Beneficial Effects of Vasopressors on Right Ventricular Function in Experimental Acute Right Ventricular Failure in a Rabbit Model

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Abstract

Background An acute increase in right ventricular (RV) afterload leads to RV dilation, reduced systolic function, and low cardiac output. It has previously been shown, experimentally, that an additional increase of left ventricular afterload by aortic constriction can reverse some of these changes. We studied the clinically more relevant effects of intravenous vasopressors on this phenomenon in an animal model.

Methods Acute RV failure was induced by pulmonary artery constriction in adult New Zealand white rabbits. We then assessed the effect of aortic constriction on the functional performance of the failing RV using conductance catheters. We compared the impact of aortic constriction on RV contractility with the effects of 0.05, 0.1, 0.5, and 1 mcg/kg $\times$ min^{-1} norepinephrine and epinephrine.

Results Aortic constriction lead to increased RV end-systolic pressure-volume relation (RVESPVR 3.2 ($\pm$0.6) versus 5.2 ($\pm$0.7) mm Hg/mL ($p = 0.0002$). Cardiac output (131 ($\pm$23.7) versus 134.8 ($\pm$32.5) mL/min), and heart rate remained unchanged. Administration of norepinephrine and epinephrine lead to similar effects on RV contractility with the maximum increase in RVESPVR observed with 0.5 mcg/kg $\times$ min^{-1} norepinephrine (RVESPVR 4.8 ($\pm$0.4) mm Hg/mL, $p = 0.007$). However, in contrast to aortic constriction, cardiac output also markedly increased during vasopressor therapy, the most significant effect seen with 1 mcg/kg $\times$ min^{-1} epinephrine (214.8 ($\pm$46.8) mL/min, $p = 0.04$).

Conclusions Aortic constriction improves RV contractility but not cardiac output in acute right heart failure. A comparable effect on RV functional performance with increased cardiac output was achieved by administration of systemic vasopressors. These data may have implications for management of clinical right heart failure.

Keywords
- right ventricular function
- pulmonary hypertension
- right ventricular failure
- conductance catheter
- pulmonary artery banding

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Introduction

An acute moderate increase in right ventricular (RV) afterload usually results in improved RV contractility,[1] whereas an acute severe increase of RV afterload such as the one that occurs in pulmonary embolism, leads to RV dilation, reduced systolic function, and low cardiac output, resulting in RV failure.[2] The mechanism of failure is not entirely understood, but both coronary ischemia and adverse ventricular-ventricular interactions have been implicated.[3] We have previously shown that isolated right coronary ischemia, even in the presence of a normotensive RV, leads not only to RV dysfunction, but also to reduced left ventricular (LV) contractility. This effect, which presumably reflects adverse ventricular-ventricular interaction, is exaggerated by pericardial constraint suggesting that right heart dilation alters LV geometry and contractile efficiency.[4]

Clinically, acute RV failure often responds poorly to treatment and there are no outcome data to support many of the currently available therapies which are mainly based on vasodilative drug effects on pulmonary arterial vessels. However, previous experimental models have demonstrated that vasoconstriction by banding of the aorta can reverse some of the aforementioned changes, presumably via beneficial ventricular-ventricular interactions or improved myocardial perfusion.[5]

However, aortic constriction is not a readily applicable therapeutic option in humans. We therefore studied the more clinically relevant effects of the vasopressor agents norepinephrine and epinephrine on RV contractility in the setting of acute RV failure induced by pulmonary artery banding. We hypothesized that norepinephrine and epinephrine can increase RV contractility in this setting.

Material and Methods

All experiments were approved by the Animal Ethics Committee of the Hospital for Sick Children, and performed in accordance with the "Guiding Principles in the Care and Use of Animals" of the American Physiologic Society.

Preparation

Ten adult New Zealand white rabbits (3.5 to 5 kg) were studied. After intravenous cannulation through the ear marginal vein with a 24G Angiocath, anesthesia was initiated by the use of isoflurane 3%, and acepromazine 1.1 mg/kg. Following intubation, ventilation was controlled mechanically to maintain PaCO2 of 32 to 35 mm Hg on the blood gas study. General anesthesia was maintained with isoflurane 1.5 to 2%. Heart rate and oxygen saturation were continuously monitored.

Banding Device

For incremental banding of the pulmonary trunk and descending aorta, we used an adjustable banding device (ABS, Silimed Inc, Rio de Janeiro, Brazil), recently introduced for pulmonary artery banding in neonates (►**Fig. 1**).[6] The band consists of the following: a banding ring, connecting tube, and an inflation reservoir. The banding ring is a C-shaped hydraulic cuff with a 5 mm width and a rigid outer layer, reinforced with a polyester mesh, which keeps it from deforming centrifugally. The cuff compresses the lumen of the vessel when expanded in proportion to the volume injected into the inflation reservoir. The connecting tube hermetically connects the banding ring to the inflation reservoir.

