Mechanisms of systemic adaptation to univentricular Fontan conversion

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Objective: After univentricular Fontan conversion, systemic venous pressure serves as the sole driving force for transpulmonary blood flow. Consequently, systemic venous return is markedly altered and ventricular filling is subnormal. The mechanisms and time course of systemic adaptation to Fontan conversion are incompletely understood. We hypothesized that acute elevation in systemic venous pressure induces an adaptive response similar to conversion to a univentricular Fontan circulation.

Methods: Adjustable vessel occluders were placed around the superior and inferior vena cavae in juvenile sheep. After 1-week recovery, occluders were tightened to acutely increase and maintain systemic venous pressure at 15 mm Hg ($n = 6$), simulating 1-stage Fontan conversion. Control animals ($n = 4$) received identical surgery, but venous pressure was not manipulated.

Results: Cardiac index decreased significantly (3.9 ± 1.0 mL/min/m² to 2.7 ± 0.7 mL/min/m², $P < .001$) and then normalized to control at 2 weeks. Circulating blood volume increased (100 ± 9.4 mL/kg vs 85.5 ± 8.4 mL/kg, $P = .034$) as a persistent response. Cardiac reserve improved and was not different from control by week 3. Resting heart rate decreased in both groups. Oxygen extraction (arteriovenous oxygen difference) and neurohormonal mediators increased transiently and then normalized by week 2.

Conclusions: Adaptation to global elevation in systemic venous pressure to Fontan levels is complete within 2 weeks. Increased blood volume and reduced heart rate are persistent responses. Increased oxygen extraction and neurohormonal up-regulation are temporary responses that normalize with recovery of cardiac output. With improved physiologic understanding of systemic adaptation to Fontan conversion, approaches to single-ventricle palliation can be more objectively assessed and optimized. (J Thorac Cardiovasc Surg 2010;140:850-6)

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Fontan repair of a functional single ventricle is performed using a staged surgical approach. This strategy, which has evolved on a clinical basis, remains problematic.¹ Although stage II volume unloading of the single ventricle provides early partial ventricular volume reduction and improvement in hypoxemia, counter to assumptions, it is not associated

with improved late ventricular function or exercise performance.² Thus, the majority of the benefit of interim staging exists early, likely from take-down of the systemic-to-pulmonary arterial shunt. Furthermore, evidence increasingly suggests that early Fontan conversion is associated with improved long-term ventricular function, incidence of normal sinus rhythm, and freedom from atrioventricular valve insufficiency (all presumably secondary to decreased interval of ventricular volume overload).^{1,2} This is consistent with current trends toward earlier repair. Because Fontan conversion at an early age may improve long-term outcome by limiting the period of ventricular volume overload and hypoxemia associated with an interim-staged approach, the best long-term status may derive from avoidance of ventricular volume load or use of a shunt altogether, thus, early primary repair.³

In select patients, Fontan conversion can be performed in 1 stage with excellent results.⁴ This has fallen out of favor because of improved safety margin and early outcomes achieved with interim palliation (earlier take-down of the systemic arterial shunt, with partial improvement in hypoxemia, partial reduction in ventricular volume load, and partial return to series circulation). Perhaps more important, however, staged conversion imposes less physiologic stress on the systemic venous, capillary, and interstitial circulation with partial (superior vena cava [SVC]), rather than global

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Abbreviations and Acronyms

Aorta _{sat}	= aortic oxygen saturation
IVC	= inferior vena cava
IVC _{sat}	= inferior vena cava oxygen saturation
RAAS	= renin-angiotensin-aldosterone system
SVC	= superior vena cava
SVC _{sat}	= superior vena cava oxygen saturation

(SVC + inferior vena cava [IVC]), increase in systemic venous pressure. Because decisions to perform Fontan staging have historically revolved around downstream pulmonary vascular resistance (ironically exacerbated by shunt physiology), the upstream systemic aspects of Fontan conversion have been largely overlooked.

Coupled with these questions, evolving circulatory support concepts are making compression of staging and earlier conversion to Fontan an increasingly realistic consideration.⁵ Temporary mechanical cavopulmonary assist can support the time-limited process of systemic and interstitial adaptation to global increase in systemic venous pressure. Although it may improve the margin of safety for direct Fontan conversion, the duration required to bridge to unsupported Fontan is not known. The goal of this study is to define the physiologic events and timeframe to Fontan steady state, with respect to the systemic circulation.

