Right heart function during left heart assist and the effects of volume loading in a canine preparation

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ABSTRACT A significant fraction of patients in whom mechanical left ventricular assist devices are implanted for refractory cardiac failure after open heart surgery have had the complication of right heart failure. To evaluate the effects of left ventricular assistance and pressure unloading on right ventricular function, we performed experiments in the normal hearts of open-chest, anesthetized, large mongrel dogs. We compared right ventricular function before and after left ventricular-to-aortic bypass with a roller pump at right atrial pressure levels of 1, 3, 5, and 7 mm Hg produced by volume loading. No significant changes were found in cardiac output or stroke volume over this range of right atrial pressures when comparing that before to that during left ventricular bypass, which at a right atrial pressure of 1 mm Hg reduced peak left ventricular pressure from 96 ± 6 to 15 ± 9 mm Hg and at a right atrial pressure of 5 mm Hg reduced it from 113 ± 3 to 29 ± 12 mm Hg, while maintaining aortic pressure. There was no evidence of right ventricular failure under these conditions: (from before to during bypass) at a right atrial pressure of 1 mm Hg cardiac output was 3.4 ± 0.4 to 3.7 ± 0.6 liter/min and stroke volume was 28 ± 5 to 33 ± 6 ml; during volume loading at a right atrial pressure of 7 mm Hg cardiac output was 5.6 ± 0.6 to 5.7 ± 0.7 liter/min and stroke volume was 47 ± 5 to 52 ± 5 ml. However, there were significant (25% to 40%) reductions in the maximum and minimum rates of change in right ventricular pressure and the maximum rate of change in pulmonary arterial flow, suggesting reductions in right ventricular contractility perhaps via reduced forces in the interventricular septum during left ventricular pressure unloading. There were also significant 10% to 30% reductions in right ventricular peak systolic pressure and in mean pulmonary arterial pressure indicative of reduced afterload apparently produced by direct reductions in left ventricular filling pressures during left ventricular bypass. In separate experiments in which right ventricular peak systolic pressure was held at constant levels, maximum dP/dt was reduced from before to during bypass from 322 ± 33 to 227 ± 28 mm Hg/sec at a right ventricular peak systolic pressure of 21 mm Hg and from 427 ± 22 to 318 ± 18 at a right ventricular peak systolic pressure of 32 mm Hg. Reduced contractility is also suggested because there was no evidence that end-diastolic volume, stroke volume, or ejection fraction changed in response to the reduced afterload. The results illustrate that the beneficial effects of right ventricular afterload reduction with left ventricular assistance can balance the detrimental effects of impairment of contractility, leaving stroke volume unchanged. Thus, in the normal dog heart no change in the ability of the right ventricle to eject a required stroke volume was detected during volume loading or during left ventricular pressure unloading with left ventricular bypass and assistance.


THE SUCCESSFUL CLINICAL use of left ventricular assist devices (LVADs) depends not only on safe blood contacting biomaterials and effective engineering performance and control features, but also on an understanding of the effects of the device on host organ systems. One major problem area demonstrated in clinical experience with LVAD for refractory cardiac failure after open heart operations is right ventricular failure. Of 103 patients with LVADs reported by nine groups, including our own, 27 patients exhibited right ventricular failure that was refractory to pharmacologic support, although 41 additional LVAD patients were reported in articles that do not adequately discuss right ventricular failure.

The exact cause of right ventricular failure during left ventricular assistance is unknown, and there is a paucity of experimental data in the few reports and
abstracts that have been published concerning the effects of an LVAD on the right ventricle. One leading possibility is that right ventricular failure in patients who have undergone open heart surgery may be due to the same myocardial ischemia and depression of cardiac function during cardiopulmonary bypass that caused the left heart to fail. This preexisting right ventricular disease and poor right ventricular function is unmasked with the increased venous return to the right heart generated by the assist device. Another possibility is that volume and pressure unloading the left ventricle with a LVAD reduces the coupling between the ventricles via the interventricular septum and reduces the contribution of left ventricular contraction to an already marginal right ventricle. Thus, abnormal septal contraction or reduced septal forces may contribute to right ventricular failure.

These are important phenomena to understand from the standpoint of proper control of the assist pump, for helping to interpret clinical findings from patients with various cardiac pathology, and for proper clinical decisions on whether to provide right or left ventricular assistance or a total artificial heart. The present study was designed to evaluate right heart function during left ventricular assistance in the normal dog heart to determine if right ventricular pump function is impaired with left ventricular pressure unloading and with increased venous return during volume loading.

