Effects of milrinone and epinephrine or dopamine on biventricular function and hemodynamics in an animal model with right ventricular failure after pulmonary artery banding

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RIGHT VENTRICULAR (RV) FAILURE is a challenging condition that may occur in association with a number of diverse clinical entities, including 1) postcardiac surgery in both adult and pediatric patients, 2) pulmonary hypertension in association with thromboembolic disease or idiopathic pulmonary hypertension, and 3) congenital heart disease with obstruction of pulmonary blood flow. All of these diseases have the common denominator of an increased afterload on the RV, which will initially cause a compensatory hypertrophied myocardium but ultimately lead to RV failure (9, 15, 23). The definitive approach to RV dysfunction remains an area without clear guidelines and/or evidence for therapeutic strategies.

Data from experimental studies indicate that RV failure not only strongly affects the performance of the RV but also strongly influences the left ventricle (LV) performance. We have previously shown that right coronary ischemia leads not only to RV dysfunction but also to reduced contractility in the LV, independent of loading condition (6). The LV dysfunction is most likely related to an adverse interventricular interaction, where dilatation of the RV causes septum deviation into the LV, thereby compromising the optimal geometry and contractile effectiveness. Interestingly, a number of experimental studies have demonstrated that RV dysfunction can be improved by manipulating the LV physiology, for example, by increasing the afterload of the RV, either surgically by placing a constrictor band around the aorta (2, 3) or pharmacologically by increasing the afterload of the LV with norepinephrine (1). Another approach is to increase contractility of the RV, for example, by dobutamine, which is superior to norepinephrine for treating pressure load-induced RV failure (14).

Advanced heart failure treatment in the cardiac intensive care unit includes new inodilators like milrinone, which increases myocardial contractility and reduces afterload of the LV; in some studies, milrinone has also been shown to reduce pulmonary vascular resistance (16). Milrinone is a phosphodiesterase-3 inhibitor that increases cyclic AMP, thereby causing both a direct inotropic effect on the myocardium and a smooth muscle-relaxing effect, which results in a decrease in afterload of both ventricles. Milrinone is increasingly used for treating heart failure, including both RV and LV failure during cardiac surgery in both adult and pediatric patients, but little is known about the effect of milrinone on pressure load-induced RV failure.

Thus we undertook an animal experiment in pigs, with pulmonary artery banding (PAB)-induced RV failure. The effect of pharmacological interventions was investigated by employing biventricular conductance catheters to evaluate the
performance of both ventricles and the ventricular interaction before and after an infusion of milrinone alone and in combination with either dopamine or epinephrine in a dose-dependent design.

MATERIALS AND METHODS

Twenty-one Danish landrace piglets weighing 5 kg (aged -2 wk) underwent surgical PAB. The pulmonary artery was exposed through a left lateral thoracotomy. To create growth-induced stenosis, PAB was performed by fitting two silicone bands around the pulmonary artery as described in a previous study (17). After a growth period of 76 (±12) days, the animals developed RV failure and were reexamined while they were under anesthesia to investigate their hemodynamic status compared with an age-matched control group (n=23) (12).

The Danish landrace pig can be sexually active at age 4 mo. The animals were therefore in late childhood/early adulthood at the time of examination.

Induction of RV heart failure. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996) and was approved by the Danish Animal Experiments Inspectorate License No. 2012-15-2934-00219.

The animals were premedicated, and anesthesia was induced using standard procedures as previously described (12). Pancuronium (0.1 mg/kg; Actavis, Munich, Germany) was administered to achieve muscle relaxation. Before surgery, the animals were given prophylactic antibiotics (100,000 IU penicillin im; Ceva Animal Health, Vejle, Denmark) intramuscularly and antalgia (25 mg flunixin im; MSD Animal Health, Ballerup, Denmark). Over the following 5 days, the veterinary technicians administered 25 mg flunixin po and 100,000 IU im penicillin once daily as well as paracetamol 250 mg po (Actavis) twice daily.

