PATHOPHYSIOLOGY AND NATURAL HISTORY

VENTRICULAR PERFORMANCE

Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure

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ABSTRACT Therapy of elevated ventricular filling pressures in patients with dilated heart failure may be limited by concern that cardiac output will be further compromised. Twenty-five patients with severe symptoms and ejection fractions of 25% or less were studied to determine the lowest ventricular filling pressures that could be achieved with vasodilator and diuretic therapy while maintaining cardiac output. In 20 of 25 patients normal pulmonary capillary wedge pressures (PCWs) were achieved (mean 10 mm Hg compared with 30 mm Hg at baseline). Stroke volume was 60 vs 39 ml at baseline. Stroke work index was 30 vs 19 g-m/m². For each patient, over the range of PCWs, stroke volume and stroke work index were maintained and were often maximal at the lowest PCW achieved. The upright position was well tolerated in patients with normal supine PCW. Normal filling pressures can be achieved in patients with congestive heart failure without compromise of cardiac output. While congestive symptoms should be improved, the feasibility and benefit of maintaining normal filling pressures over a long term must be established.

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DILATED heart failure is characterized by decreased cardiac output and elevated left ventricular filling pressure. Although many symptoms result from pulmonary congestion, aggressive therapy of elevated filling pressures may be limited by the concern that cardiac output will be further compromised.¹

Standard therapy for patients with NYHA class III or IV symptoms has focused primarily on increasing cardiac output with vasodilator therapy, although significant concomitant diuresis and reduction of left ventricular filling pressure occur. Diuretic therapy is usually adjusted empirically according to the presence of rales and peripheral edema.

This study was designed to determine with hemodynamic monitoring the lowest ventricular filling pressures that could be achieved with vasodilators and diuretics without compromise of cardiac output in patients with dilated heart failure.

Methods

Twenty-five consecutive patients referred for therapy of refractory dilated left ventricular failure were studied prospectively. Fourteen patients had coronary artery disease; none had had a myocardial infarction within 3 months. Nine patients had idiopathic dilated cardiomyopathy, and two had dilated left ventricular failure due to chronic rheumatic valvular disease. All patients had ejection fractions of 25% or less as determined by radionuclide angiography or two-dimensional echocardiography (with modified Simpson’s rule) within the preceding month. Eight patients were in class III, 17 patients were in class IV, and all had congestive symptoms for at least 3 months. Although seven patients had worsening symptoms over the preceding month, no patient was unstable at the time of evaluation. All patients were being treated with diuretics and 13 were on empiric vasodilator therapy at the time of admission. Digitalis therapy was continued in seven patients who were on the drug when referred, but was not begun in other patients. No other inotropic agents were given.

Oral diuretics and vasodilators were continued until catheterization. Informed consent for this study was obtained before right heart catheterization. A No. 7 thermodilution, balloon-tipped, triple-lumen catheter was inserted percutaneously into the internal jugular vein and passed to the pulmonary artery, where its position in the pulmonary capillary wedge during balloon inflation was confirmed by fluoroscopy and pressure. In four patients in whom wedge pressure could not be reliably obtained with stable catheter position, the relationship of pulmonary capillary wedge pressure (PCW) to pulmonary arterial diastolic pressure was verified and the latter was used in subsequent measurements of PCW. Cardiac outputs were determined in triplicate by the thermodilution technique. Blood pressures
were determined by cuff readings and mean arterial pressures (MAPs) were calculated arithmetically as:

$$2 \times \text{Diastolic pressure} + \text{Systolic pressure}$$

$$\frac{3}{\text{Cardiac output}}$$

Systemic vascular resistance was calculated as:

$$\frac{\text{MAP} - \text{Right atrial pressure}}{\text{Cardiac output}} \times 80 \text{ dynes-sec-cm}^{-5}$$

Stroke work index was calculated as:

$$\text{Cardiac output} \times \text{Heart rate} \times \text{Body surface area} \times (\text{MAP} - \text{PCW}) \times 0.0136 \text{ g-m/m}^2$$

