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Volume Expansion versus *Norepinephrine in Treatment of a Low Cardiac Output Complicating an Acute Increase in Right Ventricular Afterload in Dogs*

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The authors investigated the effects of treatment on ventricular performance when cardiac output (CO) was reduced significantly because of an acute increase in pulmonary vascular resistance (PVR).

In eight anesthetized, ventilated dogs, the effects of volume expansion (100 ml 6% dextran) on ventricular performance were determined before and after PVR was elevated. Resistance was increased by microembolization of the pulmonary vascular bed with glass beads (80–100 μm). When PVR was normal, volume expansion increased ($P < 0.05$) stroke volume (SV) and mean blood pressure (BP). Alternatively, when RV afterload was increased, volume resulted in RV failure, *i.e.*, decrease in SV ($P < 0.01$) from 9.1 to 6.3 ml and a decrease ($P < 0.05$) in mean BP from 97 to 65 mmHg, despite increased right ventricular end diastolic pressure (RVEDP) ($P < 0.05$). Right ventricular dysfunction occurred with volume expansion, despite constant PVR and a decrease ($P < 0.01$) in mean pulmonary artery pressure (PAP). In contrast to volume, norepinephrine infusion decreased biventricular filling pressures ($P < 0.01$) and increased ($P < 0.01$) SV from 6.2 to 11.3 ml. Accordingly, when RV afterload is increased significantly, even a relatively small increase in blood volume may result in RV dysfunction. Alternatively, inotropic agents with pressor effects may be the treatment of choice to increase CO when RV afterload is increased. (Key words: Heart: right ventricular failure; vascular pressures. Lung: vascular resistance.)

IN CERTAIN PATIENTS with acute respiratory failure, pulmonary hypertension develops.[1] Pulmonary hypertension occurs because of a marked increase in pulmonary vascular resistance (PVR). The mechanism of increased resistance is likely multifactoral, but the end result is a reduction in the effective cross-sectional area of the pulmonary vascular bed.[1,2] The increase in right ventricular (RV) afterload results in increased RV stroke work, increased RV_{O_2} requirements and a reduction in cardiac output (CO).[3] Such changes may limit survival in patients with acute respiratory failure.[1,3,4]

While effects of a sudden increase in RV afterload on ventricular performance have been studied,[5] effects on RV function of a marked increase in resistance due to microembolization of the pulmonary vascular bed have not been investigated previously. Also, while volume expansion has been advocated as appropriate therapy to maintain or increase CO when RV afterload is increased,[6] this approach has not been investigated systematically and could result, secondary to increased RV wall stress, in ventricular dysfunction.[3]

Accordingly, the current study was designed to determine effects of a marked increase in PVR on biventricular pumping performance and to test the hypothesis that in this setting, volume expansion will result in a deterioration in RV performance. Another aim of this study was to investigate effects of norepinephrine on ventricular function when RV afterload was elevated and CO decreased. Norepinephrine was chosen because of its direct inotropic and pressor effects and because previous work demonstrated the importance of maintaining BP and RV perfusion when RV afterload was increased.[5,7,8]

Methods

Eight mongrel dogs (15–30 kg) were anesthetized with pentobarbital (30 mg/kg), intubated, and artificially ventilated (20 ml/kg) in the supine position with 100% O_2. A catheter was placed in the femoral artery to obtain arterial blood and to monitor systemic blood pressure. Left ventricular pressure was monitored with a fluid-filled catheter. A thermistor-tipped Swan-Ganz® catheter was inserted via the external jugular vein and positioned via pressure monitoring, in a branch of the pulmonary artery. A second Swan-Ganz® catheter was positioned in the RV to obtain measurements of ventricular pressure. A third Swan-Ganz® catheter was passed into the RV and withdrawn under pressure monitoring to the right atrium for pressure recording and injection of saline boluses during cardiac output (CO) determinations. The right atrial pressure tracing was analyzed for evidence of tricuspid regurgitation. The thermal dilution curve was recorded on a separate, single-channel recorder and analyzed by computer (Columbus Instruments). All catheters were connected to Statham transducers and output displayed on a 12-channel E for M oscillograph. Transducers were positioned midway between the front and back of the

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chest. An intravenous catheter, for volume and/or drug administration, was placed in an external jugular vein.