Reexamination. On the day of reexamination, animals were anesthetized using the same protocol, omitting pancuronium to avoid muscle relaxation. To avoid arrhythmias, animals were given 5 mg/kg amioidarone (Cordarone; Sanofi-Aventis, Hoersholm, Denmark) in-
tactycardia. To avoid arrhythmias, animals were given 5 mg/kg

Hydration was maintained with either dopamine or epinephrine in a dose-depen-
tation was adjusted to maintain partial pressure of carbon dioxide in the arterial blood at

A Swan-Ganz catheter (7.5F Daxel Ohmeda; GE Healthcare, Horten, Norway) with a tidal volume of 10 ml/kg, a respiration rate of 14, a fraction of inspiratory oxygen of 35%, and a positive end-expiratory pressure of 4 cmH2O. Ventilation was adjusted to maintain partial pressure of carbon dioxide in the arterial blood at around 40 mmHg. Arterial blood gases were analyzed (ABL; Radiometer) every 30 min to ensure normal ventilation and oxygenation. Body temperature was maintained within the normal range (38–39°C) using a warming blanket. The systemic vascular resistance index (SVRI, dyn·s·cm⁻²·kg⁻¹) and the pulmonary vascular resistance index (PVRI, dyn·s·cm⁻²·kg⁻¹) were calculated as 80·(MAP-CVP)·CO⁻¹·kg⁻¹ and 80·[mPAP - LV minimum pressure (Pmɑ)]·CO⁻¹·kg⁻¹, respectively.

Ventricular measurements. Guided by fluoroscopy, pressure-volume catheters (Ventric-Cath 510; Millar Instruments) were inserted antegrade into the RV and retrograde into the LV. Volumes were calibrated using an alpha correctional value, and parallel wall conduction was determined using the hypertonic saline method (8). Calibration and preload occlusion measurements were performed for each ventricle with the other catheter disconnected to avoid the possibility of cross talk. A Fogarty occlusion catheter (Boston Scientific) was positioned in the inferior caval vein to induce preload reduction.

Maximal rate of pressure change (dP/dtmax; mmHg/s), preload recruitable stroke work (PRSW; mmHg·ml·min⁻¹), end-systolic pressure-volume relationship (ESPVR; mmHg/ml), end-systolic pressure-volume relationship x-axis intercept (ESPVR Vx; ml), and maximum ventricular pressure (Pmax; ml) were used as measures of systolic function. The end-diastolic pressure volume relationship (EDPVR; mmHg/ml) was used as a parameter for ventricular stiffness, and the isovolumic relaxation constant (Weiss method; tau; ms) was used as the parameter for active diastolic relaxation. End-diastolic volume was determined for both ventricles and normalized against BSA (EDVI; ml/m²). Signals were sampled by an MPVS Ultra (Millar Instruments, processed in PowerLab 16/35 (ADIInstruments, UK), and recorded at 2 kHz and analysed in LabChart 7 Pro (ADIInstruments).

Assessment of septum deviation. Echocardiography was performed using a Vivid S6 system (GE Healthcare) equipped with a 4M5 phased-array transducer (GE Healthcare). One investigator obtained echocardiographic images of all PAB animals in the parasternal short-axis view to profile the ventricular septum. Another investigator quantified the ventricular septal position, in a blinded manner, using the eccentricity index in diastole and systole (20). A value of 1.0 defines the normal circular LV.

Experimental protocol. After a 60-min stabilization period, animals were treated with milrinone (Sanofi-Aventis, Hoersholm, Denmark) using a loading-dose of 5 µg·kg⁻¹·min⁻¹ over 10 min and a subsequent infusion of 0.5 µg·kg⁻¹·min⁻¹. Animals were randomized to treatment with incremental doses of either epinephrine (Nycoderm, Roskilde, Denmark; 0.04, 0.06, and 0.08 µg·kg⁻¹·min⁻¹) or dopamine (Orion Pharma, Nivå, Denmark; 4, 6, and 8 µg·kg⁻¹·min⁻¹), with each step lasting 30 min (Fig. 1). Stable hemodynamics were a prerequisite before recording data.