Initial hemodynamics were measured after 3 hr in the fasting state and were stable for two measurements during the hour before therapy was begun. Vasodilator therapy was initiated with intravenous nitroprusside in all except three patients who received intravenous nitroglycerin therapy and two patients who were maintained on oral regimens. Nitroprusside was begun at 20 $\mu$g/min and the dose was increased every 30 min if PCW remained greater than 14 mm Hg, up to a maximum of 5 $\mu$g/kg/min. Intravenous furosemide was administered intravenously in doses of 40 to 200 mg every 4 to 6 hr if PCW remained greater than 14 mm Hg, and diuresis was recorded. During titration of intravenous therapy, cardiac outputs were measured every hour and PCW was determined every 30 min. Vasodilator and intravenous diuretic therapy were administered for up to 48 hr until PCW fell to 14 mm Hg or less, systemic vascular resistance fell below 800 dynes-sec-cm$^{-5}$, systolic blood pressure fell below 80 mm Hg, or the patient became clinically compromised in terms of mental status, urine output, or general comfort. When the PCW was 14 mm Hg or less, or after 48 hr, oral vasodilator therapy was begun with captopril or hydralazine and nitrates while doses of intravenous vasodilators were tapered. The maximum single dose of captopril was 100 mg, that of hydralazine 200 mg, and that of isosorbide 80 mg, given at 4 to 6 hr intervals. While oral therapy was adjusted, the catheter remained in place and hemodynamics were measured every 2 hr until a stable dosing regimen was established. The maximum length of time during which hemodynamic measurements were made was 4 days.

The lowest PCW was defined as the lowest value measured at least twice with consistent tracings and correlation with the pulmonary arterial diastolic pressure. The hemodynamic data used for analysis were those obtained in the 18 patients on oral vasodilators in whom normal PCW was attained on both oral and intravenous therapy. In two patients normal PCW was achieved only with nitroprusside, and in the five patients in whom PCW below 15 could not be attained, data were determined at the lowest PCW achieved.

Each patient’s maximum stroke volume was identified. The relationship between stroke volume and PCW was then determined in each patient for the entire range of observed PCW by calculating percent maximal stroke volume at each PCW. The same relationship was described for stroke work index versus PCW. The mean and standard deviations of these percentages were calculated to allow demonstration of the general relationship of maximal stroke volume or stroke work index to PCW. In addition, to compare stroke volume at normal PCW and stroke volume at PCW of 18 to 22 mm Hg while minimizing the effect of varying afterload, a narrow range of systemic vascular resistance (± 200 dynes-sec-cm$^{-5}$) was retrospectively sought within which stroke volume had been obtained at PCW of 18 to 22 mm Hg and subsequently at PCW of 10 to 14 mm Hg. Systolic blood pressure and heart rate were also compared at these two points. This comparison was possible for all patients in whom normal PCW was achieved except one in whom PCWs of 12 and 20 mm Hg were never achieved at a similar systemic vascular resistance.

Hemodynamics obtained in the supine position were compared with those obtained after 3 min in the standing position for two groups of patients on oral vasodilators. In all postural hemodynamics were measured at 24 hr if possible and again before removal of the catheter. Only measurements made in the presence of vasodilatation to a supine systemic vascular resistance of less than 1500 dynes-sec-cm$^{-5}$ were compared. One group consisted of 11 patients with supine PCWs of 18 to 24 mm Hg, while the other group consisted of 16 patients in whom measurements were made when supine PCW was 8 to 13 mm Hg, with three patients included in both groups. Postural changes in mean arterial pressure, stroke volume, and PCW were assessed in the two groups.

All values are expressed as the mean and SD. Significance of differences was determined by two-tailed t tests, which were applied to paired data when appropriate. A value of $p < .05$ was considered indicative of a significant difference.

