Acute Right Ventricular Dilatation in Response to Ischemia Significantly Impairs Left Ventricular Systolic Performance

Carl Brookes, MRCP; Hanne Ravn, PhD; Paul White, BSc; Ulla Moeldrup, MD; Paul Oldershaw, FRCP; Andrew Redington, FRCP

Background—Right ventricular (RV) dilatation that occurs as a consequence of RV infarction is thought to produce hemodynamic instability by reducing left ventricular (LV) preload and compliance. We hypothesized that these geometric changes may also adversely affect LV systolic performance.

Methods and Results—Twelve 40-kg pigs were studied. Integrated conductance catheters and micromanometers were placed in both the LV and RV to allow simultaneous recordings of pressure and volume and derivation of indices of contractile function. RV ischemia was induced by balloon occlusion of the proximal right coronary artery (RCA) under 3 conditions: 1) with the pericardium intact, 2) with the pericardium intact and inotropic support, and 3) with the pericardium wide open. With an intact pericardium, RCA occlusion produced a decrease in LV end-diastolic volume associated with a marked decline in the contractile function. With the pericardium open, the same ischemic insult resulted in both LV and RV dilatation, which produced a significantly smaller negative effect on cardiac output \((P<0.03)\), LV systolic pressure \((P=0.02)\), LV preload-recruitable stroke work \((P<0.01)\), and LV end-systolic pressure-volume relations \((P<0.01)\). Similarly, administration of dobutamine during RCA occlusion decreased the ventricular volume changes and produced a relative improvement in LV contractile performance.

Conclusions—The hemodynamic compromise seen in association with acute RV dilatation within an intact pericardium is partly attributable to impaired LV systolic performance and cannot be wholly ascribed to changes in LV preload or compliance. (Circulation. 1999;100:761-767.)

Key Words: contractility ■ ventricles ■ conductance ■ catheters
Methods

Animals

Twelve 40-kg Danish Landrace pigs were used in this study. Anesthesia was induced with fentanyl 0.3 mg and propofol 150 mg before intubation and ventilation with a mixture of atmospheric air and oxygen. Anesthesia was maintained with an infusion of fentanyl 0.3 mg/h, propofol 8 to 10 mg · kg⁻¹ · h⁻¹, and pancuronium 3 mg/h. Blood-gas measurements were performed hourly to maintain a physiological level of oxygenation and ventilation. All animals received a bolus of amiodarone 150 mg before instrumentation to reduce the rate of arrhythmias.

The right and left carotid arteries and the right internal jugular vein were cannulated. Access to the pericardium, pulmonary artery, and RV was obtained via a median sternotomy.

The animals were treated according to the principles stated in Danish law on animal experiments.

Instrumentation

A 6F integrated conductance catheter and micromanometer (Millar Instruments) of appropriate size was inserted into the apex of each ventricle. The LV catheter was passed retrogradely across the aortic valve via the carotid artery under fluoroscopic guidance. The RV catheter was introduced via a needle puncture in the RV outflow tract while the pericardium was maintained intact.

A transit-time flow probe (Transonic) was placed around the pulmonary artery to assess stroke volume (SV) and cardiac output.

Ventricular unloading was performed with a 20-mL catheter-mounted balloon placed in the IVC via the femoral vein.

A 7F JL4 angioplasty guiding catheter was used to engage the right coronary ostium and perform coronary angiography. A 3.0-mm angioplasty balloon mounted on a 0.014-in wire was used to occlude the RCA.

A transesophageal echocardiography probe was used to detect changes in ventricular geometry in response to ischemia.

Data Acquisition and Analysis

The amplified pressure signal (Fylde Isotransducer Amplifier) was fed directly to a committed personal computer (Vigilen), in which it was combined with volume and ECG data in custom software.