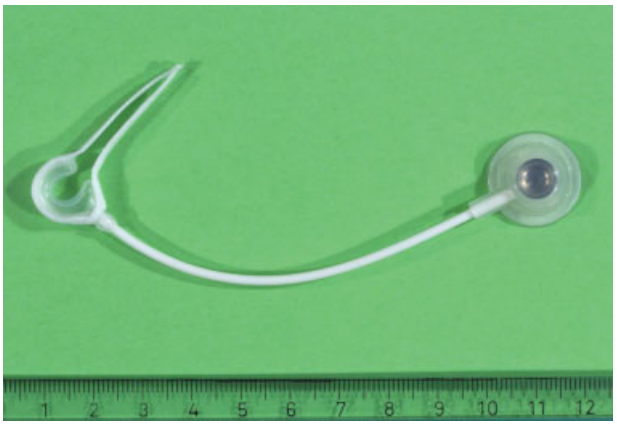

Figure 1 Picture showing the prototype of the adjustable mini-banding system ABS (Silimed Inc, Rio de Janeiro, Brazil).

Surgical Technique

►**Fig. 2** illustrates the instrumentation of the heart. In all animals, adjustable banding devices were placed on the pulmonary trunk and descending aorta via median sternotomy. A flow probe (4 mm, TS 420, Transonic Systems Inc., Ithaca, NY) was placed around the ascending aorta to calculate cardiac output and was used for calibration of the conductance catheter. For preload reduction, required to obtain pressure-volume relations, a balloon-catheter (10 mm Tyshak balloon, NuMED, Cornwall, Canada) was introduced via a groin vein and was placed in the inferior vena cava under fluoroscopic guidance. A 3F conductance catheter (Millar Instruments, Houston, TX) was advanced to both ventricles for simultaneous measurement of pressures and volumes via a neck vein and artery, respectively.

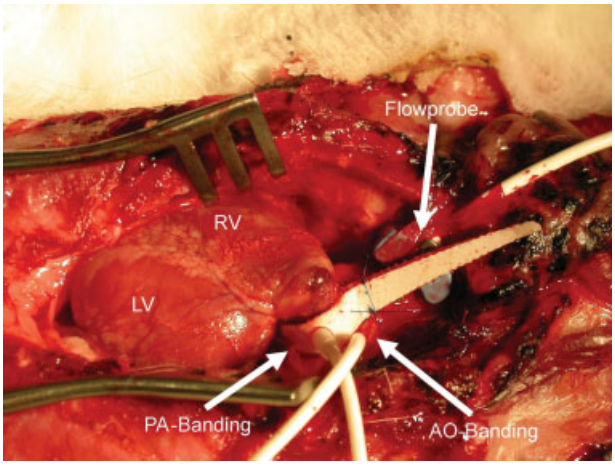

Figure 2 Picture at the time of operation showing the adjustable banding devices placed on the main pulmonary artery and on the descending aorta, respectively. The flow probe is placed on the ascending aorta. (RV, right ventricle; LV, left ventricle.)

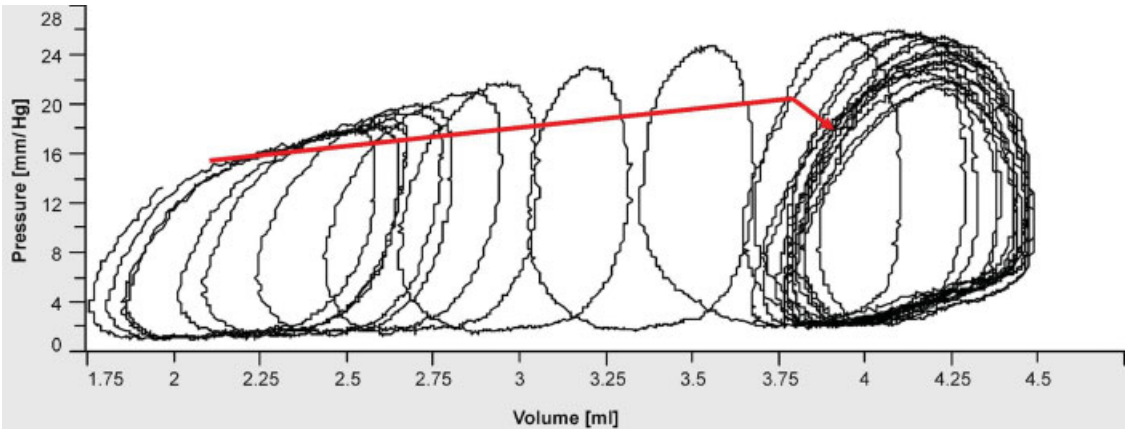

Figure 3 Representative set of pressure-volume loops of the RV recorded in an adult rabbit during incremental pulmonary artery constriction. RV systolic pressure and RV elastance increased, but failed to increase above the 2-fold of the baseline value. As failure ensued with severe PA constriction, RV systolic pressure and elastance decreased (arrow) and RV enddiastolic pressure increased.