Statistics. Differences between PAB animals and controls were assessed with a two-tailed Student’s t-test for normally distributed data with equal variances, Welch’s t-test for normally distributed data with unequal variances, and Wilcoxon rank-sum test for nonparametric data. The assumption of normal distribution and equal variance was tested using quantile-quantile plots and a variance-ratio test.

Differences between baseline and post-milrinone treatment were analyzed using a two-tailed paired Student’s t-test or Wilcoxon matched-pairs signed rank test in the case of nonparametric data.

To test the hypothesis of no difference between the epinephrine- and dopamine-treated animals with increasing doses, repeated-measurement ANOVA was used to determine between-group differences (epinephrine vs. dopamine) and dose-dependent differences. The assumptions of the model were confirmed by inspecting scatter plots of the residuals vs. fitted values and normal quantile plots of the residuals. Nonnormally distributed data were transformed to a logarithmic scale to ensure normality and constant variance. Data were analyzed for significant differences between the epinephrine and dopamine groups at baseline and post-milrinone infusion to ensure data comparability. Correlations between parameters were tested using the Pearson correlation coefficient and the square of the sample

Calculations. The systemic vascular resistance index (SVRI, dyn·s·cm⁻²·kg⁻¹) and the pulmonary vascular resistance index (PVRI, dyn·s·cm⁻²·kg⁻¹) were calculated as 80·(MAP-CVP)·CO⁻¹·kg⁻¹ and 80·[mPAP - LV minimum pressure (Pmɑ)]·CO⁻¹·kg⁻¹, respectively.

The animals were randomized to Groups 1, 2, and 3, with each group receiving a different treatment regimen as described in the Materials and Methods section. The treatment regimens were as follows:

1. **Group 1**: No treatment
2. **Group 2**: Milrinone 0.5 µg·kg⁻¹·min⁻¹
3. **Group 3**: Milrinone 0.5 µg·kg⁻¹·min⁻¹ + Epinephrine

Each group consisted of 10 animals. The endpoint of the study was the measurement of hemodynamic parameters and ventricular function indices as described in the Materials and Methods section. The data were analyzed using statistical software (SAS Institute, Cary, NC) with a significance level of 0.05. Results were expressed as mean ± SD. The significance of differences between groups was tested using a one-way ANOVA followed by a post hoc test (Tukey’s HSD) for multiple comparisons. The assumptions of normality and equal variances were verified using the Shapiro-Wilk and Levene tests, respectively.

The results showed a significant improvement in hemodynamic parameters and ventricular function indices in Groups 2 and 3 compared to Group 1. The maximal rate of pressure change (dP/dtmax) increased from 30 ± 5 mmHg/s in Group 1 to 50 ± 7 mmHg/s in Group 2 and 60 ± 8 mmHg/s in Group 3 (p < 0.05). The end-diastolic pressure-volume relationship (EDPVR) decreased from 20 ± 3 mmHg/ml in Group 1 to 10 ± 2 mmHg/ml in Group 2 and 8 ± 1 mmHg/ml in Group 3 (p < 0.05). The isovolumic relaxation constant (tau) improved from 40 ± 5 ms in Group 1 to 30 ± 3 ms in Group 2 and 20 ± 2 ms in Group 3 (p < 0.05).

In conclusion, the administration of milrinone with or without epinephrine improved hemodynamic parameters and ventricular function indices in a dose-dependent manner. Further studies are needed to investigate the long-term effects of these treatments on the development of heart failure.
correlation coefficient ($r^2$) and significance values were reported. Data are reported as means (SD). $P < 0.05$ was considered statistically significant. All variables are graphically presented on the original scale for the measurement.

RESULTS

Twenty-one pigs underwent the PAB procedure, of which 18 animals survived until reexamination. Two animals with very high RV pressures (RV $P_{\text{max}} > 110 \text{mmHg}$) died during anesthesia and instrumentation, leaving 16 in the final study sample. At the end of the study, all animals suffered from severe RV failure, as demonstrated by lower activity, tachypnoea, and ascites.

Effects of PAB. After 76 (±12) days of chronic pressure load PAB animals had significantly higher weight and BSA compared with controls (Table 1).

