.8%) than in the convalescent group (70.2±5.8%; P=.03). The arteriovenous oxygen difference for pulmonary blood flow (using pulmonary venous samples for arterial oxygen content in patients with a right-to-left shunt) was 7.4±2.7 mL/dL in acute patients and 5.3±1.3 mL/dL in convalescent patients (P=.03). The arteriovenous oxygen difference for systemic blood flow (using systemic arterial samples for arterial content in all patients) was 6.5±3.0 mL/dL in acute patients and 5.5±1.4 mL/dL in convalescent patients; this did not quite reach a level of statistical significance (P=.07). Despite having a similar arterial carbon dioxide tension, the acute patients had a significantly greater metabolic acidosis than the convalescent group.

The mean Q_p ranged from 0.56 to 4.6 L · min^{-1} · m^{-2} in the acute patients, with a mean of 2.3 L · min^{-1} · m^{-2}, and from 1.5 to 4.8 L · min^{-1} · m^{-2} in the convalescent group, with a mean of L · min^{-1} · m^{-2}. There was no difference in baseline Q_p between the two groups (P=.4). However, the acute patients were significantly more tachycardic than the convalescents, and thus their baseline "systemic" stroke volume index was much lower: 21.4 versus31.7 mL/m^2 (P=.01; Fig 2).

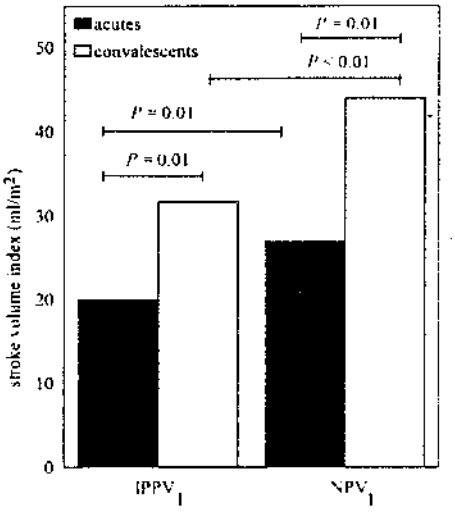

FIG 2. Stroke volume index during standard studies. The stroke volume was significantly lower for acute patients during IPPV ($IPPV_1$) and NPV (NPV_1). There was a significant improvement in stroke volume during NPV in both groups of Fontan patients.

Standard Studies

With the exception of patient 9, all patients were ventilated easily during NPV, maintaining stable systemic arterial oxygen and carbon dioxide tensions. Results of standard studies are given in Table 5. Mean oxygen consumption for acute patients increased from 146±52 to 176±55 mL · min^{-1} · m^{-2} during NPV_1 (P=.01), and in convalescent patients, it increased less markedly: from 125±35 to 136±30 mL · min^{-1} · m^{-2} (P=.07). Oxygen consumption for the group as a whole increased from 136±44 to 156±47 mL · min^{-1} · m^{-2} during NPV_1 (P=.01).

The mixed venous oxygen saturations during both $IPPV_1$ and NPV_1 were significantly lower in acute than in convalescent patients (P=.03), but values increased significantly during NPV_1 in both groups: from 56.6±16% to 60.2±19% in acute patients and from 70.2±5.8% to 77.4±5.4% in convalescents (P=.02 for both groups). The mean mixed venous saturation for all patients increased from 63.4±14% to 70.1±5.3% during NPV_1 (P=.0009).

The arteriovenous difference in oxygen content decreased significantly in acute (P=.01) and convalescent (P=.03) patients during NPV_1, and combined values for all patients decreased from 6.3±2.3 to 5.2±2.4 mL/dL (P=.0007).