Protocol

At the beginning of the protocol, blockade of cardiac autonomic nervous activity produced by an intravenous injection of 0.2 mg/kg propanolol and 0.04 mg/kg atropine was used in all animals to study exclusively the intrinsic cardiac function,[7] and was repeated every 2 hours. Adequate autonomic blockade was confirmed by the absence of reflex tachycardia during occlusion of the inferior vena cava. In addition, by the use of propranolol, direct inotropic effects mediated by agonistic action of epinephrine and norepinephrine on both β_1- and β_2-adrenergic receptors were minimized. Acute RV failure was induced by severe pulmonary trunk constriction as previously described by Greyson et al,[2] and was documented by the typical downward drift of the pressure volume loops (►**Fig. 3**), and a fall in cardiac output at baseline.

Measurements were made at baseline, after establishing RV failure, and again after aortic constriction. Following release of the aortic band, in 5 of the 10 animals norepinephrine was infused at 0.05 mcg/kg $\times$ min^{-1} started and measurements repeated after 10 minutes and establishment of a steady state. Then the norepinephrine dose was successively increased to 0.1, 0.5, and 1.0 mcg/kg $\times$ min^{-1} and measurements made at each stage after 10 minutes. After norepinephrine infusion, this protocol was repeated for epinephrine.

For all conditions, steady-state hemodynamic data were recorded during short periods of suspended ventilation at end-expiration.

Heart rate, cardiac output, endsystolic and enddiastolic pressure, and the time constant of relaxation (tau) were analyzed. Indices of systolic and diastolic function were derived from pressure-volume loops recorded during the inflation of a balloon catheter in the inferior vena cava to reduce RV preload. For systolic ventricular function, we determined end systolic elastance as the slope of the end-systolic pressure-volume relationship (ESPVR). Diastolic stiffness was determined as the slope of the end-diastolic pressure-volume relationship (EDPVR). These slopes are regarded the optimal load-independent indices of intrinsic systolic and diastolic ventricular function, reflecting contractility and lusitropy.

Statistical Analysis

Data are expressed as means + /– SEM. Results were analyzed by ANOVA for repeated measurements. GraphPad (San Diego,

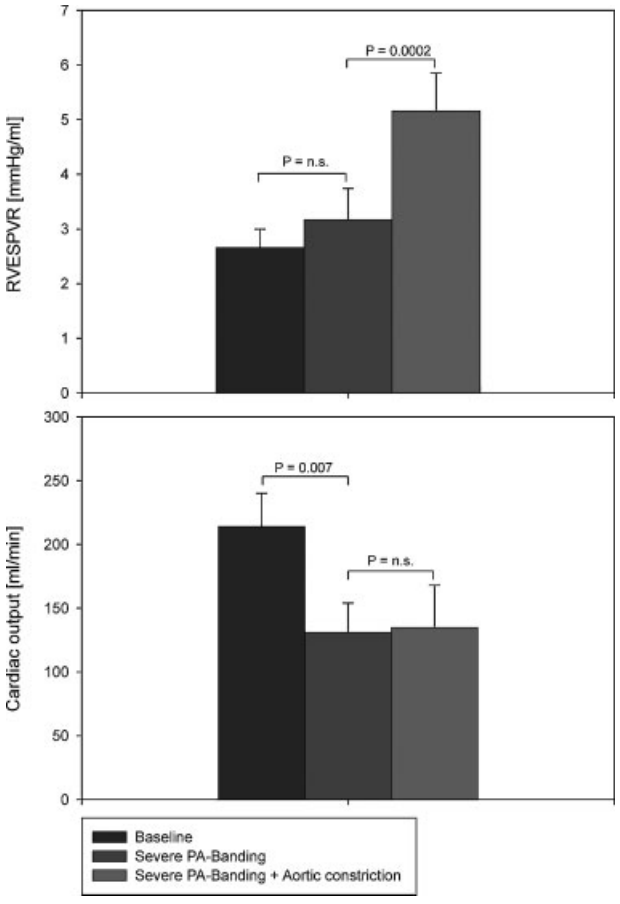

Figure 4 Schematic representation of the changes in the RV end-systolic pressure volume relation (RVESPVR), and cardiac output following pulmonary banding and subsequent aortic constriction. Data are presented as mean and standard error of mean (SEM). Aortic constriction results in a significant increase of RVESPVR, however cardiac output was not significantly increased.