MATERIALS AND METHODS

Animal Model

Juvenile sheep (3 months old, $n = 10$) underwent right thoracotomy. The right and left azygous veins were ligated. Transthoracic pressure monitoring lines were placed in the pulmonary artery, aorta, SVC, IVC, right atrium, and left atrium. An ultrasonic flowprobe (Transonic, Ithaca, NY) was placed around the ascending aorta. Percutaneous adjustable vessel occluders (Fine Science Tools, Foster City, Calif) were placed around the juxtacardiac IVC and SVC (Figure 1). During 1-week recovery, normal hemodynamics were maintained. Transthoracic pressures (zeroed at olecranon; head neutral) and cardiac output were monitored daily. Animals were allowed unrestricted access to food and water.

Systemic Venous Pressure Elevation

On experimental day 0 (day of intervention), baseline hemodynamics were measured. In 6 animals, vena caval occluders were incrementally tightened over 15 to 20 minutes to achieve SVC and IVC pressures of 14 to 15 mm Hg. This was selected as the upper limit of “normal” systemic venous pressure in patients with Fontan, a range that allows documentation of hemodynamic response with few clinical symptoms. Aortic, SVC, and IVC samples were drawn before and after the pressure increase for oxygen saturation (OSM3 hemoximeter, Radiometer, Westlake, Ohio). Venous pressure was monitored twice daily for 5 days to ensure consistency; beyond day 5, occluder adjustment was seldom required. Control animals ($n = 4$) were identically monitored, with no manipulation of venous pressure.

Assessment of Cardiac Reserve

Dobutamine infusion (10 $\mu\text{g/kg/min}$, 20 minutes) was used to quantify cardiac reserve at 5 time points: study 1, experimental day -1 (1 day before

venous restriction) for baseline; study 2, experimental day 3; study 3, day 7; study 4, day 14; and study 5, day 21. Hemodynamic variables were recorded at 5-minute intervals, including 5 minutes after termination. Aortic, SVC, and IVC samples were drawn before and after dobutamine infusion for oxygen saturation.

Cerebral Oximetry

Cerebral oximetry was monitored using near-infrared spectroscopy (Somanetics Inc, Troy, Mich) in 4 experimental animals at the time of venous pressure increase and during dobutamine challenges.

Circulating Blood Volume

Blood volume was determined at the time of surgery, the day after venous pressure intervention, and before all dobutamine studies using dilution technique (Evan's Blue dye).⁶ Absorbance of plasma drawn from the SVC was measured using a standard spectrophotometric curve. Total blood volume (milliliters/kilogram) was calculated from plasma volume and hematocrit (blood volume = plasma volume/(1 - hematocrit)). Animals were weighed the same day of blood volume determination.

Neurohormonal Markers

Serum and plasma were collected for antidiuretic hormone, aldosterone, angiotensin II, epinephrine, norepinephrine, and brain natriuretic peptide determination before administering Evan's Blue dye or dobutamine on studies 1 to 5, as well as the day after venous pressure increase. Samples were frozen at -80°C and batch analyzed (Anilytics Inc, Gaithersburg, Md).

Statistical Analysis

Results are reported as mean $\pm$ standard deviation. Data were analyzed by pairwise comparison within and between control and experimental groups, including time factor for all time points, by 2-way analysis of variance with correction for repeated measures using Student Newman-Keuls post hoc test. Cerebral oxygen saturation data were analyzed by regression. Statistical analysis was performed with SigmaStat software (Systat, Richmond, Calif).

The experimental protocol was approved by the Animal Care and Use Committee of the Indiana University School of Medicine. Animals received humane care in accordance with the “Guide for the Care and Use of Laboratory Animals” prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (publication 86-23, revised 1996).

RESULTS

Hemodynamic Response to Acute Elevation in Systemic Venous Pressure

The 3-fold elevation in systemic venous pressure was surprisingly well tolerated; only 1 animal became unsteady and needed to lie down. In all instances, venous pressure of at least 12 mm Hg was achieved at the initial intervention; goal pressure was achieved in most animals. Pressure adjustments (4–5 mm Hg) were common in the afternoon of experimental day 0, but were subsequently few and minor (<2 –3 mm Hg). SVC and IVC pressures were maintained at 15 mm Hg over the duration of the study (Figure 2). Cardiac index decreased significantly in the experimental group, but normalized by day 14 to control (Figure 3). Systemic arterial blood pressure was not affected by increased systemic venous pressure, although heart rate did decrease significantly in control animals during the last 2 weeks of the study

FIGURE 1. Experimental model. P_{SVC} , Pressure superior vena cava; P_{IVC} , pressure inferior vena cava; P_{RA} , pressure right atrium; P_{LA} , pressure left atrium; P_{PA} , pressure pulmonary artery.