Pulmonary blood flow increased during NPV_1 from 2.3±1.2 to 3.3±1.9 L · min^{-1} · m^{-2} in acute patients and from 2.6±1 to 3.7±1.1 L · min^{-1} · m^{-2} in convalescent patients (P=.01 for both groups). Pulmonary blood flow during all standard studies (acute plus convalescent) increased from 2.4±1.1 to 3.5±1.5 L · min^{-1} · m^{-2}

TABLE 5. Results of Standard Studies in All Patients During Initial Periods of $IPPV_1$ and NPV_1

Parameter	$IPPV_1$		NPV_1		P
$Paco_2$	4.7 (1.2)		4.9 (1.3)		NS
Sao_2 (syst art)	98.0 (1.8)		98.1 (1.6)		NS
Arteriovenous difference, mL/dL	6.3 (2.3)		5.2 (2.4)		.0007
	Acute	Conv	Acute	Conv	
	7.4 (2.7)	5.3 (1.3)	6.6 (2.8)	3.9 (1.1)	
Vo_2, mL · min^{-1} · m^{-2}	136 (44)		156 (47)		.01
	Acute	Conv	Acute	Conv	
	146 (52)	125 (35)	176 (55)	136 (30)	
Svo_2, %	63.4 (14)		70.1 (5.3)		.0009
	Acute	Conv	Acute	Conv	
	56.6 (16)	62.0 (19)	70.2 (5.8)	77.4 (5.4)	
Q_p, L · min^{-1} · m^{-2}	2.4 (1.1)		3.5 (1.5)		.0003
	Acute	Conv	Acute	Conv	
	2.26 (1.2)	2.6 (1.0)	3.3 (1.9)	3.7 (1.1)	
HR, bpm	110 (45)		102 (38)		NS
	Acute	Conv	Acute	Conv	
	135 (8)	89 (27)	134 (9)	87 (27)	
Sv, mL · bt^{-1} · m^{-2}	24.9 (13)		36.5 (22)		<.0001
	Acute	Conv	Acute	Conv	
	21 (8.8)	31.7 (13)	27 (13)	48.4 (21)	
Mean PA pressure, mm Hg	10 (2.6)		8.6 (2.8)		.003
PVRI, U/m^2	2.0 (1.3)		1.3 (1.2)		.01
Q_p:Q_s	0.85:1		0.78:1		.09

Conv indicates convalescent; Q_p:Q_s, pulmonary-to-systemic flow ratio; other abbreviations as in Table 4.

P values are given for the group as a whole (acute plus convalescent). Selected parameters are given separately for acute and convalescent patients.

(P=.0003, Fig 3), with a mean increase of 42±24%. There was no significant difference in the increase in pulmonary blood flow between acute and convalescent patients.

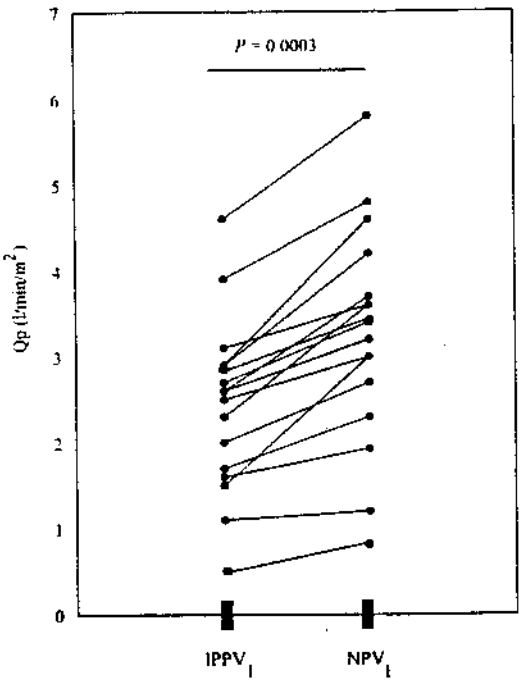

FIG 3. Q_p for all Fontan patients during standard studies increased by a mean of 42% after 15 minutes of NPV. The increase was independent of baseline values for Q_p during $IPPV_1$.

There was a slight decrease in pulmonary arterial pressure during NPV_1 and this was statistically significant (P=0.003). Left atrial (or pulmonary venous) pressure was unchanged, and the pulmonary vascular resistance index decreased from 2.0±1.3 to 1.3±1.2 Wood units/m^2 (P=.01).