Table 1 Hemodynamic Data at Baseline, after Pulmonary Artery Banding, Additional Aortic Banding, and with Increasing Doses of Norepinephrine and Epinephrine

	Baseline	PA Banding	AO Banding	Norepi 0.05	Norepi 0.1	Norepi 0.5	Norepi 1.0	Epi 0.05	Epi 0.1	Epi 0.5	Epi 1.0
HR [bpm]	201 (9.4)	195 (9.5)	194 (9.9)	193 (10.7)	189 (10.5)	193 (10.7)	196 (10.1)	195 (9.5)	192 (10.6)	193 (9.2)	196 (9.7)
RVPes [mm Hg]	14.4 (1.2)	19.5 (1.5)	21.1 (1.7)	21 (4.3)	19.2 (2.4)	21.7 (3.2)	23.4 (4.4)	18.3 (2.9)	20.0 (5.2)	19.4 (3.2)	20.8 (4)
RVPed [mm Hg]	1.6 (0.4)	2.2 (0.3)	2.4 (0.4)	3.9 (1)	4.0 (1.1)	4.2 (1.4)	5.3 (2.1)	4.8 (1.4)	4.7 (1.7)	5.6 (2.3)*	6.3 (1.7)*
RVdP/dT max [mm Hg/s]	385.5 (33.1)	428.8 (32.9)	433.6 (40.4)	476.3 (35.9) *	423.6 (49.1)	438.8 (63.3)	500.3 (61.9)*	400.5 (44.9)	371.7 (62)	401.3 (52.4)	425.4 (73.4)
RVtau	22.7 (3.4)	39 (7.7)	35.6 (6.6)	32.2 (3.1)	34.6 (5.8)	32.9 (9.1)	39.9 (9.2)	42.2 (8.8)	46.7 (9.8)	40.3 (10.2)	36.3 (10.9)
RVEDPVR [mm Hg/mL)	0.8 (0.3)	1.3 (0.4)	1.2 (0.3)	1.0 (0.2)	1.5 (0.5)	1.4 (0.3)	1.7 (0.4)	0.8 (0.6)	1.2 (0.4)	1.1 (0.4)	0.6 (0.1)
RVESPVR [mm Hg/mL]	2.7 (0.3)	3.2 (0.6)	5.2 (0.7)*	3.6 (0.3)	4.5 (0.6)*	4.8 (0.4)*	4.5 (0.7)*	3.2 (0.5)	4.9 (0.4)*	4.8 (0.7)*	4.4 (0.7)*
LVPes [mm Hg]	36.1 (2.2)	32.7 (2.6)	50.4 (4.4)*	31.8 (1)	30.4 (1.6)	30.3 (3.9)	45.8 (4.8)*	29.5 (3.3)	38.5 (1.5)*	38.5 (2.3)*	46.6 (3.9)*
LVPed [mm Hg]	3.2 (0.5)	2.6 (0.5)	3.0 (0.5)	3.9 (0.2)	3.1 (0.5)	3.2 (0.6)	4.2 (1.4)	3.0 (0.6)	3.4 (0.6)	3.2 (0.6)	4.5 (0.7)
LVdP/dT max [mm Hg/s]	958.2 (95.3)	837.3 (91.5)	976.8 (109.1)	697 (53.9)	707.8 (106.7)	802.2 (143.5)	1327.1 (259.3)*	852.3 (189)	1030.8 (78.3)	1138.3 (102.4)	1454.2 (209.4)*
LVtau	21.4 (2.1)	21.5 (1.2)	23.7 (2.6)	32.5 (4.5)	30.1 (5.8)	25.2 (3.1)	19.3 (2.4)	28.8 (4.9)	21.3 (1.8)	20.2 (1.8)	18.7 (1.3)
LVEDPVR [mm Hg/mL]	1.1 (0.1)	1.3 (0.3)	1.7 (0.4)	1.0 (0.6)	1.4 (0.3)	1.4 (0.4)	1.8 (0.3)	1.0 (0.1)	0.8 (0.1)	0.8 (0.2)	1.1 (0.2)
LVESPVR [mm Hg/mL]	10.6 (0.9)	13.9 (2.4)	18.8 (2.8)*	14.8 (2.7)	14.6 (2.5)	16.4 (3.2)	16.5 (5.1)	11.5 (3)	11.2 (1.5)	11.9 (0.9)	13.5 (2.1)

HR, heart rate; RV, right ventricular; Pes, endsystolic pressure; Ped, enddiastolic pressure; dP/dT max, maximal rate of rise of pressure in the ventricle; tau, relaxation time constant; EDPVR, enddiastolic pressure volume relation; ESPVR, endsystolic pressure volume relation; Epi, epinephrine; Norepi, norepinephrine; AO, aortic; PA, pulmonary arterial.
Data are presented as mean ±SEM.
Assessment of significant changes are related to the values after severe pulmonary banding.
*$p < 0.05$.