Methods

Eleven mongrel dogs of both sexes weighing between 27 and 35 kg were anesthetized with intravenous sodium pentobarbital (35 mg/kg), intubated, and connected to a respirator adjusted to maintain blood gases within a normal range. Anesthesia was maintained by periodic intravenous doses of fentanyl (4 to 6 μg/kg) as required. A left thoracotomy was performed on each dog and the heart was suspended in a pericardial cradle. Two No. 32F cannulas were inserted into the left atrium, one of which was placed across the mitral valve and into the left ventricle. These cannulas were attached to a Y connector and then to a roller pump that returned blood to the abdominal aorta at the bifurcation. In each of the first seven dogs, a reservoir containing dextran 40 premixed with the dog’s blood and heated to body temperature was connected to the right atrium for volume loading and for producing increases in right atrial pressure (figure 1).

The first group of dogs were instrumented for the following: High-fidelity right ventricular and pulmonary arterial pressures were measured with Konigsberg P9.5 and Millar PC350 pressure transducers, respectively. A specially modified Swan-Ganz catheter (Edwards Lab) was introduced with an injection port in the right ventricle and with a fast-response thermistor in the pulmonary artery. The average time constant of the thermistor-catheter systems was 173 msec, as measured in water baths at two different temperatures. The right ventricular and pulmonary arterial ports of the catheter were connected to Statham P23Db pressure transducers for periodic check in vivo of zero for the high-fidelity transducers. Left ventricular peak systolic and end-diastolic pressures were measured with a Millar transducer connected to a short polyethylene catheter inserted through the left ventricular bypass cannula and into the left ventricle. Cardiac output was measured from the pulmonary artery with an electromagnetic blood flowmeter and flowprobes calibrated at the factory with whole blood (Carolina Medical Electronics). Right atrial and aortic pressures were measured through polyethylene catheters connected to Statham P23Db transducers. Zero pressure was taken at the level at the right atrium.

All signals were connected to a Gould model 2800 eight-channel recorder. The first derivative of right ventricular pressure (dP/dt) and of pulmonary arterial blood flow (dQ/dt) were determined electronically with a Gould differentiator preamplifier.

Measurements of all parameters were made with the left ventricular bypass pump off and on. Flow rates of the bypass pump were adjusted to obtain a maximum unloading effect by reducing maximum left ventricular pressure to under 30 mm Hg. After baseline measurements were made with the left ventricular bypass off and on, volume from the right atrial pressure reservoir was slowly added to raise right atrial pressure by approximately 2 mm Hg after a 10 min stabilization period. Measurements were then repeated with and without left ventricular bypass. This procedure of volume loading and comparing values obtained with left ventricular bypass off and on was repeated two more times to obtain data over a range of right atrial pressures from approximately 1 to 7 mm Hg.

Estimates of right ventricular volume were determined by the thermodilution technique based on the work of Rapaport et al. and Balcon and Oram. A rapid injection of 10 ml of iced 5% dextrose solution was made into the right ventricular port on the Swan-Ganz catheter and the runoff curve was measured on the chart recorder. Injections were repeated five to seven times at each experimental intervention. Right ventricular ejection fraction (RVEF) was estimated as

\[
RVEF = \frac{(T(k-1) - T_k)}{T(k-1)}
\]

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where T_k and T_{k+1} are the kth and (k+1)th plateaus of the relative pulmonary temperature changes at successive cardiac cycles after the peak temperature. RV end-diastolic volume (RVEDV) was calculated as

\[ \text{RVEDV} = \frac{SV}{RVEF} \]

where SV = the stroke volume determined by dividing mean flow from the electromagnetic blood flowmeter by heart rate.

Changes in right ventricular function during left ventricular bypass were assessed by evaluating various parameters as indexes of right ventricular output, preload, afterload, contractility, and heart rate. Indexes of right ventricular output were assessed by determination of cardiac output, stroke volume, stroke work, and maximum pulmonary arterial flow. Indexes of preload were mean right atrial pressure and right ventricular end-diastolic volume. Indexes of afterload were peak right ventricular systolic pressure and mean pulmonary arterial pressure. Changes in contractility were assessed by changes in maximum and minimum dP/dt and dQ/dt and by right ventricular ejection fraction. Heart rate was determined by the time interval between R waves.