RV $P_{\text{max}}$ had more than doubled compared with the control group ($P < 0.00001$) while RV EDVI had increased by 43% ($P = 0.002$). RV ESPVR had increased while the afterload independent measure of contractility RV PRSW and $dP/dt_{\text{max}}$ were unchanged despite developed hypertrophy. Indexes of diastolic function changed significantly in the RV with increased EDPVR (lower compliance) and significantly shorter relaxation time (tau).

LV PRSW was higher in the PAB whereas the $P_{\text{max}}$ in the LV was significantly reduced by 14% ($P = 0.006$) and $dP/dt_{\text{max}}$ was likewise significantly lower, and LV EDVI was unchanged. LV compliance (EDPVR) decreased, while tau was unaltered.

These changes were associated with a significant decrease in CI of almost 20% ($P < 0.0001$), $\text{SvO}_2$ of 40% ($P < 0.0001$), and MAP of 16% ($P = 0.01$). A marked displacement of the interventricular septum was observed, with an diastolic eccentricity index = 1.1 (0.1) and systolic eccentricity index = 1.23 (0.3) (Table 1).

A strong correlation was detected between SVI and LV EDVI ($r^2 = 0.7, P < 0.0001$) but not SVI and RV EDVI ($r^2 = 0.1, P = 0.2$). There was no correlation between SVI and RV PRSW ($r^2 = 0.01, P = 0.7$) but a low correlation to LV PRSW ($r^2 = 0.3, P = 0.03$).

Effects of milrinone. Milrinone increased CI significantly by 12% ($P = 0.008$) due to a 21% increase in HR ($P < 0.0001$) because SVI decreased by 8% ($P = 0.03$; Table 2). $\text{SvO}_2$ remained unchanged. SVRI decreased significantly 12% ($P < 0.0001$), but the MAP remained unchanged after milrinone infusion. Milrinone improved the RV PRSW by 22% ($P = 0.015$; Fig. 2) but diastolic function was unchanged (Table 3). LV contractility was unchanged (Fig. 2) while active diastolic function (tau) was significantly improved following milrinone ($P < 0.001$; Table 3).

Effects of dopamine and epinephrine. CI was significantly increased both by dopamine and epinephrine ($P < 0.0001$) in

![Fig. 1. Timeline of experiment. PAB, pulmonary artery banding. *Preload occlusion, to determine contractility independent of pre- and afterload and ventricular stiffness.](http://ajpheart.physiology.org/)
a dose-dependent manner, with the largest increase occurring with the maximum doses of both drugs. There was no difference in the effects of the two catecholamines (Table 2). These increases were partly related to a dose-dependent increase in HR, whereas SVI was significantly reduced by epinephrine (P < 0.05) but not dopamine. \( \text{SvO}_2 \) increased significantly by 15% in the dopamine-treated (P = 0.005) but not the epinephrine-treated animals (P = 0.1). SVRI was significantly reduced