CA) software was used for statistical analysis. The null hypothesis was rejected when $p < 0.05$.

Results

Effects of Pulmonary Artery Banding

The hemodynamic effects of incremental pulmonary artery constriction are shown in ►**Fig. 3**, which shows representative recordings of pressure-volume loops from an adult rabbit. With incremental pulmonary artery constriction, RV systolic pressure increased linearly, albeit at markedly subsystemic levels. However, as failure ensued, RV systolic pressure decreased and RV end diastolic pressure and volume increased. With RV failure induced by severe pulmonary artery constriction mean RV endsystolic pressure was 19.5 (±1.5) mm Hg which is significantly higher than the baseline value (14.4 (±1.2) mm Hg; $p = 0.001$), whereas cardiac output decreased from 214 (±26.3) to 131 (±23.7) mL/min ($p = 0.007$) (►**Fig. 4**). Concomitantly, LV endsystolic pressure fell from 36.1 (±2.2) to 32.7 (±2.6) mm Hg ($p = 0.08$). RVESPVR was 2.7 (±0.3) at baseline and 3.2 (±0.6) mm Hg/mL ($p =$ n.s.) after pulmonary artery constriction (►**Table 1**).

Effects of Aortic Constriction

Aortic constriction resulted in a significant increase in the slope of the LVESPVR from 13.9 (±2.4) to 18.8 (±2.8) mm Hg/mL ($p = 0.02$) and of the RVESPVR from 3.2 (±0.6) to 5.2 (±0.7) mm Hg/mL ($p = 0.0002$) (►**Fig. 4**). Cardiac output (131 (±23.7) versus 134.8 (±32.5) mL/min; p = n.s.) and heart rate (195 (±9.5) bpm versus 194 (±9.9) bpm; p = n.s.) remained nearly unchanged.

Effects of Norepinephrine and Epinephrine

Administration of norepinephrine and epinephrine resulted in similar effects on biventricular contractility, the most significant effect being achieved with 0.5 mcg/kg × min^{-1} norepinephrine (RVESPVR 4.8 (±0.4) mm Hg/mL, $p = 0.007$; LVESPVR 16.4 (±3.2) mm Hg/mL, $p = 0.08$). However, there was a small fall in RV contractility at the highest doses, suggesting that the response to vasoconstrictors is not entirely linear (►**Fig. 5**). In contrast to aortic constriction, cardiac output was also increased, the most significant effect seen with 1 mcg/kg × min^{-1} epinephrine (214.8 (±46.8) mL/min, $p = 0.04$) and 1 mcg/kg × min^{-1} norepinephrine (191 (±45.7) mL/min, $p = 0.07$) (►**Figs. 5** and **6**). There was no significant difference between the effects of epinephrine and norepinephrine regarding the cardiac output and contractility.

Effects on Diastolic RV Function

RV end-diastolic pressure did not increase after aortic banding (2.2 (±0.3) mm Hg vs. 2.4 (±0.4) mm Hg; p = n.s.), however, RV end-diastolic pressure increased from 2.2 (±0.3) mm Hg to 6.3 (±1.7) with epinephrine (1.0 mcg/kg × min^{-1}) ($p = 0.04$) and to 5.3 (±2.1) mm Hg with norepinephrine (1.0 mcg/kg × min^{-1}) ($p = 0.06$). Tau and RV end-diastolic pressure-volume relation were not significantly impaired with aortic banding, or with norepinephrine and epinephrine, respectively.