(Table E1). A trend toward lower mean pulmonary arterial pressure in experimental animals reached significance on experimental days 2, 4, 5, 7, 8, 10, and 16. Pulmonary vascular resistance increased in the experimental group in concert with decreased right ventricular preload and cardiac index.

Cardiac Reserve

A significant heart rate response occurred in both groups to dobutamine infusion, with no between-group difference (Figure E1, A, B). In the experimental group, cardiac index was significantly decreased in comparison with control at baseline for studies 2 and 3, and after dobutamine for studies 2, 3, and 4 (Figure E1, C, D). Controls had a significant increase in cardiac index from baseline for all 5 studies, but experimental animals did not significantly augment cardiac index in response to dobutamine during studies 2 and 3.

Blood Volume

Blood volume increased in the experimental group and was significantly higher than baseline on days 3, 7, 14, and 20. Blood volume was significantly higher than control on days 14 and 20 (Figure 4).

Neurohormonal Markers

Aldosterone and angiotensin II were significantly elevated in the experimental group early after the increase in systemic venous pressure, but normalized to control after week 1 (Figure 5). Antidiuretic hormone also increased

FIGURE 2. Systemic venous pressure: increased and maintained at goal range (14–15 mm Hg) in SVC (A) and IVC (B) distributions days 1 to 20. Adjusted measurement indicates adjustment required in vena caval restriction to maintain measured systemic venous pressure within goal parameters after the initial value at that time interval had been determined.

early, but was not significant (Table E2). No statistical difference was seen in brain natriuretic peptide, epinephrine, and norepinephrine levels in experimental versus control groups (Table E2).

Blood Gases and Cerebral Oximetry

Aortic oxygen saturation ($Aorta_{sat}$), SVC oxygen saturation (SVC_{sat}), and IVC oxygen saturation (IVC_{sat}) data are presented in Table E1. SVC_{sat} was significantly decreased at baseline for studies 2 and 3, and increased significantly in response to dobutamine during studies 2, 3, and 4 (Figure E2, B). IVC_{sat} was significantly decreased at baseline for all studies and did not increase in response to dobutamine (Figure E2, D). There was no change in SVC_{sat} or IVC_{sat} in controls (Figure E2, A, C). Cerebral saturation increased in response to dobutamine in all cases (Figure E2, E). Oxygen extraction ($Aorta_{sat} - SVC_{sat}$ or IVC_{sat}) was calculated. Significant group differences in SVC oxygen extraction were seen on days 1, 2, 3, 7 (Figure E3, A). Group

FIGURE 3. Cardiac index: significant reduction after intervention, with normalization by day 14. *Significant difference between experimental and control groups ($P \leq .05$).

differences in IVC oxygen extraction were seen on days 2 and 3 (Figure E3, B). Cerebral oximetry correlated with SVC and IVC oxygen saturation both before and after the increase in venous pressure and dobutamine studies. A total of 48 measurements were taken each for cerebral oximetry, SVC_{sat} and IVC_{sat} using 4 experimental animals. Cerebral oximetry values correlated significantly with SVC_{sat} ($R = 0.789$, $P < .001$) and IVC_{sat} ($R = 0.525$, $P < .001$) (Figure E4).

Necropsy

Left and right azygous vein ligation was confirmed in all cases. There was no evidence of venous thrombus. Small right pleural effusion (<100 mL) was present in most animals. One animal exhibited significant ascites (6 liters).

Comment

With increasing numbers of Fontan survivors reaching adulthood, the long-term sequelae of single-ventricle Fontan palliation is now recognized as an emerging public health

FIGURE 4. Blood volume. *Significant difference ($P \leq .05$) from control. #Significant difference ($P \leq .05$) from baseline.

A

B

FIGURE 5. Serum aldosterone (A) and angiotensin II (B). *Significant difference ($P \leq .05$) from control.

concern.⁷ Regression from compensated to uncompensated systemic venous hypertension is integral to the pathogenesis of both early and late Fontan failure.^{8,9} Although long proposed, medical therapies aimed at controlling fluid retention, decreasing pulmonary resistance, and optimizing ventricular function via increased contractility or afterload reduction remain limited and suboptimal.