**Results**

The 25 patients had a mean ejection fraction of 18% (range 10% to 25%). Initial mean cardiac index was $1.9 \pm 0.4$ liters/min/m$^2$, with an initial mean PCW of 31 $\pm$ 5 mm Hg. In 20 of 25 patients, normal PCW could be established ($\leq 12$ mm Hg in all patients except one patient with the lowest PCW of 14 mm Hg). For these 20 patients, mean minimum PCW was 10 mm Hg. Eighteen patients who developed normal PCW did so first on intravenous vasodilators and subsequently on oral vasodilators, while two reached a low PCW only on nitroprusside despite achievement of a similar stroke volume resistance on oral agents. At the normal filling pressures, cardiac index was 3.4 liters/min/m$^2$ compared with 1.9 liters/min/m$^2$ initially (table 1). Stroke volume rose from 39 to 60 ml, while stroke work index rose from 19 to 30 g-m/m$^2$. Net diuresis achieved between baseline and normal PCW measurements averaged 3.4 liters, with a range of 0 to 11 liters. The heart rate at normal PCW was 89 $\pm$ 11 beats/min compared with 91 $\pm$ 15 beats/min initially.

The five patients in whom normal PCW was not achieved had similar initial PCWs (33 vs 30 mm Hg). However, cardiac index, stroke volume, stroke work index, and mean arterial pressure were lower in this group, although there was considerable overlap and the differences between the two groups were not statistically significant. This group had less diuresis in spite of administration of similar diuretic doses, with a mean fluid loss of 1 liter.

The stroke volume and stroke work index at normal filling pressure were compared with maximal stroke volume and stroke work index for each patient. Maximal stroke volume was achieved in 12 patients only with normal PCW; maximal stroke work index was
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TABLE 1

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Lowest PCW ≤14</th>
<th>Lowest PCW ≥16</th>
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<tbody>
<tr>
<td></td>
<td>Initial (n = 20)</td>
<td>Initial (n = 5)</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>30 ± 5</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>1.9 ± 0.4</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>39 ± 10</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Stroke work index (g·m/m²)</td>
<td>19 ± 11</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes·sec·cm⁻¹)</td>
<td>1800 ± 400</td>
<td>1700 ± 200</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>89 ± 15</td>
<td>77 ± 12</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>91 ± 15</td>
<td>100 ± 20</td>
</tr>
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</table>

Values are expressed as the mean ± SD.

achieved in 15 patients only at a normal PCW and in nine patients only at a PCW of 10 mm Hg or less. The two patients who could not produce their maximal stroke work index at a normal PCW were the two in whom normal PCW could be established with nitroprusside but not with oral vasodilators.

Stroke volume and stroke work index were then determined over a range of PCWs for each patient and normalized by comparison with the patient’s maximal stroke volume or stroke work index. These percentages of maximal stroke volume and stroke work index were averaged over the 20 patients to determine the overall relationship between PCW and stroke volume (figure 1, top) and between PCW and stroke work index (figure 1, bottom). Stroke volume and stroke work index were both shown to be maintained at normal filling pressures.

To estimate the effect of a reduction in PCW without a simultaneous reduction in stroke volume reduction, for each of 19 patients a range of stroke volume reduction ± 200 dynes·sec·cm⁻³ was retrospectively identified at which stroke volume had been measured with PCW of 18 to 22 mm Hg and subsequently with PCW of 10 to 14 mm Hg. Stroke volume was compared at these values of PCW (figure 2). There was no decline in stroke volume when PCW was lowered to the normal range. In fact, there was a statistically significant improvement with mean difference in stroke volume of 5.2 ± 5.4 ml (p < .05). Mean systolic blood pressure was 102 mm Hg at both PCW levels.

For the five patients in whom normal PCW was not achieved, the lowest PCW ranged from 16 to 22 mm Hg. At their lowest PCW, four of the five patients developed their maximal stroke volume and five of five developed their maximal stroke work index.

When patients were studied in the upright position while they were on oral vasodilators, mean arterial pressure was well maintained among those with normal supine PCW (figure 3). There was no significant change in systolic blood pressure (103 ± 15 mm Hg supine to 105 ± 22 mm Hg standing). Standing stroke volume fell slightly in both groups but was not lower in the group with normal supine PCW than in the group with elevated supine PCW. There were no postural symptoms in either group.