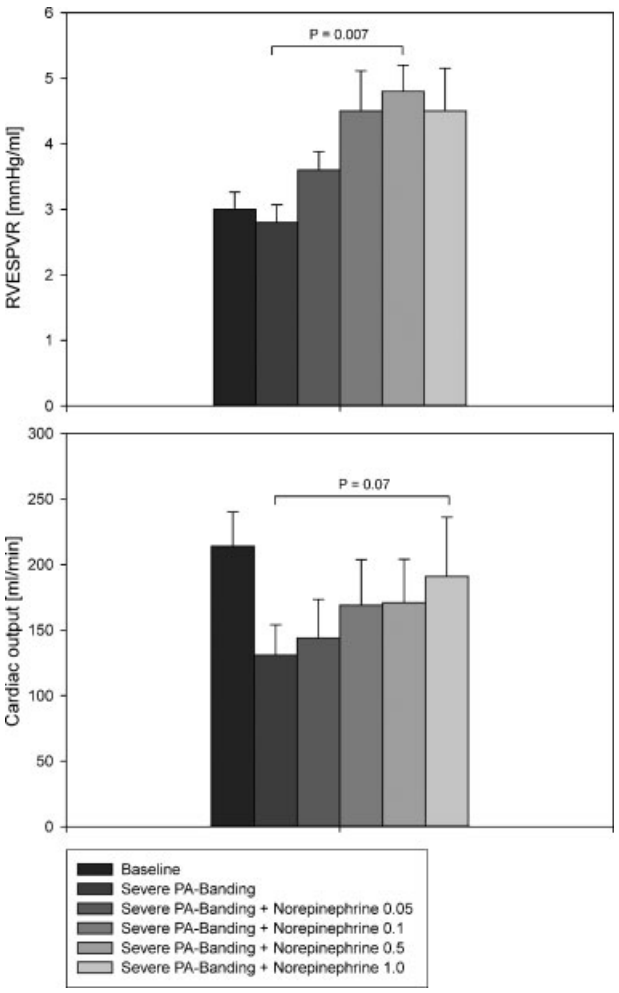

Figure 5 Schematic representation of the changes in the right ventricular endsystolic pressure volume relation (RVESPVR), and cardiac output following increasing doses of norepinephrine. Data are presented as mean and standard error of mean (SEM). The most significant effect on RV contractility has been achieved with 0.5 mcg/kg × min^{-1} norepinephrine (RVESPVR 4.8 mm Hg/mL, $p = 0.007$), whereas the most relevant effect on cardiac output was with 1 mcg/kg × min^{-1} norepinephrine.

Discussion

This study shows that norepinephrine and epinephrine have important effects on biventricular myocardial function and cardiac output in acute RV failure secondary to acute RV afterload. These data suggest a potential role for systemic vasoconstriction in improving RV contractility, presumably via beneficial ventricular-ventricular interactions.

The adverse effects of ventricular-ventricular interactions are becoming increasingly understood in acquired and congenital heart diseases. For example, in chronic pulmonary hypertension, right heart dilation alters LV geometry and diastolic function, and is associated with worse outcomes.[8] Furthermore, Gan et al demonstrated, using magnetic resonance imaging assessment of patients with pulmonary hypertension, that cardiac output was inversely related to LV end-diastolic dimension (as it is compressed by the RV), rather than RV function per se.[9] Experimentally, acute right

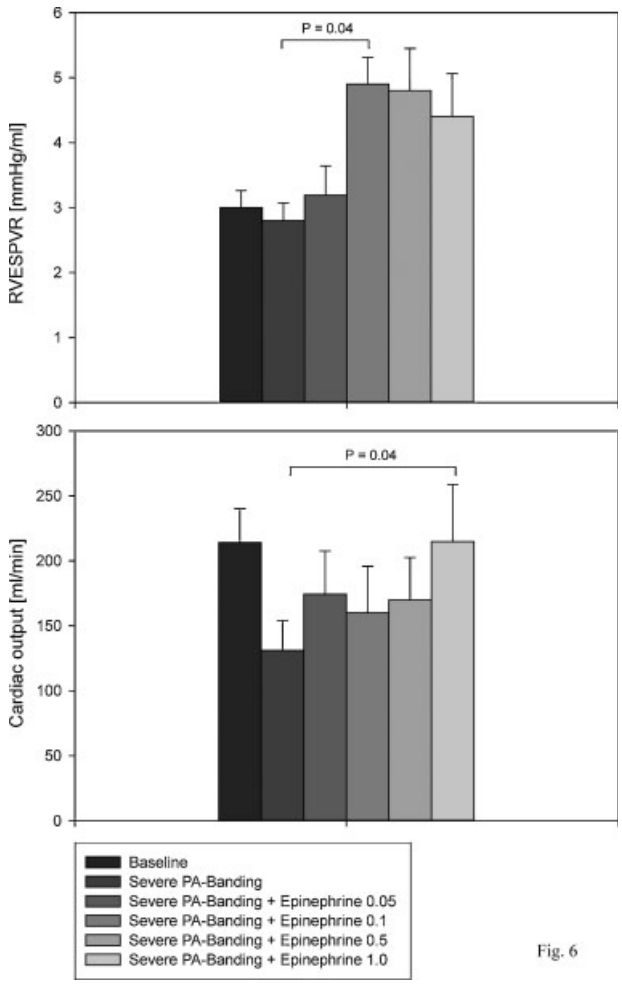

Figure 6 Schematic representation of the changes in the right ventricular endsystolic pressure volume relation (RVESPVR), and cardiac output following increasing doses of epinephrine. Data are presented as mean and standard error of mean (SEM). The most significant effect on RV contractility has been achieved with 0.1 and 0.5 mcg/kg × min^{-1} epinephrine. There was a small fall in RV contractility at the highest doses, suggesting the response to vasoconstrictors is not entirely linear. However, the most significant effect on cardiac output was with 1 mcg/kg × min^{-1} epinephrine.