Data from the first seven dogs were grouped and averaged at right atrial pressure levels of approximately 1, 3, 5, and 7 mm Hg. The null hypothesis tested was as follows: There is no significant change in any right ventricular parameter from before to during left ventricular bypass. Statistical comparisons between left ventricular bypass off and on were performed for each parameter by a three-way analysis of variance with repeated-measures design, allowing for partitioning of treatment variance into the effects of volume loading and left ventricular bypass and among animals. This method uses all of the repeated-measures data collected at different right atrial pressures to provide one comparison between values on and off left ventricular bypass for each parameter. Thus, we tested the effect of left ventricular bypass on each parameter after variability of data among animals and due to volume loading had been taken into consideration. Data are presented as mean ± SEM.

In four additional experiments right ventricular dP/dt was determined with no volume loading over a range of right ventricular systolic pressures. Measurements before and during left ventricular bypass were made while banding the pulmonary artery to hold right ventricular peak systolic pressure at approximately 15, 20, 25, and 30 mm Hg. Data from these four dogs were averaged at these pressure ranges and statistical comparisons were again performed by a three-way analysis of variance, this time allowing for partitioning of treatment variance into effects of right ventricular systolic pressure and left ventricular bypass and among animals.

**Results**

A representative chart recording from one experiment (figure 2) shows the hemodynamic measurements during left ventricular bypass off (panel A) and left ventricular bypass on (panel B). This example illustrates unloading of left ventricular pressure to less than 10 mm Hg during left ventricular bypass, with mean aortic pressure maintained. Reductions in pulmonary arterial and peak right ventricular pressure and dP/dt were also noted.

A summary of results of the analysis of variance on the experimental data from the first group of dogs is as follows. After accounting for the variability of data due to volume loading, the effects of left ventricular bypass were found to be significant at the p < .01 level for pulmonary arterial pressure, right ventricular peak systolic pressure, maximum and minimum dP/dt, and left ventricular peak systolic and end-diastolic pressures, and significant at p < .05 for maximum and minimum dQ/dt. No other parameter was significantly changed by left ventricular bypass. The effects of volume loading, after accounting for the variability of data due to left ventricular bypass, were found to be significant at p < .05 for all parameters except heart rate, mean aortic pressure, left ventricular peak systolic pressure, and maximum and minimum dQ/dt.

The average values (± SEM) of hemodynamic pressure measurements for all experiments show a significant reduction in left ventricular systolic pressure to less than 30 mm Hg during left ventricular bypass over the range of right atrial pressures studied (figure 3). No change was detected in mean aortic pressure, but mean pulmonary arterial pressure and peak right ventricular pressure were significantly (p < .01) reduced during left ventricular bypass. Left ventricular end-diastolic pressures also showed significant reductions from left ventricular bypass off to bypass on (from 3 ± 2 to 2 ± 2, 5 ± 2 to −1 ± 1, 7 ± 2 to −1 ± 1, and 17 ± 3 to 1 ± 2 mm Hg at right atrial pressures of 1, 3, 5, and 7
Changes in right ventricular stroke work from before to during left ventricular bypass also were not statistically significant; at right atrial pressures of 1 mm Hg, stroke work was 519 ± 113 (before bypass) and 549 ± 97 ml·mm Hg (left ventricular bypass) and increased with volume loading at 5 mm Hg to 1090 ± 93 (before bypass) and 912 ± 99 ml·mm Hg (bypass).

In the second group of dogs, the analysis of variance revealed significant (p < .01) effects of left ventricular bypass and of right ventricular peak systolic pressure on the maximum but not the minimum dp/dt. At each level of right ventricular peak systolic pressure there

FIGURE 3. Effects of left ventricular (LV) bypass on left (top) and right side (bottom) pressures. Significant (p < .01) decreases in right ventricular peak systolic pressure (RVPSP) and mean pulmonary arterial pressure (PAP) were noted with reductions in LV peak systolic pressure (LVPSP) during LV bypass. Mean aortic pressure (AoP) was not changed.

FIGURE 4. No significant changes in peak pulmonary arterial (PA) blood flow or in mean cardiac output were found during left ventricular (LV) bypass, although there were significant increases in these parameters with increases in right atrial pressure (RAP) due to volume loading. There were no significant changes during LV bypass in heart rate.
were significant reductions in maximum dP/dt during left ventricular bypass (figure 8). In these non-volume loaded animals right atrial pressures increased from approximately 0 to 1 mm Hg when right ventricular peak systolic pressure was increased from 15 to 30 mm Hg during banding, but there was no significant change in right atrial pressure with left ventricular bypass.