All patients were placed, over the long term, on the oral vasodilator regimen that established PCW closest to the normal range. Of the five patients in whom PCW

FIGURE 1. Maintenance of stroke volume (SV) (top) and stroke work index (SWI) (bottom) at normal PCW. For each patient, maximal SV and SWI were identified and compared with values obtained at different PCWs. At each PCW, the ratios of SVs to maximal SV (top) or SWIs to maximal SWI (bottom) were then averaged for the 20 patients. SDs are indicated.
of less than 15 mm Hg could not be achieved, three required subsequent intravenous inotrope therapy and died of heart failure during the same period of hospitalization, one died suddenly at 6 months, and one died of sepsis at 1 year. Of the other 20 patients, two underwent transplantation within 1 month of study, 16 of the remaining 18 (89%) were alive at 3 months, and 12 (67%) were alive at 11 ± 6 months follow-up. Mortality in the group in whom normal PCW was established was due to circulatory failure in one patient, noncardiac death in one patient, and sudden death in four patients.

Discussion

This study demonstrates that normal left ventricular filling pressures can be achieved in patients with class III or IV symptoms of congestive failure and ejection fractions less than 25%. Stroke volume was maintained and was often maximal at normal PCW. In a study of the safety of intravenous nitroprusside, Fransos et al. suggested that normal filling pressures may be tolerated in some patients with congestive heart failure, although in his population the baseline ventricular impairment was less severe. Yin et al. also described seven patients in whom left ventricular end-diastolic pressure fell from 24 to 11 mm Hg during the short-term infusion of nitroprusside in their investigation of the effects of nitroprusside on the hydraulic vascular load of the right and left ventricles. Since normal filling pressures are established in the presence of vasodilator therapy, it might be argued based on these previous studies that decreased peripheral afterload allows stroke volume to be maintained even though actual ventricular performance is limited by suboptimal filling. However, in the current study stroke work was determined and found to be not only maintained but frequently higher at normal ventricular filling pressures, which were achieved with oral vasodilators as well as intravenous nitroprusside.

To demonstrate more directly that the maintenance of cardiac output at normal filling pressures is not due exclusively to simultaneous afterload reduction, stroke volumes at PCWs of 18 to 22 mm Hg were compared with those obtained at PCWs of 14 mm Hg or less, with the same peripheral afterload, whether estimated by systemic vascular resistance or by systolic blood pressure. In this comparison as well, stroke volumes were maintained.

The five patients in whom normal filling pressures were not achieved appeared as a group to have worse
hemodynamic impairment and worse short-term survival. However, they could not be identified individually from baseline data, because other patients with similar hemodynamic characteristics responded to therapy and had normal PCWs. It is not clear whether further therapy in these patients with drug-refractory diseases could have established normal filling pressures or whether these patients had higher optimum filling pressures. The latter appears unlikely because at the lowest filling pressure documented in these patients, all five developed their maximal stroke work index.

The standard approach to dilated heart failure has assumed that aggressive therapy of congestive symptoms by reduction of left ventricular filling pressure would decrease cardiac output, such that a compromise must be made between the achievement of normal filling pressures and the maximization of cardiac output. Whether or not such a compromise should be necessary depends on the pressure-volume relationship in the chronically dilated ventricle.

In the acute systolic dysfunction of ischemia, diastolic compliance is decreased and the maintenance of adequate volume has been shown to require an elevated ventricular filling pressure. Thus, in the management of acute infarction, a PCW of at least 18 mm Hg is necessary to maximize cardiac output. In chronic ventricular dilatation, however, the pressure-volume curve may shift to the right such that high volumes can be maintained with normal filling pressures, as has been demonstrated in dogs with chronic volume overload due to arteriovenous fistulas. The difficulty of equating ventricular filling pressures and ventricular volumes has been emphasized previously by Braunwald and Ross. Our study demonstrates that normal filling pressures can be achieved clinically in the chronically dilated left ventricle of the patient with systolic failure.

However, the study further demonstrates that after patients have already responded to vasodilator and diuretic therapy with a reduction in systemic vascular resistance and PCW, ventricular filling pressure can be further reduced to normal while stroke volume is maintained, even without a further reduction in systemic vascular resistance. This suggests that the end-diastolic pressure does not correlate with ventricular stroke volume in this situation. There are at least three potential mechanisms by which stroke volume may be preserved during a fall in ventricular filling pressure.

The fall in pressure could occur without a significant fall in volume if the ventricle functions on the vertical limb of the pressure-volume curve. Left ventricular volume could also be preserved if an improvement in right ventricular function allowed increased left ventricular compliance. The relationship between right and left ventricular function has been emphasized by Yin et al. and Baker et al. and may relate partly to the mutual constraint of the ventricles by the pericardium.