The total conductance signal was generated and processed in a Sigma-5 DF unit. The principles of conductance catheter technology are described in detail elsewhere. Briefly, the conductance catheter is a modified angiography catheter with a series of equally spaced electrodes at the distal end, designed so that the proximal and distal electrodes span as much of the ventricular cavity as possible. A 30-μA, 20-kHz current is generated between the proximal and distal electrodes, and the intervening electrodes measure conductances between electrode pairs located in the ventricles. The conductances are summed and converted to a time-varying volume signal.

The volume, V, of the ventricle at a given time, t, is \( V(t) = (1/\mu L^2) \mu (G(t) - G(c)) \), where \( L \) is the interelectrode distance, \( \mu \) is the blood resistivity that is measured, \( \dot{a} \) is the ratio of conductance volume to true ventricular volume, \( G(t) \) is the sum of conductances at any time \( t \), and \( G(c) \) is the parallel conductance.

The pressure and volume data were sampled at 250 Hz and transferred through a 12-bit, 16-channel, analog-to-digital converter into custom software, and calculations of \( \dot{a} \), \( V_c \) (parallel conductance volume), corrected end-diastolic volume (EDV), and contractile function were made offline.

All measurements were made in duplicate with ventilation held at end expiration and then averaged.

Conductance SVs were determined from 2 recordings at steady state. In each recording, the maximum and minimum volumes for 5 consecutive cardiac cycles were identified, and the SV for that run was defined as the mean difference between maximum and minimum volumes. This was then repeated for the second recording, and the mean of the 2 SVs was divided by the flow probe SV to yield \( \dot{a} \).

Parallel conductance was estimated by use of a modification of the hyperpolarized saline injection method developed by Baan et al. A slow bolus of 7 mL of 10% saline was injected into the superior vena cava, causing a transient change in conductivity of the blood within the ventricular cavity without any detectable change in LV or RV pressure.

Two injections of hypertonic saline were used to calculate \( V_c \). End-systolic volume (ESV) and EDV from individual cardiac cycles during the saline injection were plotted and the lines regressed to the point at which ESV = EDV; this volume was taken as \( V_c \). The correlation coefficient for the regression line was recorded as an index of precision; coefficients of < 0.9 were not accepted.

Absence of Catheter Cross Talk

There is a theoretical possibility that the electric field generated by one catheter might affect volume transduction by the other. Using a specially adapted generator/processing unit, we were able to alter the current frequency on one catheter from 5 kHz to 40 kHz but were unable to detect any change in the volume signal from the catheter in the contralateral ventricle. The current frequencies used were therefore 20 kHz in the LV and 19.5 kHz in the RV.

Calculation of indices of contractile function during transient inferior vena cava (IVC) occlusion was performed with ≥ 5 consecutive cardiac cycles. The slope of the end-systolic pressure-volume relation (ESPVR) was determined by linear regression from the points of maximum pressure/volume in each cycle during the occlusion and was corrected for the absolute volume of each ventricle. The slope of the preload-recruitable stroke work (PRSW) was calculated from the plot of stroke work against EDV (end diastole being defined by the ECG R wave). The slope of the EDP-volume relation (EDPVR) was determined by linear regression of the points at end diastole during IVC occlusion.

Protocol

Pilot studies were conducted in 6 animals to establish the maximum duration of ischemia that could be tolerated reproducibly without the development of dysrhythmias. Approximately 70% of the animals developed ventricular fibrillation during protocols using ≥ 4 minutes of ischemia; therefore, 3.5 minutes was chosen for the study protocol. This duration of ischemia has the added advantage that it is unlikely to induce significant preconditioning in pigs.

RCA ischemia was induced by balloon occlusion in the proximal segment just distal to the conus and right atrial branches. Simultaneous pressure, volume, and flow data were obtained from each ventricle at baseline and after 3.5 minutes of occlusion under 3 conditions: (1) with the pericardium intact and the chest resutured, (2) as above plus dobutamine infusion, and (3) with the chest and pericardium wide open.

