Studies on Starling’s Law of the Heart

IX. The Effects of Impeding Venous Return on Performance of the Normal and Failing Human Left Ventricle

By John Ross, Jr., M.D., and Eugene Braunwald, M.D.

In the experiments performed on the canine heart-lung preparation, Patterson, Piper, and Starling observed that when venous return was augmented, cardiac performance initially increased, but when venous return was elevated beyond a critical level, the performance progressively declined, i.e., there was a descending limb of the Starling curve. During the past 20 years a number of studies have been carried out in order to determine whether or not the human heart also exhibits a descending limb of the Starling curve. This problem has been explored by acutely reducing the venous return to the heart by either mechanical or pharmacologic means and determining the induced changes in the cardiac output, and in the venous, right atrial, or right ventricular end-diastolic pressures. In general, these studies have indicated that in patients without congestive heart failure, impeding the venous return results in a fall in the cardiac output, whereas in patients with congestive heart failure, small increases in cardiac output sometimes occur. In some of the studies the relationships between the changes in right heart filling pressure and cardiac output were inconsistent. It appeared that a more direct approach to this problem could be achieved by relating the end-diastolic pressure of the left ventricle to the mechanical activity of this chamber during alterations of venous return. In the present investigation, venous return was impeded by progressively inflating a balloon in the inferior vena cava while left ventricular end-diastolic pressure, output, and work were measured. The studies were performed in patients with and without clinical and hemodynamic evidence of left ventricular disease.

Methods

Fourteen patients were studied in the post-absorptive state after premedication with 100 mg. of sodium pentobarbital. An indwelling needle was placed into the brachial artery, and catheterization of the left ventricle was performed by either the transseptal or retrograde arterial technic. A specially constructed catheter with a balloon at its tip, similar to the one designed and employed by Farber and Eichna, was then inserted through a saphenous vein. The rubber balloon had a capacity of approximately 60 ml.; a second lumen of the catheter opened proximal to the balloon to permit measurement of the pressure in the vena cava distal to the balloon. Under fluoroscopic guidance the tip of the catheter was positioned just caudad to the liver. A small amount of contrast material was added to the saline used for inflating the balloon.

Left ventricular pressure was recorded both at low and high sensitivities simultaneously with the systemic arterial pressure; cardiac output was measured by the indicator-dilution technic, as described previously. Left ventricular stroke work index was calculated from the formula

\[ \frac{SV \times (LVS - LVED) \times 1.36}{100 \times BSA} \]

where \( SV \) equals the stroke volume in ml., \( LVS \) equals the mean left ventricular pressure during ejection, determined by planimetric integration, \( LVED \) equals the left ventricular end-diastolic pressure expressed in mm. Hg and BSA equals body surface area in M.²

Following the measurement of pressures and cardiac output during the control period, the balloon was slowly inflated until a discernible fall in left ventricular end-diastolic pressure had occurred, and after a period of stabilization, all of the measurements were repeated. In some of the patients the balloon was then gradually inflated further, pressure and flow were determined.


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Circulation, Volume XXX, November 1964 719
### Table 1