It has been shown that patients with heart failure can undergo diuresis without a change in left ventricular echocardiographic dimension. However, echocardiographic measurement of dilated ventricles may not reflect small changes in volume.

If diastolic volume were unchanged, stroke volume would be preserved. However, as an alternative explanation, even if ventricular volume were decreased, stroke volumes could be preserved if there were compensatory benefits of decreased ventricular volume. Although adequate preload is necessary for optimal sarcomere overlap, in the normally compliant ventricle this occurs with a left ventricular filling pressure of 10 to 12 mm Hg. Ventricular volumes above the optimum merely exhaust preload reserve and contribute to increasing wall tension (T = PR/h by Law of La Place). This imposes an increased mechanical burden on left ventricular performance by necessitating greater energetic effort to develop the appropriate wall tension. Additionally, the myocardial oxygen supply-demand relationship is adversely affected both by the need for greater energetic support for the wall tension and the reduction in coronary diastolic filling gradient consequent to the increased left ventricular diastolic pressure. In this study ventricular size and wall thickness were not measured, so wall stress could not be determined. However, reduction in ventricular volume should reduce the requisite wall tension, with both mechanical and energetic benefit to the failing heart. Reduction of filling volume below that required for optimal sarcomere overlap may have opposing effects on ventricular performance; the balance between these effects depends on such factors as coronary reserve, ventricular wall thickness, and myocardial energetic state.

A third explanation for the maintenance of stroke volume depends on the presence of significant mitral regurgitation. Effective forward stroke volume could be preserved if the regurgitant fraction were reduced by a decrease in ventricular volume. Mitral regurgitation has been commonly observed in patients with dilated heart failure as a result of coronary artery disease and idiopathic cardiomyopathy in whom the geometry of the mitral apparatus is distorted. The reduction in primary mitral regurgitation that has been shown with vasodilator therapy may result not only from the
decreased systemic vascular resistance, but also from a concomitant reduction in ventricular volume.

This study was designed to determine the lowest filling pressure that could be achieved on standard therapy. Although it has been our experience that normal filling pressures cannot be achieved in individuals with severe dilated heart failure without both vasodilation and diuresis, the separate role of each was not determined. This was a short-term study that did not attempt to address the long-term hemodynamic effects of normal filling pressures in patients with congestive heart failure. Although the upright posture was demonstrated to be well tolerated, exercise or sudden afterload stress might require more volume reserve. This study was not designed to assess long-term survival, but preliminary information is available. While the high early mortality of patients in whom normal PCW was not achieved was due to circulatory failure, death among the larger group was usually sudden. The initial mortality of 20% and total mortality of 40% are comparable to those reported by others for patients with disease of this clinical and hemodynamic severity.15, 16

It has not been established whether or not normal filling pressures can be maintained over a long term, and if so, what benefits on functional status and survival can be gained.

For patients with class III or IV dilated heart failure, dyspnea is the most disabling symptom. Because orthopnea and dyspnea at rest appear to be related to elevated filling pressures, maintenance of normal filling pressures might be expected to prevent these symptoms. The dyspnea that occurs with prolonged activity or with formal exercise testing appears to be multifactorial and may include reflex responses to tissue hypoxia.17 The impact of normal resting filling pressures on this dyspnea will be difficult to separate from the concomitant effects of the vasodilator therapy on cardiac output and peripheral perfusion.

The long-term maintenance of normal filling pressures might serve not only to improve symptomatic status, but also to retard the progression of dilated heart failure. Decreased wall tension in the left ventricle may decrease secondary ischemic injury and limit further ventricular dilatation, while normal left-sided filling pressure may allow preservation of right ventricular function. The full potential of “afterload reduction”18 for treatment of dilated heart failure may not be realized until the internal ventricular load and that imposed by the peripheral circulation have been optimally reduced. In conclusion, this short-term study demonstrates that normal filling pressures can be achieved with vasodilators and diuretics in patients with severe dilated heart failure without compromise of cardiac output. The feasibility and utility of maintaining normal filling pressures over the long term has not been established.

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References
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