Under condition 2, dobutamine was started at a rate of 10 μg · kg⁻¹ · min⁻¹ after 90 seconds of occlusion and continued for 2 minutes. After each period of occlusion, heart rate, LV pressure, and cardiac output were allowed to return to baseline values for a period of 10 minutes before a new set of baseline variables was recorded. The entire data set was collected over a period of ~60 minutes.

Statistics

Data presented in the Table and in the figures are the changes from baseline during balloon occlusion of the pRCA. Comparisons are made between before and after pericardiomyotomy (P1) and with and without dobutamine in the intact pericardium (P2) by Student’s paired t test.

Results

All 12 animals had dominant right coronary anatomy, and all survived the period of study. There was no significant difference between baseline variables before and after pericardiomyotomy.

With the pericardium intact, balloon occlusion of the pRCA for 3.5 minutes produced RV dilatation, a reduction in LV cavity size, and a marked fall in cardiac output. Transesophageal echocardiography showed concomitant inferior
wall and septal hypokinesis associated with septal shift toward the free wall of the LV (Figure 1). After either pericardiotomy or dobutamine administration, balloon occlusion produced both LV and RV dilatation with little movement of the septum. This geometric change was associated with a significantly smaller fall in cardiac output: $20.3 \text{ L/min}$ versus $20.7 \text{ L/min}$ before and after pericardiotomy, $P=0.03$; $20.3 \text{ L/min}$ versus $20.7 \text{ L/min}$ with and without dobutamine, $P=0.05$ (Figure 2).

**Effects of pRCA Occlusion on the RV**

Proximal RCA occlusion produced an increase in RV EDV from a mean ($\pm$SEM) of 104 (9.4) to 117.4 (9.9) mL, $P<0.01$, and a fall in RV systolic pressure from 31.2 (1.6) to 26.3 (1.4) mm Hg, $P<0.01$, with the pericardium intact (Table). These changes were associated with a reduction in the slope of the RV PRSW from 15.4 (2.1) to 12.7 (1.5) mm Hg, $P=0.05$, and a fall in the slope of the corrected RV ESPVR, corrected for volume, from 0.6 (0.1) to 0.5 (0.1) mm Hg/mL, $P=0.7$.

Proximal RCA occlusion after pericardiotomy produced less marked changes from baseline in all parameters of RV function (Table). The RV EDV increased by 10.2 (3.5) mL, the RV systolic pressure fell by 3.9 (2.1) mm Hg (Figure 3), and the slope of the RV PRSW fell by 1.5 (3.2) mm Hg.