Discussion

Right ventricular failure can be defined as the inability of the right ventricle to produce a cardiac output equal to venous return and to the needs of the body. In clinical cases of right ventricular failure with left heart assist, this is demonstrated by reductions in cardiac output with an increase in right atrial pressure and perhaps a visual assessment in the operating room of poor right ventricular contraction as soon as the left ventricular assist pump is turned on or soon thereafter. In the present study in the normal dog heart we found no such evidence of right ventricular failure. The major changes found were (1) significant (10% to 30%) reductions in mean pulmonary arterial pressure and in maximum right ventricular pressure, demonstrating reduced right ventricular afterload since cardiac output was unchanged, and (2) significant (25% to 40%) reductions in maximum and minimum dP/dt and dQ/dt during both the contraction and relaxation phases, which along with unchanged right ventricular end-diastolic volume, right ventricular ejection fraction, and stroke volume in response to the reduced afterload, suggest reductions in right ventricular contractility.

The reduction in contractility, which should impair right ventricular function, appears to be balanced by a reduction in afterload, which should improve right ventricular function. No major changes in the ability of the right ventricle to produce a stroke volume or cardiac output over a wide range of right atrial pressures were found during left ventricular bypass in this normal canine heart preparation.

There are two major concepts of ventricular interaction that explain how right ventricular function might be altered by the perturbation of left heart bypass and

**FIGURE 5.** No significant changes in right ventricular end-diastolic volume (RVEDV), stroke volume (SV), or right ventricular ejection fraction (RVEF) were found during left ventricular (LV) bypass.

**FIGURE 6.** Significant (p < .01) decreases in the magnitude of the maximum (max) and minimum (min) dP/dt were found during left ventricular (LV) bypass.
assistance: (1) the two hearts operate in series, and (2) the right ventricle is closely coupled anatomically to the left ventricle. The in-series concept explains how an LVAD can unmask preexisting right ventricular failure or dysfunction by increasing venous return to a level too great for the right ventricle to handle. For example, a patient in severe left heart failure with low cardiac output and no reserve may have a right heart functioning at the peak of an already depressed Starling function curve. Turning on an LVAD would result in markedly increased cardiac output and increased venous return to the right heart, which could overload the right ventricle and cause failure. The impaired right heart function may only become clinically apparent, however, after the left side is assisted. The in-series concept also explains how beneficial reductions in pulmonary arterial pressure as seen in this study during left ventricular bypass can be produced passively by reductions in left ventricular filling pressures.

The second hypothesis deals with the mechanical interdependence of the ventricles through the interventricular septum and through common muscle fibers that encircle both ventricles. In certain patients, perhaps with septal wall contraction abnormalities or ischemia, right ventricular performance may be greatly dependent on the position of, or the normal stresses developed in, the interventricular septum during left ventricular contraction. This is supported by the studies of Agarwal et al. and Tanji in which septal arterial ligation in dogs resulted in global right ventricular dysfunction. The mechanism for right ventricular contraction is a uniform reduction in right ventricular free wall surface area and septal-to-free wall distance. If there is a postinfarction septal scar and left ventricular assistance reduces left ventricular pressure, the interventricular septum may bulge into the left ventricle during right ventricular systole. This will reduce the septal contribution to the function and efficiency of right ventricular contraction and may trigger the right ventricle into failure.

Reductions in right ventricular dP/dt during left ventricular bypass, as seen in our study when cardiac output was allowed to change during volume loading and as reported by Miyamoto et al. in a similar preparation but in which cardiac output was held constant,
are indicative of a reduced septal contribution to right ventricular contraction and reduced coupling of the right and left ventricles. Since we also found a decrease in right ventricular afterload along with the decrease in dP/dt during left ventricular bypass, the second group of experiments was performed to separate these effects. These studies resulted in lower values of dP/dt than in the volume loading experiments, illustrating a greater dependence of this parameter on preload than afterload, as reported by others. The afterload dependence of right ventricular dP/dt is illustrated in figure 8, but at each right ventricular systolic pressure there were significant reductions in maximum dP/dt during left ventricular bypass. Part of the reductions in dP/dt during left ventricular bypass is therefore due to reduced pulmonary arterial pressure and part is a direct consequence of left ventricular decompression. A decrease in right ventricular contractility also is suggested by our results because there was no evidence that stroke volume, ejection fraction, or right ventricular end-diastolic volume changed in response to the reduction in afterload pressure.