heart dilation modifies both RV and LV function,[10] although previously it was difficult to dissect whether this was a series effect (decreased cardiac output from the RV leading to reduced LV output) or a direct parallel effect (right heart dilation modifying LV contractility). To address this question, we used conductance catheter assessment of LV contractility in response to RV dilation secondary to isolated coronary occlusion.[4] Even in the setting of normal RV pressure, the geometric change in the RV under these circumstances led to a significant fall in LV contractile function, an effect amplified by pericardial constraint. Conversely, numerous previous studies have shown that changes in LV function can lead to improved RV function.[11–16] It is well known that superficial myocardial fibers are shared and continuous between the RV and LV, providing an anatomic basis for ventricular-ventricular interactions.[17] The common interventricular septum is another major facilitator of these. Indeed, Damiano et al showed an elegant study of normal hearts, where the ventricles were electrically isolated but mechanically intact. Under basal conditions, LV contraction contributed more than 65% of the work of the normal RV.[11]

Thus, not only are adverse ventricular-ventricular interactions an important element of the pathogenesis of right heart disease, they may also be therapeutic targets. Others have hypothesized that by increasing the workload of an otherwise healthy LV, there may be beneficial effects on RV performance via myocardial cross-talk. Yamashita et al emphasized the adverse effects of septal shift in a dog model of pulmonary embolic shock.[18] They showed that both aortic ligation and bolus doses of norepinephrine reversed the septal shift, and restored LV dimensions. Similarly, Belenkie et al showed a beneficial effect of aortic constriction in experimental RV failure.[5] In their study, they controlled coronary artery perfusion by using a roller pump thereby showing the effects of LV afterload independent of changes in coronary perfusion. Their findings in regard to LV functional responses to aortic constriction were compatible with our data. However, they showed an increase in LV stroke work, whereas we confirmed that this is associated with improved intrinsic contractility, as demonstrated by an increase in the slope of the LVESPVR. Our data are also unique in measuring RVESPVR, which also increased, presumably reflecting this beneficial myocardial cross-talk. Furthermore, our data are perhaps more clinically relevant in including dose–response data regarding the effects of norepinephrine and epinephrine. It is clear that both therapies have a beneficial response on both RV and LV contractility and a greater effect on cardiac output in our model.

While there were subtle differences between the two therapies, the overall benefit was similar, despite norepinephrine having greater vasoactive than inotropic effects compared with epinephrine. Furthermore, the effects on contractility were essentially the same as that seen with aortic banding suggesting that direct inotropic action is relatively unimportant to modification of RV function in this way. In addition, by the use of Propranolol, a nonselective β blocker that blocks the action of epinephrine and norepinephrine on both β_1- and β_2-adrenergic receptors, direct inotropic effects of epinephrine and norepinephrine were minimized, but cannot be excluded entirely, in our model.

While our study was not designed to compare the mechanisms of effect of norepinephrine and epinephrine, it is possible that the benefits of what was a high dose of epinephrine came at a greater cost in terms of myocardial oxygen consumption, given its known inotropic and direct myocardial effects, but this must remain speculative. What is clear, is that norepinephrine alone, presumably via its predominant vasoconstrictor effects, is able to modify adverse hemodynamic effects of acute RV failure, and may therefore be a viable clinical tool in conditions associated with acute "isolated" RV failure such as after revascularization surgery, heart and heart-lung transplantation, and congenital heart surgery, after appropriate clinical testing. Clinical use of norepinephrine to harness this phenomenon, should only be performed in the setting of a research study, and specific confirmatory preclinical experiments would need to be performed prior to using other vasoconstrictors in the setting of isolated RV failure.

Study Limitations

Our study was not designed to assess differences in coronary perfusion, and it is possible that some of the effects were mediated via improved coronary blood flow. However, as discussed, Belenkie et al showed that the benefits of aortic constriction were independent of coronary blood flow in their model.[5] Although in our animal model, we used pressure-volume loop-analysis by conductance-catheter technique which is currently considered the most reliable method to assess load-independent RV function,[19] there might be some limitations. Tricuspid regurgitation due to RV dilatation following pressure overload could contribute to a decrease in measured global cardiac output, since retrograde flow across the tricuspid valve would not be measured by the aortic flow probe. Finally, we are unable to comment on the mechanisms of adaptation in regard to the position of the ventricular septum. Furthermore, our experimental preparation precluded the assessment of the influence of pericardial constraint, which has been previously shown to be an important modifier of ventricular-ventricular interaction.[20]