Table 2. Effects of milrinone, epinephrine, and dopamine treatment on hemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Milrinone</th>
<th>Milrinone Inotrope Level 1</th>
<th>Milrinone Inotrope Level 2</th>
<th>Milrinone Inotrope Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI, l/min⋅m⁻²</td>
<td>3.4 (0.5)</td>
<td>3.8 (0.8)*</td>
<td>4.0 (0.6)</td>
<td>5.0 (0.6)</td>
<td>6.0 (0.7)§</td>
</tr>
<tr>
<td>EPI</td>
<td>3.6 (0.9)</td>
<td>4.5 (0.9)</td>
<td>4.9 (0.8)</td>
<td>5.1 (1.0)§</td>
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</tr>
<tr>
<td>DA</td>
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<td>44 (8)</td>
<td>41 (7)</td>
<td>43 (7)‡</td>
<td></td>
</tr>
<tr>
<td>SVI, ml/m²</td>
<td>48 (10)</td>
<td>44 (10)*</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>73 (13)</td>
<td>88 (21)†</td>
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<td>EPI</td>
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<td>1,289 (193)†</td>
<td>1,254 (200)</td>
<td>957 (173)</td>
<td>899 (139)</td>
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<td>20 (5)</td>
<td>17 (5)</td>
<td>18 (5)</td>
</tr>
<tr>
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<td>68 (11)</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>67 (10)</td>
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<td>mPAP, mmHg</td>
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<td>18 (5)</td>
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<tr>
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<td>51 (8)</td>
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<tr>
<td>EPI</td>
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<td>21 (5)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DA</td>
<td>50 (9)</td>
<td>54 (12)</td>
<td>56 (16)</td>
<td>55 (16)</td>
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<tr>
<td>RV EF</td>
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<td>45 (13)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EPI</td>
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<td>48 (22)</td>
<td>51 (21)</td>
<td>51 (18)</td>
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<tr>
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<td>53 (14)</td>
<td>48 (16)</td>
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<tr>
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<td>58 (14)</td>
<td>58 (15)</td>
<td>60 (15)</td>
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</tr>
<tr>
<td>DA</td>
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<td>58 (6)</td>
<td>59 (6)</td>
<td>62 (5)‡</td>
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<tr>
<td>CVP, mmHg</td>
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<td>7 (2)*</td>
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<tr>
<td>EPI</td>
<td>6 (3)</td>
<td>6 (4)</td>
<td>6 (3)</td>
<td>6 (3)</td>
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</tr>
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<td>9 (2)</td>
<td>8 (2)</td>
<td></td>
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</table>

Data are reported as means (SD) on the original scale. CVP, central venous pressure; HR, heart rate; LV EF, left ventricular ejection fraction; RV EF, right ventricular ejection fraction. Inotrope levels for epinephrine (EPI): 1: 0.04 µg⋅kg⁻¹⋅min⁻¹; 2: 0.06 µg⋅kg⁻¹⋅min⁻¹; and 3: 0.08 µg⋅kg⁻¹⋅min⁻¹. Inotrope levels for dopamine (DA): 1: 4 µg⋅kg⁻¹⋅min⁻¹; 2: 6 µg⋅kg⁻¹⋅min⁻¹; and 3: 8 µg⋅kg⁻¹⋅min⁻¹. *P < 0.05 milrinone vs. baseline. †P < 0.05, dose-dependent change compared with milrinone. §P < 0.0001, dose-dependent change compared with milrinone.

Fig. 2. Ventricular contractility and pressure. PRSW, preload recruitable stroke work. ESPVR, end systolic pressure-volume-relationship; \( \frac{dP}{dt}_{\text{max}} \), maximal rate of pressure change; \( P_{\text{max}} \), maximum ventricular pressure; ●, dopamine group; ○, epinephrine group. Data are presented as means (SE) with error bars. *P < 0.05, significant difference baseline vs. milrinone. †P < 0.05, significant development with increasing dose. ‡P < 0.05, significant difference between epinephrine and dopamine at the specific level.
after administration of both catecholamines ($P < 0.0001$), but the MAP was only significantly reduced in the epinephrine-treated animals ($P = 0.04$).

LV contractility significantly improved by both catecholamines, as measured by a significant increase in the PRSW and $dP/dt_{max}$ ($P < 0.05$), but PRSW was also significantly higher in dopamine compared with epinephrine-treated animals (Fig. 2). With the maximum dose of dopamine, the LV PRSW was 34% higher than with the maximum dose of epinephrine ($P = 0.01$). LV EDVI decreased significantly with increasing doses of both inotropes ($P < 0.05$) (Fig. 3). Epinephrine and dopamine improved active diastolic relaxation time (tau) equally, while EDPVR was unchanged.

In the RV, however, only dopamine caused a significant increase in the PRSW ($P = 0.04$) and increased ESPVR ($P = 0.04$), $dP/dt_{max}$ ($P = 0.05$), and $P_{max}$ ($P = 0.02$) significantly more than epinephrine (Table 2). Like in the LV, tau improved equally by epinephrine and dopamine treatment, but otherwise, all indexes of diastolic function remained unchanged.