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### Mean ($\pm$SE) Changes in Hemodynamic Parameters From Baseline With 3.5 Minutes of pRCA Occlusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>+Pericardium</th>
<th>−Pericardium</th>
<th>$P1$</th>
<th>+Dobutamine</th>
<th>$P2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO, L/min</td>
<td>3.0 (0.3)</td>
<td>−0.7 (0.1)</td>
<td>−0.3 (0.1)</td>
<td>0.03*</td>
<td>−0.3 (0.1)</td>
<td>0.05*</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>73.0 (5.9)</td>
<td>9.5 (2.0)</td>
<td>9.0 (2.0)</td>
<td>0.87</td>
<td>14.5 (2.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td>112.0 (4.6)</td>
<td>−27.8 (4.0)</td>
<td>−19.2 (3.9)</td>
<td>0.02*</td>
<td>−14.7 (14.0)</td>
<td>0.0002†</td>
</tr>
<tr>
<td>RVSP, mm Hg</td>
<td>31.2 (1.6)</td>
<td>−4.9 (1.4)</td>
<td>−3.9 (2.1)</td>
<td>0.46</td>
<td>−1.6 (1.1)</td>
<td>0.01†</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>7.7 (0.8)</td>
<td>1.5 (0.4)</td>
<td>0.0 (0.2)</td>
<td>0.05*</td>
<td>1.1 (0.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>RVEDP, mm Hg</td>
<td>7.0 (1.5)</td>
<td>0.1 (0.7)</td>
<td>0.0 (0.2)</td>
<td>0.68</td>
<td>−0.9 (1.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>99.3 (7.8)</td>
<td>−6.5 (4.5)</td>
<td>1.7 (3.2)</td>
<td>0.02*</td>
<td>1.3 (3.5)</td>
<td>0.04*</td>
</tr>
<tr>
<td>RVEDV, mL</td>
<td>104.0 (9.4)</td>
<td>13.4 (4.3)</td>
<td>10.2 (3.5)</td>
<td>0.65</td>
<td>4.6 (3.6)</td>
<td>0.002*</td>
</tr>
<tr>
<td>SV, mL</td>
<td>47.1 (4.1)</td>
<td>−12.1 (1.8)</td>
<td>−9.6 (2.1)</td>
<td>0.32</td>
<td>−10.2 (1.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>11.4 (2.1)</td>
<td>0.6 (0.3)</td>
<td>0.1 (0.1)</td>
<td>0.1</td>
<td>0.2 (0.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>LV PRSW, mm Hg</td>
<td>78.3 (6.6)</td>
<td>−30.2 (4.3)</td>
<td>−9.8 (4.0)</td>
<td>0.001†</td>
<td>−10.8 (6.3)</td>
<td>0.002†</td>
</tr>
<tr>
<td>RV PRSW, mm Hg</td>
<td>15.4 (2.1)</td>
<td>−2.7 (1.5)</td>
<td>−1.5 (3.2)</td>
<td>0.89</td>
<td>3.1 (2.0)</td>
<td>0.01†</td>
</tr>
<tr>
<td>LV ESPVR, mm Hg/mL</td>
<td>2.2 (0.4)</td>
<td>−0.9 (0.3)</td>
<td>−0.1 (0.1)</td>
<td>0.006†</td>
<td>−0.3 (0.3)</td>
<td>0.04*</td>
</tr>
<tr>
<td>RV ESPVR, mm Hg/mL</td>
<td>0.6 (0.1)</td>
<td>−0.0 (0.1)</td>
<td>0.1 (0.1)</td>
<td>0.08</td>
<td>0.1 (0.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>LV EDPVR, mm Hg/mL</td>
<td>0.2 (0.0)</td>
<td>0.1 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.19</td>
<td>0 (0.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>RV EDPVR, mm Hg/mL</td>
<td>0.1 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.07</td>
<td>−0.4 (0.4)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CO indicates cardiac output; HR, heart rate; LVSP and RVSP, left and right ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; CVP, central venous pressure; PRSW, slope of PRSW; ESPVR, slope of ESPVR corrected for volume; EDPVR, slope of linear EDPVR. $P1$, comparison of intact (+) and open (−) pericardium; $P2$, comparison of +pericardium and +dobutamine.

*$P<0.05$ and †$P<0.01$. 

- Figure 1. Transesophageal echocardiogram showing change in septal position during RCA occlusion with intact pericardium.
The changes from baseline induced by RCA ischemia after pericardiotomy were not significantly different from those with the pericardium intact.

Dobutamine infusion similarly reduced RV dilatation but produced a significant relative improvement in both RV systolic pressure generation and contractile performance (Figures 3 and 4). The RV PRSW increased from 14.4 (6.9) to 16.8 (6.3) mm Hg, \( P < 0.04 \). There was little change in the slope of the corrected RV ESPVR after pericardiotomy or dobutamine (Figure 4).