Measurements of CO, heart rate (HR), BP, ventricular pressures, and pulmonary artery pressure (PAP) were obtained under baseline conditions (condition A) and following volume expansion with 100 ml of warmed 6% dextran infused over 3–4 min via a catheter placed in the external jugular (condition B). Then after waiting approximately 10 min for a steady state, *i.e.*, constant BP, CO, and PAP for approximately 5 min, measurements were repeated (condition C) and, following these measurements, RV afterload was increased. To increase the resistance impeding RV injection, glass beads (80–100 μm) were injected through a catheter placed in the external jugular vein. Previous studies demonstrated that injection of 100 μm glass beads increased PVR by mechanical obstruction, thrombosis, and release of humoral factors.[9–11] To test effects of treatment on ventricular function when CO is reduced because of increased RV afterload, beads (10–15 g) were injected in increments over approximately 2 h until CO had fallen approximately 50%. During catheter placement and during the first hour of increasing PVR, dogs were given as required, several (three to five) 25-mg injections of pentobarbital by slow iv push. There was a transient, small reduction in BP with each injection that recovered within approximately 2 min. When PVR had increased significantly, dogs did not require additional anesthesia. Subsequently, with dogs in a steady state for approximately 10 min, a fourth set of measurements was obtained (condition D). Then a second, identical volume load was infused and measurements repeated (condition E). Following these measurements, an iv bolus of norepinephrine (100–200 μg) was given, followed by continuous infusion (0.08–0.16 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The rate of infusion was titrated until one of the following end points was reached: 1, until CO approximately doubled; 2, until mean BP reached approximately 140 mmHg; 3, until heart rate exceeded 190 beats $\cdot$ min^{-1}. Final measurements were obtained approximately 20 min later, approximately 5 min after a steady state had been achieved (condition F).

In all dogs, sodium bicarbonate (range, 20–50 mEq) was given as required to maintain arterial pH > 7.25. In repeat measurements of arterial blood gases, O_2 tension was always greater than 87 mmHg and ventilatory rate adjusted to maintain Pa_{CO_2}, 35–45 mmHg. By means of a heating blanket, core temperature was maintained between 38 and 39° C.

The reported RVSP was the peak systolic pressure. Pulmonary vascular resistance was calculated according to the equation PVR $(mmHg \cdot l^{-1} \cdot min) = \frac{PAP-LVEDP}{CO}$ and systemic vascular resistance (SVR) equals $\frac{BP-RVEDP}{CO}$.

To determine effects of specific interventions on cardiopulmonary function, data were tested for significance using repeated measures ANOVA.

Results

The mean (±SD) hemodynamic effects of increased PVR, volume expansion, and norepinephrine on ventricular performance are given in table 1.

When PVR was normal, volume expansion increased ($P < 0.05$) SV and mean BP.

Approximately 10 min after volume expansion, a new set of measurements was obtained (condition C), and, following these measurements, PVR was increased as described under methods. A fourth set of measurements was obtained when CO had decreased approximately 50% and dogs were hemodynamically stable for approximately 10 min (condition D). As illustrated in table 1, there was a marked deterioration in RV performance as PVR increased, *i.e.*, despite increased ($P < 0.01$) RVEDP, there was a marked decrease ($P < 0.01$) in CO and SV.

In contrast to hemodynamic effects of volume when PVR was normal, in the setting of increased PVR, volume expansion resulted in RV dysfunction. Despite increased RVEDP ($P < 0.05$), mean CO, SV ($P < 0.01$), and RVSP ($P < 0.01$) decreased. The deterioration in pump performance was not due to increased afterload, because PVR remained constant and PAP was decreased ($P < 0.01$).