Systemic compensatory mechanisms undoubtedly play an important role in Fontan homeostasis, including hemodynamic, interstitial, oncotic, neuroendocrine, and renin-angiotensin axis regulation. These mechanisms are poorly understood. Venous hypertension, construed as an immutable consequence of Fontan physiology, has been clinically approached as a problem to minimize or avoid. An impediment to objective resolution of this problem is that chronic models of Fontan do not exist; mechanisms underlying Fontan homeostasis and failure are not well defined. Complete¹⁰ and partial right-sided heart bypass¹¹ in the context of mechanical support of cavopulmonary flow have been reported, but none have achieved chronic survival, limiting the ability

to test therapies or draw conclusions beyond the perioperative period.

Hemodynamic Response to Restricted Systemic Venous Return

In this study, systemic venous pressure was acutely and globally (both SVC and IVC distributions) elevated in awake, conscious animals as a systemic physiologic mimic of 1-stage Fontan conversion. This differs from clinical staged Fontan conversion where pressure elevation in the SVC and IVC distributions are punctual events separated in time and occur in a setting of general anesthesia and cardiopulmonary bypass-associated myocardial dysfunction and capillary leak. Without superimposed capillary leak and third spacing, the findings in this study suggest that 1-stage Fontan conversion may be readily achievable once perioperative fluid shifting is complete and lung parenchymal function is optimized. Normalization of cardiac reserve may reflect a recovered ability to fill the right ventricle as the result of increased preload, although this is not borne out by measured left atrial pressure values. This demonstrates adaptation beyond resting cardiac index, for which increased blood volume presumably plays a key role.

Heart Rate Response to Restricted Systemic Venous Return

Heart rate disturbances and autonomic dysfunction are well documented late after Fontan.¹² Sinus node dysfunction and bradycardia have been attributed to surgical injury near the atrial pacemaker complex. In this study, there was no difference in heart rate between control and experimental animals at any time point. There was an overall trend toward decreasing heart rate for both groups that reached significance after week 2 for control animals. The cause of the heart rate decrease is unclear, but it may be attributed to acclimatization to the testing procedures or postsurgical recovery. Both groups retained equivalent ability to increase heart rate in response to dobutamine, with no difference in basal epinephrine and norepinephrine levels, indicating no endogenous catecholamine response to systemic venous restriction. Counter to expectations that an increase in heart rate will occur in response to reduced cardiac output after Fontan, a decrease in heart rate may represent a natural compensatory mechanism aimed to prolong diastolic filling time. It may also be secondary to increased cerebral venous pressure. This has clinical implications for low resting heart rate in patients undergoing the Fontan procedure; recent studies have, in fact, independently associated low resting heart rate with higher functional status.^{13,14}

Cerebral Oximetric Response to Restricted Systemic Venous Return

Despite the inability to increase cardiac index in response to dobutamine, cerebral oximetry values and SVC_{sat}

increased during dobutamine infusion. IVC_{sat} remained unchanged or decreased. This indicates that blood flow is preferentially shifted to the cerebral circulation in response to dobutamine. SVC_{sat} and IVC_{sat} both correlated well with cerebral oximetry, but oximetry values more closely approximated the change in SVC_{sat} in response to dobutamine when initial saturation was subnormal. In agreement with clinical findings, cerebral oximetry strongly predicts SVC_{sat} .¹⁵

Neuroendocrine Response to Restricted Systemic Venous Return

The neurohormonal response to intervention includes the following: (1) up-regulation of the renin-angiotensin-aldosterone system (RAAS) by increase in angiotensin II and aldosterone, with subsequent normalization beyond 1 week (Figure 5); (2) increased blood volume in the period that RAAS is up-regulated, and which persists after angiotensin II and aldosterone have normalized. Therefore, adaptive mechanisms beyond RAAS up-regulation must remain in play to maintain increased blood volume. There is likely a shift in RAAS over time because its role in chronic Fontan physiology seems to differ from that in the immediate postoperative period.