**Effects of pRCA Occlusion on LV Function**

With an intact pericardium, RV dilatation after pRCA occlusion caused a leftward shift of the interventricular septum, with a resultant fall in the LV EDV from 99.3 (7.8) to 89.5 (6.3) mL, \( P = 0.03 \), and a rise in LV EDP from 7.7 (0.8) to 9.2 (1.0) mm Hg, \( P < 0.01 \) (Table, Figure 3). This change produced a dramatic fall in both LV systolic pressure, from 111.7 (4.6) to 83.9 (3.1) mm Hg, \( P < 0.01 \), and LV contractile function. The slope of the LV PRSW fell from 78.3 (6.6) to 53.7 (4.6) mm Hg, \( P < 0.01 \), and that of the corrected LV ESPVR from 2.2 (0.4) to 1.5 (0.2) mm Hg/mL, \( P = 0.07 \). There was also a significant rise in the LV EDPVR from 0.2 (0.002) to 0.3

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**Figure 2.** Change in cardiac output (CO) from baseline in response to RCA ischemia.

**Figure 3.** Changes in ESP and EDV from baseline in response to RCA ischemia.

**Figure 4.** Change in slopes of the PRSW and ESPVR from baseline in response to RCA ischemia.
After pericardiomyotomy, however, the changes induced by pRCA occlusion were significantly less marked. Under these conditions, the interventricular septum did not move leftward, and pRCA occlusion instead led to a small increase in LV EDV with no change in LV EDP and a significantly smaller drop in LV systolic pressure, from 107.4 (4.3) to 88.2 (4.8) mm Hg (Figure 3). As a result of the geometric changes allowed by pericardiodyotomy, there was much smaller fall in LV performance after pRCA occlusion. The slope of the LV PRSW fell by only 9.8 (4.0), from 73.5 (6.1) to 62.4 (5.7) mm Hg, and that of the corrected LV ESPVR by 0.11 (0.14), from 1.8 (0.2) to 1.7 (0.2) mm Hg/mL, P<0.01 compared with changes seen with pericardiodyotomy intact (Figures 4 and 5).

Administration of dobutamine with the pericardium intact again produced effects similar to those with pericardiomyotomy. There was a small but significant increase in LV cavity dimensions, with less of a fall in LV systolic pressure generation (Table). These changes were associated with a significant improvement in systolic performance compared with no dobutamine. The LV PRSW fell only from 86.9 (7.4) to 78.1 (7.4) mm Hg, and that of the corrected LV ESPVR fell from 2.2 (0.4) to 1.9 (0.3) mm Hg/mL, P=0.04 (Figure 4).

**Discussion**

This study has demonstrated for the first time that the geometric changes induced by RCA occlusion cause significant impairment of LV contractile function, in addition to the diastolic filling abnormalities that have been documented previously. These changes are evidenced by a fall in the slopes of both the LV PRSW and LV ESPVR. Furthermore, restoration of LV cavity geometry by either pericardiomyotomy or administration of dobutamine can significantly improve LV performance.

RV infarction is associated with substantial morbidity and mortality.1–3 The mechanism of the acute hemodynamic compromise seen in this condition and the optimal method of treatment has been the subject of a number of studies.

In 1982, Goldstein et al12 demonstrated that RV infarction in dogs caused acute RV dilatation associated with a fall in cardiac output and that this reduction could be partially improved by pericardiomyotomy. Using the same model, they went on to show that the cardiac output could also be increased by volume loading and that the hemodynamic improvement could be further augmented by pericardiomyotomy.4 It thus appears that the normal pericardium plays an important role in determining hemodynamics in conditions associated with acute RV dilatation. Studies of RV infarction in dogs, however, are difficult to apply to humans because the RCA in dogs does not supply the interventricular septum. Clinical studies of volume loading in humans with acute RV infarction have provided variable results. Despite optimization of LV preload, the maximum improvement in cardiac index is only on the order of 10% and is not seen in all patients studied.6–8 The precise reasons for the inconsistent results seen in humans are not well understood but may reflect the various degrees of septal involvement in RV infarction.