Heart rate was unchanged during NPV, and stroke volume for the group as a whole increased during NPV from 24.9±13 to 36.5±22 mL/m,^{2} with a mean increase of 44% (P<.0001). The systemic stroke volume of the acute patients increased from 21±8.8 to 27.2±13 mL/m^2 during NPV (P=.01), and increased from 31.7±13 to 48.4±21 mL/m^2 in convalescent patients (P<.01). The stroke volume was significantly lower for acute patients during both $IPPV_1$ and NPV_1 (P=.01; see Fig 2). The right-to-left shunt fraction was unchanged during NPV_1.

Extended Studies

Subgroup 1: $IPPV_1 \rightarrow NPV_1 \rightarrow IPPV_2$

The hemodynamic data for this subgroup are given in Table 6. The mixed venous oxygen saturation increased significantly during NPV_1, the increase in oxygen consumption was not significant, and pulmonary blood flow increased by 43% (Fig 4). After IPPV was reinstituted ($IPPV_2$), all parameters tended to return to baseline, with a significant reduction in mixed venous oxygen saturation (P=.02) and a fall in oxygen consumption that did not quite reach a level of statistical significance (P=.08).

Subgroup 2: $IPPV_1 \rightarrow NPV_1 \rightarrow NPV_2$

The data for this subgroup are given in Table 7. Mixed venous oxygen saturation and oxygen consumption both

TABLE 6. Subgroup 1: Hemodynamic Data for 7 Children in Whom a Third Measurement Was Made After Reinstitution of $IPPV_2$

Parameter	$IPPV_1$	NPV_1	$IPPV_2$	P
$\dot{V}O_2$	158 (52)	176 (54)*	152 (57)	
SvO_2	69.3 (6.4)	75.5 (7.4)*	70 (5.7)†	
Q_p	3.2 (1.1)	4.5 (1.5)*	3.3 (0.8)†	
Change in Q_p, %				
$IPPV_1 \rightarrow NPV_1$	+43 (24)			.0008
$NPV_1 \rightarrow IPPV_2$		−28 (15)		.001
$IPPV_1 \rightarrow IPPV_2$		None		NS

See Table 4 for abbreviations. *Significant change from $IPPV_1$ to NPV_1.
†Significant change from NPV_1 to $IPPV_2$.

increased significantly during NPV_1. Pulmonary blood flow in this subgroup increased by 36.2% during NPV_1, and continued to do so during NPV_2, with an ultimate total increase of >53% during a 30- to 45-minute period of negative pressure ventilation (Fig 5).

Predictors of Hemodynamic Improvement During NPV

The data from standard studies were examined to investigate any possible predictors of the ultimate hemodynamic improvement that could be achieved during NPV (Table 8). In the convalescent patients, there was no correlation between the increase in Q_p during a standard study and pulmonary arterial pressure, left ventricular end-diastolic pressure, transpulmonary gradient, pulmonary vascular resistance, or baseline Q_p during $IPPV_1$. In the acute patients, patients with a higher preoperative left ventricular end-diastolic pressure ($R=.83$, $P=.02$) and a higher postoperative pulmonary arterial pressure ($R=.87$, $P<.01$) tended to derive a greater improvement during NPV. Fig 6 shows the correlation between increase in pulmonary blood flow and postoperative pulmonary arterial pressures in the acute patients.

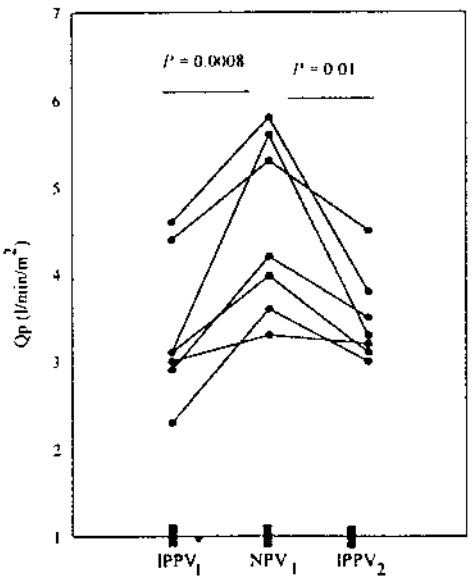

FIG 4. Subgroup 1: Q_p for patients in whom a third measurement was made after reinstitution of IPPV ($IPPV_2$) at the end of a standard study. Values returned toward baseline when NPV was discontinued.