In animal models, acute and chronic restriction of the IVC alone has been used to induce low cardiac output and an antinatriuretic response.¹⁶⁻¹⁸ In these studies, diminished cardiac output, ascites formation, increased total peripheral resistance, decreased sodium and potassium excretion, decreased glomerular filtration rate, and antinatriuresis are secondary to decrease in cardiac output and sodium retention mediated by RAAS. RAAS response has been examined clinically early and late after Fontan. RAAS response is up-regulated early after Fontan and bidirectional Glenn cavopulmonary anastomosis¹⁹ and has been implicated in the development of effusions, but trials using angiotensin-converting enzyme inhibitors have mixed results. Chronically after Fontan, adrenergic tone and RAAS are up-regulated,²⁰ although in one study blood volume was not significantly different from biventricular circulations.²¹ A randomized controlled trial of angiotensin-converting enzyme inhibitor administration late after Fontan demonstrated no improvement in exercise performance.²²

Is Staged Palliation the Best Long-Term Strategy?

Interim staged palliation may represent a trade-off between improved early outcomes, but worsened long-term status. Basal health of the pulmonary vascular bed, in part a reflection of previous staging procedures in which a shunt was used,²³ is the critical inflection point on which ultimate Fontan upstream systemic venous pressure and downstream ventricular filling depend. As a result, a palliative strategy designed to preserve ventricular function and basal pulmonary vascular resistance is of prime importance. Because

a strategy of shunt palliation and intermediate staging may induce irreversible alterations in the myocardium before volume unloading, it can be argued that this may *worsen* candidacy for Fontan conversion and long-term functional status.^{1,2} Consideration of approaches that may reduce, or eliminate, use of a shunt or interval staging is timely and clinically relevant, and merits investigation.

The Case for Direct Fontan Repair

The best strategy may be primary Fontan repair with no staging at all: Precisely how this can be accomplished is a provocative and complex matter. Minimizing or avoiding Fontan staging (combined stage 2 and 3, or stage 1, 2, and 3 Fontan conversion) by performing primary Fontan repair, with temporary mechanical cavopulmonary assist, has compelling theoretic advantages.^{3,10} The interval of ventricular volume overload and hypoxemia is reduced or eliminated, which may reduce the incidence of ventricular hypertrophy and diastolic dysfunction. Also, minimization of hypoxemia and early return to normoxia would reduce the stimulus for pulmonary hypertension and pathologic pulmonary vascular remodeling. Finally, the interstage interval and a second or third open procedure, all significant risk factors for mortality, would be obviated by direct conversion to Fontan.

Duration of Support as Bridge to Fontan

Adaptation to Fontan venous pressure is complete within 2 weeks; this is a reasonable duration within which percutaneous mechanical circulatory support can be applied. During support, 2-ventricle physiologic conditions are replicated, with no unsafe upper limit to oxygenation, a more stable series circulation, and no ventricular volume overload. An obvious concern is risk of elevated pulmonary resistance in newborns. However, in normal human neonates, pulmonary resistance decreases rapidly to within 10% of adult values within the first 2 to 3 days of life.^{24,25} Experimental data that we have generated in newborn lambs with mechanically assisted cavopulmonary blood flow also support this, with normalization of pulmonary resistance in response to mechanical cavopulmonary assist within 8 hours.³ Physiologic details remain to be determined, but, under ideal physiologic conditions, neonates are clearly capable of maintaining low pulmonary resistance. Adjuncts, such as selective pulmonary vasodilators, may facilitate transition from supported to unsupported neonatal Fontan repair of single ventricles.

Study Limitations

This is not a true model of a Fontan circulation, but rather a model of systemic venous hypertension in a biventricular circulation. Although the model produces chronic elevation in systemic venous pressure, it differs in important ways from a Fontan procedure. The right ventricle is maintained in the circulation, and the downstream resistor to venous re-

turn is a fixed anatomic obstruction rather than physiologic pulmonary resistance. Blood is still pumped to the lungs by the right ventricle, rather than being driven passively by systemic venous pressure. The interactions of respiration, gravity, IVC, and hepatic venous and transpulmonary blood flow, all of which are important in the Fontan circulation, are not accounted for. Also, the effects of pulmonary resistance on systemic impedance when added in series to the systemic circulation are not examined or accounted for.

CONCLUSIONS

Absent an existing chronic model of Fontan, the model provides a reasonable estimate of the systemic transitional events that occur in 1-stage Fontan conversion and may serve for study of systemic Fontan pathophysiology. In this analysis, selective restriction of SVC and IVC return to model intermediate staging was not performed; studies of this nature must account for venous collateral shunting to the opposing unrestricted venous territory. Because the study was performed in juvenile animals, firm conclusions regarding neonatal adaptation to elevated systemic venous pressure cannot be drawn. The findings in this study elucidate the mechanisms of global adaptation to Fontan-level venous pressure and define the time course for this transition to stably occur. This information may be useful to guide optimization strategies for Fontan palliation.