It is hypothesized in all these studies that the fall in cardiac output seen in acute RV dilatation is due to impairment of LV diastolic filling caused by a leftward septal shift resulting in decreased LV compliance. Although this hypothesis is intuitively simple and has been validated to some extent by the finding of increased LV EDPs and reduced LV transmural pressures in acute RV dilatation,4,5 no studies to date have examined LV systolic performance in this context.

**Figure 5.** Example of LV pressure-volume cycles during IVC occlusion before and after occlusion of the pRCA.
tion of cavity shape and septal position. The anatomic basis for this hypothesis is unknown but may be related to changes in the alignment of the septal elements of the bulbospiral and sinuspiral fibers, which play an integral part in the coordinated contraction of both ventricles. It is of note that restoration of septal position also appears to improve cardiac function in the setting of acute RV hypertension. In this study of experimental acute RV pressure loading, aortic constriction was associated with a rightward septal shift (ie, normalization of septal position), improvement in SV, and reversal of circulatory collapse, but LV contractile function was not directly assessed.

Clinical Implications
If, indeed, LV geometry has important effects on systolic performance, then this may explain why volume loading in the context of RV dilatation may not improve overall cardiac function. Interestingly, it has recently been shown that volume offloading by use of lower-body suction can improve LV filling by normalizing septal curvature in a group of patients with congestive cardiac failure. This was interpreted by the authors as a change in diastolic interaction, but it is also possible, given the findings of our study, that LV systolic function improved as a result of restoration of LV geometry.

How, then, can these findings be applied in the clinical context? Clearly, not every patient with an RV infarct can undergo pericardiectomy.

First, normalization of septal position could be promoted by reversing RV ischemia and clearly should be attempted whenever possible. This was achieved in a recent study of primary angioplasty in acute RV infarction. Complete reperfusion of the RV branches led to a dramatic improvement in RV performance and overall circulatory status and was associated with an absence of leftward septal shift on echocardiography. Although LV ejection fraction was only mildly impaired before PTCA, it is not clear from the study whether improvements in this parameter were seen after PTCA.

Second, increasing LV systolic pressure generation could theoretically restore septal position and improve the septal contractile contribution to RV performance. Studies in both humans and dogs have demonstrated that inotropic stimulation with dobutamine in the context of acute RV infarction improves both LV and RV function as determined by radionuclide angiography and echocardiography, respectively. The mechanism by which this improvement occurred was attributed to exaggerated septal movement toward the RV in systole with enhanced systolic ventricular interaction. Our data clearly support these findings, because we have demonstrated that the enhanced LV systolic pressure generation during dobutamine infusion acts to reduce RV cavity dilatation, thus maintaining LV cavity geometry and enhancing contractile performance.

Limitations
We chose to assess 2 well-characterized indices of systolic function, the slope of the ESPVR and that of the stroke work–EDV relation or PRSW. The ESPVR slope is a well validated index of LV contractile function but is affected by chamber size in smaller hearts, and we have thus corrected our values for EDV. This relationship is also harder to define in the RV because of the difficulty in determining the exact timing of end systole and may explain the increase in RV ESPVR seen with ischemia after pericardiectomy. The PRSW slope has the advantage that it is minimally affected by chamber size, and it has been shown to be reproducible in both the RV and LV.

Although we established, during the pilot phase of the study, that a 2-minute infusion of dobutamine was sufficient to improve cardiac output during ischemia, the short duration of administration may limit its clinical relevance.

Conclusions
This study has demonstrated, for the first time, that part of the hemodynamic compromise seen in association with acute RV dilatation is due to reduced LV systolic performance and therefore cannot be wholly ascribed to changes in either LV preload or compliance. Instead, it is partly due to alterations in LV cavity geometry resulting from changes in position of the interventricular septum that adversely affect the mechanical efficiency of systolic contraction. Restoration of LV geometry and septal position by pericardiectomy or dobutamine therapy produced significant hemodynamic improvements.

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References


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