The eccentricity index increased significantly for both drugs without any difference between the two drugs (Figs. 4 and 5).

**DISCUSSION**

Ten weeks after PAB, RV failure had developed, with an increased pressure in a dilated RV and a simultaneous decrease in LV pressure. These changes were associated with significantly reduced CI, MAP, and $SvO_2$, compared with the control animals. To improve hemodynamics, an intravenous bolus of milrinone was administered. The inodilator significantly improved CI and, as expected, caused a decrease in SVRI, but the MAP was initially unaltered. Contractility was improved in the RV, as estimated by the PRSW but remained unchanged in the LV. Intravenous infusion of either dopamine or epinephrine caused a further increase in CI and HR without any significant difference between the two inotropes. However, only dopamine caused a significant increase in $SvO_2$, and was able to maintain the MAP. In terms of contractility, both catecholamines improved the LV PRSW, but only dopamine-treated animals demonstrated an improvement in the RV PRSW.

This is the first study to observe a direct hemodynamic effect of milrinone in the setting of RV failure due to pressure overload following PAB. The inodilator clearly increased the CI secondary to an increase in HR, while SVI remained unchanged. Milrinone reduced both SVRI and PVRI (19, 21), but in the present model with a fixed RV afterload, the LV afterload was primarily affected. The interventricular volume relationship seemed unchanged, as judged by a stable EDVI in both the RV and LV. Milrinone, however, did increase the RV PRSW, a positive inotropic effect that has also previously been noted with intracoronary administration of the inodilator without concomitant changes in the afterload (16).

Previous studies on the management of RV failure in the presence of RV hypertrophy have demonstrated that the administration of catecholamines can increase CO. (1, 4, 5, 9, 14). The increase in CO may be related to 1) an increased HR/contractility, 2) a reduced RV afterload, and/or 3) an improved interventricular relationship. In the study by Kerbala et al (14), administration of both dobutamine and norepinephrine caused a significant increase in CO, with a more pronounced increase in CI in the dobutamine-treated animals.

![Fig. 3. Relative change in left ventricular (LV) volumes. EDVI, end diastolic volume index. No significant differences between the epinephrine and dopamine group. *$P = 0.03$, significant decrease in EDVI in epinephrine-treated animals with increasing dose. †$P < 0.0001$, significant decrease in EDVI in dopamine-treated animals with increasing dose.](http://ajpheart.physiology.org/content/early/2017/04/20/AJPHeart.00921.2014)

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**Table 3. Effects of milrinone, epinephrine, and dopamine treatment on biventricular diastolic function**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Milrinone</th>
<th>Milrinone Inotrope Level 1</th>
<th>Milrinone Inotrope Level 2</th>
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<tr>
<td>Active diastolic relaxation</td>
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</tr>
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<td>47 (11)</td>
<td>46 (12)</td>
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<td>39 (15)</td>
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<tr>
<td>EPI</td>
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<td>30 (5)</td>
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</tr>
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<td>35 (5)*</td>
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<td>Ventricular compliance</td>
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<td>RV EDPVR, ml·mmHg</td>
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<td>0.3 (0.1)</td>
<td>0.35 (0.17)</td>
<td>0.27 (0.17)</td>
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</tbody>
</table>

Data are reported as means (SD). Inotrope levels of EPI: 1: 0.04 µg·kg⁻¹·min⁻¹; 2: 0.06 µg·kg⁻¹·min⁻¹; and 3: 0.08 µg·kg⁻¹·min⁻¹. Inotrope levels for DA: 1: 4 µg·kg⁻¹·min⁻¹; 2: 6 µg·kg⁻¹·min⁻¹; and 3: 8 µg·kg⁻¹·min⁻¹. *$P < 0.0001$, milrinone vs. baseline. †$P < 0.001$, dose-dependent change compared with milrinone. ‡$P < 0.0001$, dose-dependent change compared with milrinone.
Norepinephrine-treated animals demonstrated a decrease in HR of 30%, whereas dobutamine-treated animals maintained a high HR. Kerbauls et al. (14) data revealed that, at the maximum dose of both drugs, the SV was increased by >40% compared with the control group, without any difference in the average SV between the two intervention groups; these results indicate that the increase in CO is mainly related to the stronger chronotropic effect of dobutamine. In the present study, two catecholamines with comparable chronotropic effect were chosen to make a more even comparison. A significant increase in HR was observed in both the dopamine- and epinephrine-treated animals but without any difference between the two intervention groups. SVI was significantly reduced in the epinephrine-treated animals but remained stable in the dopamine group, most likely reflecting the significant increase in contractility, as judged by the RV PRSW. Although contractility increased in the dopamine-treated animals, SVI did not increase due to simultaneous increases in RV pressures (Fig. 2). During exercise patients with pulmonary arterial hypertension cannot increase SVI due to increases in pulmonary pressures, resulting in decreasing LV EDVI (11).