Discussion

This study showed that a brief period of cuirass NPV increased the pulmonary blood flow of patients with the Fontan circulation by 42% and that the improvement was not only sustained but further continued if the period of NPV was extended. The mixed venous saturation increased significantly, and improvement in cardiac output was achieved by an augmentation in stroke volume with the heart rate remaining constant.

Although pulmonary blood flow is a marker of total cardiac output, many of the patients in this study group had a significant right-to-left shunt, so pulmonary and systemic flow were not always equal. For this reason, before a discussion of clinical implications of the study, it is necessary to reemphasize that NPV did not alter the shunt fraction. In other words, the pulmonary blood flow did not increase at the "expense" of the systemic blood flow during NPV, so one can reasonably surmise that changes in pulmonary blood flow accurately represented changes in the systemic cardiac output.

Patient 9 could not effectively be ventilated using NPV. This child was receiving cyclical peritoneal dialysis and was one of the first patients on the intensive care unit to be included in this study. In retrospect, a likely explanation for poor gas exchange was that the increase in intraperitoneal fluid must have significantly compromised the potential for diaphragmatic movement—an important component of effective NPV. The use of continuous "cross-flow" peritoneal dialysis in subsequent cases in which children were receiving therapeutic NPV (not reported here) has reassuringly avoided the large shifts in intraperitoneal volume, allowing NPV to be effectively combined with supplementary renal support.

Baseline Hemodynamics

The baseline cardiac output of the acute and convalescent patients during IPPV were very similar. Implicit in this comment lies the inference that the convalescent patients had a low cardiac output. Why should this be so? Was their cardiac output significantly reduced by the very conservative levels of IPPV used in this study? This would seem unlikely, and there was no reason why the cardiac output of convalescent patients should have been any more affected by IPPV than that of the acute patients. Furthermore, it is widely accepted that Fontan patients have a lower resting cardiac output than healthy individuals,[14] and indeed the baseline cardiac index and stroke volume of the ventilated convalescent patients in this study are comparable to measurements made in

TABLE 7. Subgroup 2: Hemodynamic Data for 6 Patients Who Received an Extended Period of NPV

Parameter	$IPPV_1$	NPV_1	NPV_2	P
$\dot{V}O_2$	156 (42)	176 (49)*	179 (55)	
SvO_2	60.2 (10)	66.7 (12)*	68.9 (11)	
Q_p	2.5 (0.7)	3.4 (1.4)	3.8 (1.2)	
Increase in Q_p, %				
$IPPV_1 \rightarrow NPV_1$	36.2 (16)			.02
$NPV_1 \rightarrow NPV_2$		18.0 (8)		.08
$IPPV_1 \rightarrow NPV_2$		53.6 (17)		.01

See Table 4 for abbreviations.
*Significant change from $IPPV_1$ to NPV_1.

other studies of spontaneously breathing Fontan patients.[14–16] The baseline values in this study were an expression of the cardiovascular responses under very specific (and quite different) conditions in the two subgroups. In the acute patients, there was a higher resting metabolic demand with a consequent need for an appropriate augmentation of cardiac output. This response may, however, have been inadequate because this group had a greater metabolic acidosis and higher arteriovenous oxygen difference. The metabolic demands of the anesthetized convalescent patients, who, in contrast, were not acidotic and had a lower arteriovenous oxygen difference (and therefore oxygen extraction), were presumably much less at the time of study, and in the simplest terms, these patients may not "have needed" a higher cardiac output. All of the acute patients were receiving vasoactive drugs, and although these agents generally offer little beneficial clinical effect on the systolic ventricular function or the peripheral vascular tone of Fontan patients, their presence would almost certainly have contributed to the marked tachycardia. From this point follows the observation that although the total pulmonary blood flow was similar in both patient groups, the stroke volume of convalescent patients was significantly higher than that of the tachycardic acute patients, suggesting that there were important differences both in the mechanisms for the maintenance of a given cardiac output and for the degree of hemodynamic reserve that was present in the two subgroups.