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FIGURE E1. Heart rate in control (A) and experimental (B) groups, and cardiac index in control (C) and experimental (D) groups at baseline and after 20-minute dobutamine infusion. Study 1: 1 day before intervention. Study 2: 3 days postintervention. Study 3: 7 days postintervention. Study 4: 14 days postintervention. Study 5: 21 days postintervention. *Significant difference ($P \leq .05$) from control. #Significant difference ($P \leq .05$) from study 1. †Significant difference ($P \leq .05$) from baseline.

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FIGURE E2. Blood oxygen saturation in SVC in control (A) and experimental (B) animals and IVC in control (C) and experimental (D) animals at baseline after 20-minute dobutamine infusion. E, Represents near-infrared spectroscopy measurements in experimental animals (n = 4) at baseline after 20-minute dobutamine infusion. Study 1: 1 day before intervention. Study 2: 3 days postintervention. Study 3: 7 days postintervention. Study 4: 14 days postintervention. Study 5: 21 days postintervention. *Significant difference ($P \leq .05$) from control. #Significant difference ($P \leq .05$) from study 1 values. †Significant difference ($P \leq .05$) from baseline. SVC, Superior vena cava; IVC, inferior vena cava; NIRS, near-infrared spectroscopy.

A Time (days)

B Time (days)

FIGURE E3. Oxygen extraction in the SVC (A) and IVC (B) versus time. *Significant difference ($P \leq .05$) from control. #Significant difference ($P \leq .05$) from baseline. SVC, Superior vena cava; IVC, inferior vena cava.

FIGURE E4. Correlation between cerebral near-infrared spectroscopy measurements and SVC (A) and IVC (B) blood oxygen saturation in experimental animals ($n = 4$). $P < .001$.