**Clinical and Basal Hemodynamic Findings in the Patients Studied**

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>ECG</th>
<th>Funct. class</th>
<th>HR</th>
<th>Syst. art. pr. S/D</th>
<th>LV. pr. S/ED</th>
<th>C.I. L./min./M.²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.F.</td>
<td>40</td>
<td>F</td>
<td>Funct. murmur</td>
<td>Normal</td>
<td></td>
<td>102</td>
<td>107/54</td>
<td>102/4</td>
<td>4.13</td>
</tr>
<tr>
<td>P.C.</td>
<td>16</td>
<td>M</td>
<td>Postop. PS</td>
<td>RVH</td>
<td>I</td>
<td>90</td>
<td>117/77</td>
<td>112/7</td>
<td>3.38</td>
</tr>
<tr>
<td>W.O.</td>
<td>15</td>
<td>M</td>
<td>Circulatory hyperkinesia</td>
<td>Normal</td>
<td></td>
<td>96</td>
<td>164/86</td>
<td>143/6</td>
<td>5.57</td>
</tr>
<tr>
<td>C.D.</td>
<td>19</td>
<td>M</td>
<td>Postop. PS</td>
<td>RVH</td>
<td>I</td>
<td>82</td>
<td>112/75</td>
<td>112/10</td>
<td>2.84</td>
</tr>
<tr>
<td>L.H.</td>
<td>18</td>
<td>M</td>
<td>Circulatory hyperkinesia</td>
<td>Probable</td>
<td></td>
<td>72</td>
<td>130/65</td>
<td>120/15</td>
<td>4.34</td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.U.</td>
<td>44</td>
<td>M</td>
<td>CM</td>
<td>IVCD, 1*Bl.</td>
<td>IV</td>
<td>72</td>
<td>123/86</td>
<td>122/21</td>
<td>1.33</td>
</tr>
<tr>
<td>J.W.</td>
<td>53</td>
<td>M</td>
<td>CM</td>
<td>Low EMF, RAE</td>
<td>IV</td>
<td>96</td>
<td>128/73</td>
<td>125/5</td>
<td>2.88</td>
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<tr>
<td>J.H.</td>
<td>51</td>
<td>M</td>
<td>ASCVD</td>
<td>AMI</td>
<td>III</td>
<td>100</td>
<td>98/70</td>
<td>96/21</td>
<td>1.66</td>
</tr>
<tr>
<td>C.De.</td>
<td>35</td>
<td>M</td>
<td>CM</td>
<td>IVCD, LVH, LAE</td>
<td>III</td>
<td>96</td>
<td>138/89</td>
<td>138/48</td>
<td>2.12</td>
</tr>
<tr>
<td>L.M.</td>
<td>19</td>
<td>F</td>
<td>CM</td>
<td>LVH, RVH, RVCD</td>
<td>II</td>
<td>114</td>
<td>140/75</td>
<td>123/16</td>
<td>3.95</td>
</tr>
<tr>
<td>I.G.</td>
<td>48</td>
<td>M</td>
<td>Familial CM</td>
<td>IVCD, LAD, LAE, 1*Bl.</td>
<td>II</td>
<td>75</td>
<td>132/77</td>
<td>122/10</td>
<td>1.98</td>
</tr>
<tr>
<td>I.G.</td>
<td>50</td>
<td>M</td>
<td>CM</td>
<td>LBBB</td>
<td>IV</td>
<td>84</td>
<td>95/58</td>
<td>104/34</td>
<td>2.12</td>
</tr>
<tr>
<td>J.T.</td>
<td>29</td>
<td>M</td>
<td>CM</td>
<td>LVH, LAE</td>
<td>II</td>
<td>114</td>
<td>113/75</td>
<td>111/27</td>
<td>4.32</td>
</tr>
<tr>
<td>G.S.</td>
<td>43</td>
<td>M</td>
<td>CM</td>
<td>LVH</td>
<td>II</td>
<td>48</td>
<td>140/65</td>
<td>121/23</td>
<td>2.46</td>
</tr>
</tbody>
</table>

*Abbreviations: Funct. Class = N. Y. Heart Association Classification; HR = heart rate; Syst. art. pr. S/D = systemic arterial pressure, systolic/diastolic; LV pr. S/ED = left ventricular pressure, systolic/end-diastolic; C.I. = cardiac index; Funct. murmur = functional heart murmur; Postop. PS = postoperative pulmonic stenosis; CM = cardiomyopathy; ASCVD = arteriosclerotic cardiovascular disease; RVH = right ventricular hypertrophy; LVH = left ventricular hypertrophy; IVCD = intraventricular conduction defect; RVCD = right ventricular conduction defect; EMF = electromotive force; RAE = right atrial enlargement; LAE = left atrial enlargement; LAD = left axis deviation; LBBB = left bundle-branch block; AMI = old anterior myocardial infarction; 1*Bl. = first-degree heart block.*
again and the balloon was deflated. When the balloon was maximally inflated, the venous pressures measured in the inferior vena cava distal to the balloon averaged 23 mm. Hg. In one patient (C.De), balloon inflation was performed twice in the course of a single cardiac catheterization, and both of these studies are included in the figures. There were no untoward reactions to these procedures.

**Clinical Material**

The 14 patients ranged in age from 15 to 51 years (table 1). There were five patients without clinical evidence of left ventricular disease (group I). Two of these patients had previously undergone surgical correction of valvular pulmonic stenosis; at postoperative cardiac catheterization one patient (P.C.) was found to have no residual pressure gradient between the right ventricle and the pulmonary artery, and the other (C.D.), had a systolic gradient of 65 mm. Hg. Two other patients (W.O. and L.H.) exhibited mild systolic arterial hypertension and elevated cardiac indices, and were considered to represent examples of the hyperkinetic circulatory state. The fifth patient (E.F.) had a functional cardiac murmur and no organic heart disease. All five of these patients were without symptoms of diminished cardiac reserve and none was receiving digitalis.