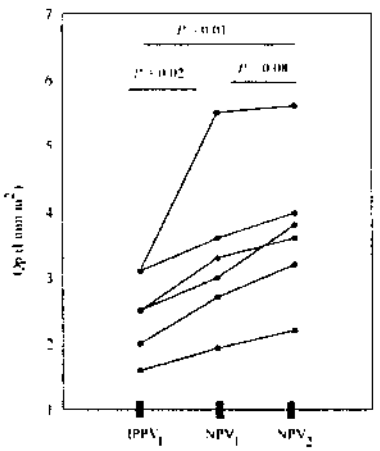

FIG 5. Subgroup 2: Q_p for patients in whom the period of NPV was extended after completion of a standard study. A third measurement was made after an additional 30 to 45 minutes of NPV (NPV_2).

Mechanisms for Increases in Pulmonary Blood Flow During NPV in Fontan Patients

The cardiac output of all individuals theoretically can be improved by increasing the heart rate, stroke volume, or, indeed, both. The cardiac output of children in general is more heart rate than stroke volume dependent, but an exaggeration of this "normal" phenomenon is seen in Fontan patients who even at rest tend to have a faster heart rate than healthy control subjects.[17] Similarly, the chronotropic augmentation of cardiac output in response to an increase in metabolic demand—for example, during exercise or after cardiopulmonary bypass—predominates. In contrast, an increase in stroke volume in either response to endogenous demand or by exogenous manipulation is much more difficult to achieve in Fontan patients and is often unchanged or can even be reduced during exercise.[18,19] There are a number of potential reasons for this. First, the systemic ventricle has been chronically volume loaded preoperatively, and changes in ventricular geometry[19] and regional abnormalities of wall motion[20] after surgery affect systolic and diastolic functions. Second, the combination of a relatively high systemic venous pressure—a necessary driving force in the Fontan circulation—and a generally low cardiac output results in an elevated systemic vascular resistance, which by increasing the total afterload limits the potential for an increase in stroke volume. In addition, individual patients will be further limited if there is more overt systemic ventricular dysfunction or their pulmonary blood flow is restricted by conduit obstruction,[14] an abnormal pulmonary vascular response, or an elevated left ventricular end-diastolic pressure.

TABLE 8. Results of Regression Analysis to Evaluate Possible Predictors of Quantity of Increase in Pulmonary Blood Flow During Standard Studies in Acute and Convalescent Fontan Patients

	Acute		Convalescent	
Parameter	R	P	R	P
PA press	.83	.02	−.26	NS
LVEDP*	.88	.009	.14	NS
TPG	.483	NS		
Baseline Qp	.02	NS	−.51	NS
PVRI	.68	.08	.25	NS

See Table 4 for abbreviations.
Pulmonary arterial (PA) pressure, transpulmonary gradient (TPG), Q_p, and PVRI are given during baseline $IPPV_1$.
*LVEDP at preoperative cardiac catheterization is given for acute patients, and values during current cardiac catheterisation are given for convalescent patients.