TABLE E1. Hemodynamic and blood gas data

Parameter	III	Group	Baseline (day 0 preintervention)		Day 1			Day 3		
			Value	II	Value	I	II	Value	I	II
Heart rate (beats/min)	.048	Control	151 ± 11.6	.391	145 ± 18	.865	.868	138 ± 39	.641	.274
		Experimental	139 ± 8.6		148 ± 31	.075		122 ± 31	.987	
Systolic blood pressure (mm Hg)	.869	Control	98 ± 5	.510	103 ± 3	.988	.053	100 ± 7	.992	.130
		Experimental	95 ± 10		94 ± 10	.996		93 ± 9	.996	
Diastolic blood pressure (mm Hg)	.982	Control	76 ± 6		79 ± 4		NS	75 ± 4		NS
		Experimental	76 ± 7		73 ± 12			70 ± 9		
Superior vena cava pressure (mm Hg)	<.001	Control	5 ± 2	.496	4 ± 2	.899	<.001	5 ± 2	1.000	<.001
		Experimental	4 ± 2		14 ± 1	<.001		15 ± 1	<.001	
Inferior vena cava pressure (mm Hg)	<.001	Control	5 ± 2	.339	3 ± 2	.199	<.001	5 ± 3	.999	<.001
		Experimental	3 ± 2		15 ± 1	<.001		15 ± 1	<.001	
Cardiac index (cardiac output/weight, expressed in units L/min/m ²)	<.001	Control	4.2 ± 0.9	.547	4.5 ± 0.9	1.000	.001	4.4 ± 1.1	1.000	.002
		Experimental	3.9 ± 1.0		2.7 ± 0.7	<.001		2.7 ± 0.4	<.001	
Mean pulmonary arterial pressure (mm Hg)	.960	Control	17 ± 2	.156	16 ± 1	.935	.351	17 ± 1	.970	.139
		Experimental	15 ± 2		15 ± 2	.999		15 ± 2	.995	
Right atrial pressure (mm Hg)	.169	Control	3 ± 2		1.3 ± 2.3		NS	2 ± 2.6		NS
		Experimental	0.8 ± 1.8		-0.8 ± 1.9			0.4 ± 4		
Left atrial pressure (mm Hg)	.119	Control	2.3 ± 2.1		2.5 ± 1.9		NS	1.8 ± 2.2		NS
		Experimental	1.2 ± 2.2		0.8 ± 3			0.7 ± 2.7		
Pulmonary vascular resistance, calculated as (P _{PA} - P _{LA}) × 80/(cardiac output/weight), expressed as 10 ³ dynes/cm ⁻⁵ /kg	.001	Control	9.4 ± 2.6	.827	8.6 ± 1.9	.999	.021	9.9 ± 4.0	1.000	.058
		Experimental	9.9 ± 3.2		14.8 ± 4.9	.027		14.8 ± 4.7	.025	
Arterial oxygen saturation (%)	.255	Control	89.5 ± 4.7		90.1 ± 2.4			91 ± 4.4		
		Experimental	89.7 ± 5.2		90.3 ± 2.0			89.8 ± 2.6		
SVC oxygen saturation (%)	.001	Control	52.5 ± 2.8	.651	54.4 ± 4.0	.984	<.001	57.1 ± 3.7	.839	<.001
		Experimental	54.1 ± 7.5		40.1 ± 7.5	<.001		39.6 ± 8.7	<.001	
IVC oxygen saturation (%)	<.001	Control	56.7 ± 7.1	.678	55.7 ± 5.0	.947	.287	57.2 ± 7.7	.873	.003
		Experimental	58.7 ± 4.6		50.6 ± 7.2	.018		40.5 ± 12.4	<.001	
Plasma volume (mL/kg)	.059	Control	85.8 ± 12	.876	87.3 ± 14	.945	.444	87.8 ± 13	.972	.058
		Experimental	84.8 ± 8.7		92.3 ± 13	.059		100.7 ± 7.3	.002	
Parameter	Group	Day 7			Day 14			Day 21		
		Value	I	II	Value	I	II	Value	I	II
Heart rate (beats/min)	Control	128 ± 21	.458	.827	111 ± 11	.028	.89	103 ± 23	.006	.297
	Experimental	124 ± 15	.972		113 ± 16	.908		119 ± 20	.967	
Systolic blood pressure (mm Hg)	Control	94 ± 5	.657	.762	98 ± 7	.898	.844	99 ± 9	.949	.303
	Experimental	95 ± 8	1.000		97 ± 6	.954		94 ± 4	.997	
Diastolic blood pressure (mm Hg)	Control	74 ± 3		NS	76 ± 5		NS	75 ± 6		NS
	Experimental	73 ± 8			75 ± 6			71 ± 5		
Superior vena cava pressure (mm Hg)	Control	5 ± 1	.999	<.001	5 ± 2	.880	<.001	3 ± 2	.316	<.001
	Experimental	14 ± 1	<.001		14 ± 1	<.001		14 ± 2	<.001	
Inferior vena cava pressure (mm Hg)	Control	5 ± 1	.993	<.001	7 ± 4	.955	<.001	5 ± 4	.998	<.001
	Experimental	14 ± 1	<.001		15 ± 1	<.001		15 ± 1	<.001	
Cardiac index (cardiac output/weight, expressed in units L/min/m ²)	Control	4.2 ± 0.7	1.000	.038	4.2 ± 0.9	.999	.074	4.0 ± 0.6	.775	.789
	Experimental	3.2 ± 0.7	.129		3.3 ± 0.9	.302		3.9 ± 0.7	.977	
Mean pulmonary arterial pressure (mm Hg)	Control	20 ± 4	.718	.023	17 ± 1	.965	.124	17 ± 1	.990	.194
	Experimental	16 ± 3	.944		15 ± 2	.995		15 ± 2	.981	
Right atrial pressure (mm Hg)	Control	4.7 ± 3.2		NS	2.3 ± 3.5		NS	2.7 ± 2.3		NS
	Experimental	-0.2 ± 1.8			-0.2 ± 2.5			1.4 ± 1.7		

(Continued)