In addition, previous studies have shown dQ/dt to be a sensitive index of contractile function in the left ventricle, which either decreases with increases in afterload or shows insignificant changes. If the right ventricle responds in a similar manner, we would expect to see either an increase or no change in dQ/dt with the reduction in afterload. The decrease in dQ/dt thus suggests a reduction in contractility and in the total force applied to the blood by the right ventricle during left ventricular bypass at a given preload, since the mass of the blood to be moved (stroke volume) is unchanged. We cannot explain the apparent reductions in dQ/dt and dP/dt seen at right atrial pressures above 5 mm Hg under both left ventricular bypass and pre bypass conditions, although perhaps this is the beginning of a descending limb of right ventricular function at high filling pressures.

Other studies also support a reduced coupling between the ventricles and reduced right ventricular function with left ventricular unloading. Santamore et al., in an isolated heart preparation with the left ventricle unloaded, showed that a decrease in left ventricular pressure resulted in movement of the ventricular septum to the left and showed a reduction in right ventricular developed pressure. In another isolated heart preparation, Elzinga et al. also showed a reduction in isovolumetric right ventricular developed pressure when the left ventricle was completely unloaded. Others have also noted, using two-dimensional echocardiography, leftward septal displacement during right ventricular volume loading in man and in cases of right ventricular hypertension in children and in dogs. Therefore, during volume or pressure unloading of the left ventricle during left ventricular assistance, abnormal septal contraction may contribute to right ventricular failure due to leftward septal shift.

It is commonly thought that for LVADs to perform properly in reversing temporary heart failure there should be substantial reductions in left ventricular pressure in order to reduce myocardial oxygen demand and thereby provide a sufficient recovery period for the ventricle and perhaps reduce infarct size. It is possible that this could have a detrimental effect on the right ventricle by reducing the septal contribution to right ventricular performance. However, complete left ventricular decompression with an LVAD, which is usually only achieved with left ventricular cannulation, does not adequately explain right ventricular failure. Left atrial cannulation has actually been performed with better success than left ventricular cannulation in terms of ventricular recovery, but there are still some instances of right ventricular failure. Perhaps volume unloading without complete pressure unloading of the left ventricle, which could occur with either left ventricular or left atrial bypass cannulation, may play a role by also reducing the stresses in the septum and impairing septal contribution to right ventricular function.

The thermodilution estimates of right ventricular volume in the present study provide no evidence that left ventricular unloading changes right ventricular volume. This is somewhat surprising since other studies with analogous interventions show dimensional changes and leftward septal shifts when the right ventricle is overloaded compared with the left ventricle. The thermodilution technique, however, because of its limitations, may not provide enough accuracy and consistency to determine subtle changes. Still, the finding of no significant changes in right ventricular ejection fraction with the thermodilution technique during left ventricular bypass is consistent with diminished right ventricular contractility. Since pulmonary arterial pressure decreased with left ventricular bypass, one would expect right ventricular ejection fraction to increase, as shown by Korr et al., unless contractility was indeed reduced.

The results of this study can be explained by a hypothetical pressure-volume relation for ventricular contraction such as that of Suga and Sagawa and similar to that constructed by Maughan et al. for the right ventricle. Since we found no evidence of changes in preload, stroke volume, or ejection fraction, but did
find reductions in right ventricular systolic pressure, the changes in right ventricular function during left ventricular bypass can be described by pressure-volume relations illustrated in figure 9. One representation of a reduction in contractility suggested in our work is hypothetically illustrated here and is consistent with a reduction in E_max, or the slope of the end-systolic pressure-volume relation, with no change in volume intercept. If contractility did not change or it increased, one would expect the loop to shift to the left during the afterload reduction seen with left ventricular bypass. A reduction in contractility or E_max alone would be detrimental to the right ventricle, but with concomitant afterload reductions as seen with left ventricular bypass, stroke volume can be maintained. This model shows how right ventricular stroke volume can remain constant with reductions in right ventricular pressure and contractility during left ventricular bypass. Further studies are necessary to confirm this relationship and to determine the functional changes during various disease states.

Thus, in the normal dog heart, left ventricular assistance with left ventricular pressure unloading produces no evidence of right ventricular failure. However, the data suggest some impairment in right ventricular contractility, perhaps due to reduced septal forces. In addition to potential adverse effects on the right ventricle during left ventricular assistance, the present study demonstrates that there also can be substantial beneficial effects on the right ventricle by decreased right ventricular afterload during left ventricular bypass. In patients with elevated pulmonary pressures secondary to compromised left ventricular performance, the beneficial effects may outweigh any adverse effects. Thus, an LVAD may unload the right ventricle indirectly by directly unloading the left ventricle.

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