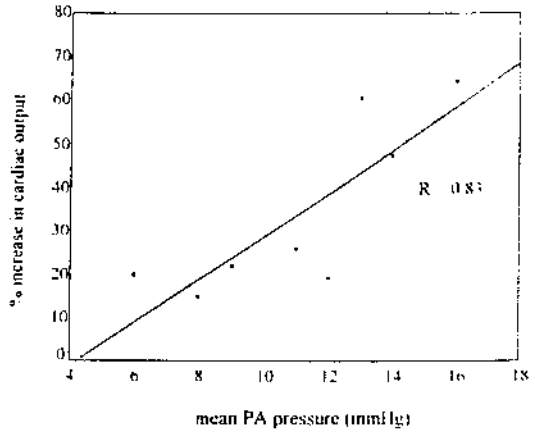

FIG 6. Relationship between mean postoperative pulmonary arterial (PA) pressure during baseline IPPV and increase in pulmonary blood flow during NPV in acute Fontan patients. A strong and positive correlation existed between postoperative PA pressures and the increase in pulmonary blood flow during NPV, suggesting that children with higher postoperative PA pressures were likely to benefit more from NPV.

Clearly, however, this study tests the therapeutic benefits of manipulation of the interplay between pulmonary blood flow and spontaneous and mechanical ventilation in Fontan patients. It is now well known that spontaneous inspiration enhances pulmonary blood flow and stroke volume in both atriopulmonary and total cavopulmonary circulations.[2,3] We previously speculated that the work of breathing may be one of the more significant sources of energy in the latter circulation, both at rest and during exercise.[8] Given that these patients are normally so dependent on physiological respiration to maintain pulmonary blood flow, one might have expected to see an even greater enhancement of cardiac output than that seen during negative pressure ventilation. The first important observation was that in subgroup 2, the pulmonary blood flow continued to increase if the period of NPV was extended. Presumably, there must lie a plateau (which has not been demonstrated here) beyond which cardiac output can no longer continue to improve, and this maximal improvement may exceed that which we have shown. It would have been interesting to have further lengthened the period of NPV to explore this hypothesis. However, in the catheter laboratory, the constraints of time with patients under general anesthesia would not allow a longer study period. In the intensive care unit, the assumption of a steady state for a longer period so soon after cardiopulmonary bypass, aside from the fact that blood transfusion, colloid administration, or chest physiotherapy is often required, would have rightly exposed the protocol to criticism.

Nevertheless, in patients whose total cardiac output is normally so dependent on heart rate, an improvement of >50% in pulmonary blood flow and stroke volume alone coupled with a marked rise in mixed venous saturation is probably unmatched by any other current therapeutic alternative that is available and applicable to this complex group. In this study, the improvement in cardiac output during NPV was comparable to the maximal response demonstrated in exercising Fontan patients,[15,18] further emphasizing the potential for exploitation of cardiac output during NPV.

Although the average rise in cardiac output was >50% in extended studies, the range of increase in cardiac output during NPV was between 10% and 100%. The individual response to NPV was difficult to predict. There was no relationship between the improvement in cardiac output during NPV and any hemodynamic parameters that we though may have influenced this in the convalescent patients. In the acute patients, however, possibly a very encouraging finding was that the improvement in pulmonary blood flow was completely independent of baseline pulmonary blood flow at the onset of the study. In addition, patients with a higher postoperative pulmonary arterial pressure seemed to benefit more from NPV. A similar relationship was seen in those patients who had a higher preoperative left ventricular end-diastolic pressure, underscoring the desirability of an improvement in diastolic filling of the ventricle by directly increasing pulmonary blood flow. One might speculate, therefore, that NPV may be of most benefit to patients who had higher risk factors for postoperative morbidity. It is important to mention, however, that all of the acute patients had relatively favorable postoperative hemodynamics, with no child having a pulmonary arterial pressure of >16 mm Hg.

Conclusions

Patients who have undergone Fontan-like operations often have signs of a low cardiac output state in the early postoperative period. Obviously in the presence of systemic ventricular dysfunction, a degree of pharmacological myocardial and renal support may be desirable, but often the unwanted side effects of inotropes, such as an increase in pulmonary and systemic vascular resistance or inappropriate tachycardia, are superimposed on their positive hemodynamic influences. These effects can be particularly detrimental to the sensitive Fontan circulation, and a nonpharmacological approach may be very desirable under these circumstances.

NPV improved the cardiac output of Fontan patients by manipulating the important cardiopulmonary interactions that exist in this patient group to produce a highly significant increase in stroke volume, the degree of which may be unrivaled.

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