Propanolol affects the β adrenoceptor response and shifts the effects of epinephrine and norepinephrine more to an α adrenergic response. In this study, we wanted to look at pure α stimulation because we were interested in mechanisms induced by increased peripheral arterial afterload. Therefore, direct inotropic effects mediated by agonistic action of epinephrine and norepinephrine (and endogenous catecholamine responses to aortic constriction) on both β_1- and β_2-adrenergic receptors were minimized. While the propanolol was used primarily to avoid autonomic responses, it was a beneficial by-product of the protocol that it blocked also the β-stimulating effects of epinephrine and norepinephrine.

In conclusion, acute RV failure can be rescued by harnessing beneficial ventricular-ventricular interactions. Increasing LV afterload with vasoconstrictor agents leads to improved load-independent indices of biventricular systolic function, and improved cardiac output. These data may have implications for management of clinical right heart failure.

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Invited Commentary

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Right ventricular failure is a severe complication in cardiovascular medicine with high mortality typically occurring (e.g., in the course of acute pulmonary embolism, or during severe attacks of bronchial asthma, or in acute right coronary artery occlusion). However, right ventricular failure often also impairs left ventricular function due to inter-ventricular interaction and dyssynchrony. It has been suggested that the dilation of the right ventricle may change left ventricular geometry and thereby the left ventricular contractile efficiency.[1]

Clinical therapy of right ventricular failure is difficult and often not effective. An option that was shown experimentally is aortic constriction, which may improve interventricular interaction and elevate coronary perfusion.[2] The new idea originating from these previous findings that was followed in the present study in this issue,[3] was that elevation of the afterload as aortic constriction may change left ventricular geometry and thereby indirectly improve ventriculo-ventricular interaction and right ventricular contractility.

Thus, the authors induced right ventricular failure by pulmonary banding and thereafter elevated afterload by application of norepinephrine or epinephrine. However, they had to circumvent the problem that this treatment would directly affect the heart. For that purpose the hearts were pharmacologically denervated by the application of propranolol and atropine. Under this condition, the idea was that a mainly vascular response with elevated afterload remains. Indeed the authors found (see Fig. 5 of the article) that norepinephrine restored cardiac output and right ventricular contractility indices.

This is in principle very interesting and seems to corroborate the theory that the dilation of the right ventricle may compress the left ventricle and thereby might alter left ventricular output as was also suggested from a patient study.[4]

The use of vasoconstrictors in this specific setting is—from a pharmacological point of view—problematic. The authors used in each animal i.v. application of propranolol and later on investigated the effects of norepinephrine and epinephrine. Since propranolol effects will follow the normal pharmacokinetics with a half-life time of about 3 hours (single dose), the effects of norepinephrine and epinephrine are overshadowed by this. Moreover, the effect of norepinephrine is altered since it normally will affect both alpha and beta adrenoceptors and under this protocol will be shifted more to an alpha adrenergic response. This must be taken into account since alpha-adrenoceptors are also present in the heart, and in particular in the rabbit heart,[5–7] which upon activation mediate phosphoinositide hydrolysis with subsequent production of inositol 1,4,5-trisphosphate (IP(3)) and diacylglycerol and PKC activation. The resulting positive inotropic effect typically is accompanied by a negative lusitropic effect.[8] This can indeed be seen in the data of the authors of the present article as left ventricular dPdt max is clearly elevated under the influence of norepinephrine (Table 1 of the article).

Moreover, it was not confirmed in the present study that complete beta-adrenergic denervation was really achieved. However, the data in Table 1 show at least that there was no longer a positive chronotropic effect of epinephrine, which is in favor of the view that beta-adrenoceptors were widely blocked. It needs to be noted, however, that epinephrine also exerts alpha-adrenergic effects.

Thus, the interpretation of the present study is not easy and is overshadowed by the effects described above. However, in principle the idea is interesting, and if one looks at the effects of lower doses of norepinephrine (0.1 to 0.5 µgkgmin), there is already a positive effect on right ventricular performance at doses that did not elevate left ventricular dPdtmax. Thus, it seems that the concept of increasing afterload to improve right ventricular performance via a left-right-interventricular interaction might be efficient.

The merit in the present study is that the authors clearly have shown that right ventricular failure affects left ventricular performance, and that there is a good argument for afterload-enhancing therapies to be of possible relevance. For future studies on this, really interesting, idea I see two possibilities to circumvent the problem described above: either the use of a surgical denervation strategy, or the use of a different vasoconstrictor such as vasopressin or terlipressin, which do not directly interfere with cardiac adrenoceptors or M-cholinoceptors.

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