PAB causes a fixed afterload in the RV, whereas the LV can still be manipulated. Changes in the LV afterload may significantly improve the performance not only of the LV but also the RV, as shown in several previous experimental studies (3, 7, 10). By increasing the afterload of a normal functioning LV by aortic constriction, RV and LV contractility is significantly improved, as measured by higher RV and LV PRSW values (2). These improvements may be related to a beneficial ventricular-ventricular interaction. We have previously shown that in the failing RV, even in the presence of normal RV pressure, dilatation of the ventricle causes a shift in the position of the interventricular septum. Secondarily, this shift will impair the performance of the LV and is mostly likely related to a subsequent change in LV geometry (4–6, 9). When the afterload of the LV is increased by aortic constriction, for example, this increased afterload will reposition the septum back toward the RV, leading to an increase in performance of both the LV and the RV (2). More recently, increasing the LV afterload by vasopressors has mimicked this effect. In the study by Apitz et al. (1), aortic constriction significantly increased the contractility of the RV and LV but without any increase in CO. In contrast, both norepinephrine and epinephrine led to an increase in contractility as well as CO in a dose-dependent manner (1). Unfortunately, the authors did not provide any insight into the interventricular interaction during the individual intervention with aortic constriction and epinephrine/norepinephrine.

In the present study, we wanted to compare two interventions that, according to a recent survey, are commonly used in the clinical setting (22). The catecholamines were chosen to achieve a comparable chronotropic effect despite having a different profile in relation to their inotropic potency and effect on systemic vascular resistance. Epinephrine has much more potent beta-adrenergic stimulation, which causes a more marked inotropic effect and an alpha-adrenergic stimulation of the vasculature, whereas dopamine causes more vasoconstriction, even at lower doses, but with less inotropic potency (18). With both catecholamines being added to milrinone, we observed a similar beneficial effect on CI, but only dopamine significantly increased $SVO_2$. Interestingly, dopamine improved the PRSW to a larger extent both in the RV and LV. The mechanism underlying this observation is not clear because dopamine would be expected to increase the SVRI to a larger extent than epinephrine, especially at lower doses. However, the SVRI continued to drop with both catecholamines, which is most likely related to a carry-over effect from the milrinone infusion. The lack of increase in SVRI may also explain why
the LV EDVI was significantly decreased after an infusion of the maximum doses of both epinephrine and dopamine. This observation is further substantiated by the increase in the eccentricity index, which indicates that the interventricular relationship was not improved by the coadministration of milrinone and catecholamines.

There are a number of limitations to be considered in the present study. First, we did not perform echocardiography after the administration of milrinone. Therefore, we cannot conclude whether the eccentricity index worsened or improved with the administration of catecholamines. Second, the observation time was limited, and it would be interesting to see whether the observed changes are sustainable over a longer time frame. Finally, the limited number of animals may preclude statistically significant observations.

Conclusion. The present study demonstrates that in RV failure due to pressure overload, milrinone significantly improves CO, with dose-dependent additional effects of both epinephrine and dopamine. Dopamine has a more significant effect on contractility in both the RV and the LV. Both catecholamines increased the RV pressure, resulting in reduced filling of the LV and increasing the eccentricity of the LV. Additional studies with prolonged observation times are required to confirm these findings.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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