TABLE E1. Continued

Parameter	Group	Day 7			Day 14			Day 21		
		Value	I	II	Value	I	II	Value	I	II
Left atrial pressure (mm Hg)	Control	3.5 ± 2.6		NS	3 ± 2.8		NS	3.3 ± 3.2		NS
	Experimental	0 ± 1.3			0 ± 0.6			2.5 ± 2.6		
Pulmonary vascular resistance, calculated as $(P_{PA} - P_{LA}) \times 80 / (\text{cardiac output} / \text{weight})$, expressed as $10^3 \text{ dynes/cm}^5/\text{kg}$	Control	10.7 ± 4.1	.999	.134	9.3 ± 3.4	1.000	.159	9.5 ± 2.5	1.000	.895
	Experimental	14.5 ± 5.1	.036		12.8 ± 3.8	.308		9.2 ± 3.1	.941	
Arterial oxygen saturation (%)	Control	91.4 ± 3.9			92.8 ± 1.3			91.2 ± 0.6		
	Experimental	90 ± 2.9			90.6 ± 2.5			88.1 ± 2.7		
SVC oxygen saturation (%)	Control	56.7 ± 1.3	.009	.001	53.7 ± 3.4	.985	.165	59.5 ± 0.9	.487	.057
	Experimental	44.2 ± 6.9	.835		48.7 ± 5.1	.240		52.7 ± 7.4	.516	
IVC oxygen saturation (%)	Control	55.1 ± 7.4	.985	.436	55.1 ± 6.2	.957	.312	56.5 ± 1.2	.817	.206
	Experimental	51.3 ± 7.1	.027		50.2 ± 5.4	.018		51.2 ± 5.0	.030	
Plasma volume (mL/kg)	Control	86.8 ± 4.7	.841	.072	87.9 ± 9.1	.992	.020	85.5 ± 8.4	.950	.034
	Experimental	98.8 ± 7	.002		104 ± 8.5	<.001		100 ± 9.4	.002	

SVC, Superior vena cava; IVC, inferior vena cava; SD, standard deviation. Values expressed as mean ± SD. Control group includes n = 4 measurements; experimental group includes n = 6 measurements for all variables and time points. Columns headed by I are *P* values for within-group comparisons with baseline. Columns headed by II are *P* values for between-group comparisons. The column headed by III shows *P* values for 2-way analysis of variance group effect for time. Significant *P* values are in bold.

TABLE E2. Serum neurohormonal markers

	Group	Study 1 (Day -1)	Postintervention (Day 0)	Study 2 (Day 3)	Study 3 (Day 7)	Study 4 (Day 14)	Study 5 (Day 21)
ADH (pg/mL)	Control	1.15 ± 1.11	2.11 ± 0.9	1.64 ± 1.13	2 ± 0.83	2.72 ± 1.07	2.85 ± 0.64
	Experimental	2.6 ± 1.03	21.14 ± 38.64	3.82 ± 2.31	4.39 ± 1.82	3.1 ± 2.31	3.43 ± 2.09
Aldosterone (pg/mL)	Control	58.2 ± 18.59	41.68 ± 42.43	59.44 ± 41.88	17.82 ± 27.55	16.62 ± 22.09	47.78 ± 56.15
	Experimental	106.7 ± 116.9	252.3 ± 230.4	284.7 ± 230.1	58.6 ± 86.8	107.2 ± 203.8	32.5 ± 32.5
Angiotensin II (pg/mL)	Control	506.5 ± 306	601 ± 206.8	518.6 ± 174.1	424.1 ± 108.4	474.3 ± 230.9	550.1 ± 160.7
	Experimental	1610.1 ± 701.3	3261.2 ± 2394.3	4576.8 ± 3894.5	2840.6 ± 2528.7	1745.4 ± 1337.4	1759.3 ± 1109.5
BNP (ng/mL)	Control	0.25 ± 0.03	0.26 ± 0.06	0.31 ± 0.08	0.32 ± 0.12	0.38 ± 0.12	0.33 ± 0.1
	Experimental	0.3 ± 0.07	0.22 ± 0.03	0.21 ± 0.02	0.27 ± 0.08	0.27 ± 0.05	0.28 ± 0.03
Epinephrine (ng/mL)	Control	0.09 ± 0.05	0.05 ± 0.05	0.07 ± 0.05	0.04 ± 0.03	0.09 ± 0.09	0.07 ± 0.09
	Experimental	0.08 ± 0.03	0.15 ± 0.09	0.11 ± 0.07	0.02 ± 0.02	0.00 ± 0.01	0.01 ± 0.02
Norepinephrine (ng/mL)	Control	0.58 ± 0.29	0.42 ± 0.22	0.63 ± 0.22	0.51 ± 0.38	0.61 ± 0.5	0.58 ± 0.44
	Experimental	1.25 ± 0.75	1.2 ± 0.88	1.48 ± 1.36	0.97 ± 0.69	0.22 ± 0.16	0.47 ± 0.26

ADH, Antidiuretic hormone; BNP, brain natriuretic peptide. Values expressed as mean ± SD. Control group includes n = 4 measurements and experimental group includes n = 5 measurements for all variables and time points, except angiotensin II, for which n = 3 in the experimental group.