After volume expansion, dogs were given an intravenous bolus of norepinephrine (100–200 μg), followed by continuous infusion (0.08–0.16 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Final measurements were obtained approximately 20 min later, 5 min after a steady state had been achieved. Effects of norepinephrine on ventricular function are given in table 1. Note the marked increase in CO ($P < 0.05$) and SV ($P < 0.01$). These changes occurred despite a decrease in RVEDP ($P < 0.01$) and LVEDP ($P < 0.01$). Systemic and PVR did not increase with inotropic intervention. When norepinephrine was discontinued, RV function deteriorated rapidly, confirming that spontaneous changes in PVR had not occurred.

Discussion

We demonstrated that in the presence of increased RV afterload, volume expansion resulted in a marked deterioration in RV performance. Because RV afterload did not increase with volume, it is possible that this therapy increased wall stress so that the deterioration in RV function occurred because of ischemia. Other possibilities include mechanical overstretch of the RV and/or reflex depression in contractility. In contrast to volume, treatment with norepinephrine resulted in a marked improvement in ventricular pump performance. Most likely, nor-

TABLE 1. Effect of Volume and Norepinephrine on Right Ventricular Function

	CO ($l \cdot min^{-1}$)	SV (ml)	RVEDP (mmHg)	RVSP (mmHg)	PAP (mmHg)	PVR ($mmHg \cdot l^{-1} \cdot min$)	LVEDP (mmHg)	BP (mmHg)	SVR ($mmHg \cdot l^{-1} \cdot min$)	HR ($beats \cdot min^{-1}$)
Baseline (cond. A)	2.8 ± 1.6	17.4 ± 4.4	0.17 ± .4	19.4 ± 2.4	11.0 ± 2.3	1.9 ± 1	5.8 ± 1.3	122 ± 21	44 ± 11	164 ± 23
Volume (cond. B)	3.4 ± 0.6	23.5 ± 6.5*	1.3 ± .93	21.2 ± 1.6	12.3 ± 1.8	1.2 ± .1	10.3 ± 5.8*	131 ± 13*	38 ± 9	148 ± 20
Baseline (cond. C)	3.0 ± 1.5	18.7 ± 8.3	0.42 ± 2.5	18.7 ± 8.3	13.8 ± 4.4	1.7 ± 2.3	6.4 ± 1.3	123 ± 18	41 ± 10	160 ± 26
PVR (cond. D)	1.4 ± 0.2†	9.1 ± 1.3†	9.4 ± 4.8†	71.3 ± 6.8†	55.4 ± 5.8†	37.0 ± 5.9†	8.9 ± 3.1*	97 ± 25†	63 ± 13†	152 ± 19
Volume (cond. E)	0.94 ± .4	6.3 ± 2.3†	11.9 ± 4.7†	52.1 ± 18.7†	42.3 ± 16.0†	36.7 ± 5.9	12.1 ± 5.8	65 ± 35*	56 ± 12	150 ± 13
Norepinephrine (cond. F)	1.9 ± .2*	11.2 ± 2.1†	4.7 ± 4.3†	81.8 ± 15.5†	60.2 ± 7.1†	29.7 ± 4.1	4.4 ± 5.3†	121 ± 34†	61 ± 11	170 ± 25

Values are mean ± SD.
* Denotes significance ($P < 0.05$) from previous value.
† Denotes significance ($P < 0.01$) from previous value.

epinephrine improved RV performance because of an increase in BP and improved RV coronary artery perfusion and/or because of a direct increase in contractility.

With respect to the left ventricle, despite increased LVEDP, CO decreased as PVR increased. Accordingly, RV dysfunction caused LV failure or the increased RV end-diastolic volume altered LV diastolic mechanics.

Investigators have suggested that in the setting of severe respiratory failure and increased PVR, volume expansion could result in depressed ventricular performance.[3] Alternatively, in a symposium on cardiovascular function in respiratory failure, volume expansion was advocated as the treatment of choice to increase mean systemic pressure and CO when flow was decreased because of increased RV afterload.[6]

In the current study, while volume expansion increased BP and SV when RV afterload was normal, an identical volume load resulted in RV failure when PVR was increased. That is, despite an increase in RVEDP with volume, CO, SV, and RVSP decreased. Because mean pulmonary artery pressure decreased and PVR remained constant with volume expansion, the deterioration in RV function is not explained by increased afterload. It is possible that volume expansion increased RV wall stress so that function deteriorated because of ischemia. A previous study documented the importance of ischemia in depressing RV performance in the setting of increased afterload.[5] However, direct markers of ischemia were not measured in the current study. Also, volume may have caused mechanical dysfunction by placing the ventricle on the descending limb of its Starling function curve. However, because function began to deteriorate with volume at a mean RVEDP of only 9.4 mmHg, we consider this possibility less likely. It is also conceivable that in the setting of increased RV afterload volume expansion depressed ventricular performance secondary to altered reflex activity.

The volume-induced depression in RV function was reversed with norepinephrine and is explained by a direct increase in contractility or increased contractility secondary to increased BP and improved RV perfusion. In support of the latter possibility, Vlahakes *et al.*[5] demonstrated that RV ischemia was reduced and performance improved when BP and RV perfusion increased with phenylephrine.

While increased contractility *per se* would increase O_2 consumption, enhanced systolic performance with norepinephrine could result in a reduction in ventricular volumes so that wall stress and O_2 consumption could decrease despite increased contractility.

As illustrated in table 1, with increased PVR and volume expansion, LVEDP remained constant or increased when SV fell. These changes may be explained by right to left septal shift and ventricular interdependence.[12,13]

Other studies have demonstrated that an increase in RV afterload can alter LV diastolic mechanics and have implicated septal shift as the mechanism.[12,14]

The authors conclude that when RV afterload is increased significantly, volume expansion may result in a deterioration in ventricular performance. Alternatively, pressor agents may be the treatment of choice to increase CO when flow is reduced secondary to increased pulmonary vascular resistance. Because in this study, RV performance began to deteriorate with volume at a relatively low RVEDP, RV filling pressure may be a poor predictor of the response to volume when a low CO complicates an increased RV afterload.

References

1. Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476–480, 1977
2. Snow RL, Davies P, Pontoppidan H, Zapol WM, Reid L: Pulmonary vascular remodeling in adult respiratory distress syndrome. Am Rev Respir Dis 126:887–892, 1982
3. Laver MB, Strauss WH, Pohost GM: Herbert Shubin Memorial Lecture—Right and left ventricular geometry: Adjustments during acute respiratory failure. Crit Care Med 7:509–519, 1975
4. Pontoppidan H, Wilson RS, Rie MA, Schneider RC: Respiratory intensive care. ANESTHESIOLOGY 47:96–116, 1977
5. Vlahakes GJ, Turley K, Hoffman JIE: The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. Circulation 63:87–95, 1981
6. Goldberg HS, Rabson J: Control of cardiac output by systemic vessels—circulatory adjustments of acute and chronic respiratory failure and the effects of therapeutic interventions. Am J Cardiol 47:696–702, 1981
7. Salisbury PF: Coronary artery pressure and strength of right ventricular contraction. Circ Res 3:633–638, 1955
8. Fineberg MH, Wiggers CJ: Compensation and failure of the right ventricle. Am Heart J 11:255–263, 1936
9. Malik AB, van der Zee H. Pulmonary microembolization. Circ Res 42:72–79, 1977
10. Malik AB, van der Zee H: Lung vascular permeability following progressive pulmonary embolization. J Appl Physiol 45:590–597, 1978
11. Malik AB, van der Zee H: Time course of pulmonary vascular response to microembolization. J Appl Physiol 43:51–58, 1977
12. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP: Influence of positive end expiratory pressure on left ventricular performance. N Engl J Med 304:387–392, 1981
13. Taylor RR, Covell JW, Sonnenblick EH, Ross J: Dependence of ventricular distensibility on filling of the opposite ventricle. Am J Physiol 213:711–718, 1967
14. Stool EW, Mullins CB, Leshin SJ, Mitchell JH: Dimensional changes of the left ventricle during acute pulmonary arterial hypertension in dogs. Am J Cardiol 33:868–875, 1974