There were nine patients with left ventricular dysfunction (group II). The diagnosis in eight of them was considered to be cardiomyopathy, one of a familial variety (I.Gl.). The ninth patient (J.H.) had arteriosclerotic cardiovascular disease and a history of myocardial infarction. All nine patients in group II had symptoms of diminished cardiac reserve; four of them were considered to be in functional class II (N.Y.H.A.), two patients were in functional class III, and three were in functional class IV. None of the patients was considered to have aortic or mitral valvular regurgitation, and all of them were in sinus rhythm. All nine patients exhibited roentgenographic evidence of cardiomegaly with left ventricular enlargement, had abnormal electrocardiograms, and were receiving digitalis (table 1).

**Results**

**Group I.** In the five patients without clinical evidence of disease involving the left ventricle, the cardiac indices prior to inflation of the balloon were normal or slightly elevated, and in four patients the left ventricular end-diastolic pressures were within normal limits (table 1). One patient (L.H.) with the hyperkinetic circulatory syndrome, exhibited a slightly elevated left ventricular end-diastolic pressure of 15 mm. Hg. In every patient in this group, balloon inflation resulted in a decline in left ventricular end-diastolic pressure. The maximum reductions ranged from 2 to 12 mm. Hg, and averaged 5 mm. Hg. In each instance the fall in the left ventricular end-diastolic pressure was accompanied by a reduction in the cardiac index, which ranged from 0.43 to 3.12 L./min./M.², and averaged 1.43 L./min./M.² (fig. 1). In four of the five patients, some increase in the heart rate occurred, although one of these four patients (W.O.) showed a biphasic response (fig. 2); in the fifth patient no change in heart rate was noted. The stroke volume, left ventricular systolic pressure, and the minute work decreased in all five patients (figs. 2 and 3). In four of the five patients the maximum decreases in the systemic arterial diastolic pressures ranged from 0 to 12 mm. Hg; and averaged 7 mm. Hg, in the fifth patient a larger decline occurred (fig. 4). The ventricular function

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

Relationship between cardiac index and left ventricular end-diastolic pressure before and during balloon inflation. The open circles and dashed lines represent the patients in group I; the closed circles and solid lines indicate the patients in group II. The control measurement in each patient is shown next to the patient’s initials; the arrows point to the measurements made during maximal inflation of the balloon in each patient.
The maximum changes in heart rate, left ventricular systolic pressure (LVS Pr.), and minute work index (MWI) induced by balloon inflation in the patients in groups I and II. The biphasic response in heart rate in patient W.O. is indicated by the dotted line, the arrow pointing to the heart rate change during maximum inflation of the balloon. The open circles indicate the changes occurring during the second balloon inflation in patient C.De.

The relationship between the stroke volume index (SVI) and the left ventricular end-diastolic pressure before and during balloon inflation in the patients studied. Symbols are the same as those in figure 1.

Curves, i.e., the relationships between the left ventricular stroke work and left ventricular end-diastolic pressure, are shown in figure 5. It is apparent that in every instance, decreases in the left ventricular end-diastolic pressures were accompanied by reductions in the left ventricular stroke work indices.

Group II. The cardiac indices during the control periods prior to inflation of the balloon were below normal (<2.50 L./min./M.²) in six of the nine patients in this group (table 1). The left ventricular end-diastolic pressures were elevated (>12 mm. Hg) in seven of the patients and within normal limits in the other two (table 1). In all of the patients in group II, balloon inflation resulted in reductions in left ventricular end-diastolic pressures, which ranged from 2 to 17 mm. Hg and averaged 10 mm. Hg. Associated with these changes were declines in the cardiac indices in eight of the nine patients, which ranged from 0.23 to 1.61 and averaged 0.61 L./min./M.²; in one patient (C.De.) no change in the cardiac index occurred (fig. 1). The changes in heart rate were variable (fig. 2). The left ventricular systolic pressure decreased during balloon inflation in every patient; in eight patients the stroke volume diminished (figs. 2 and 3), while in the ninth (C.De.) there was no
change of this variable. The minute work was reduced in six patients and essentially unchanged in three (fig. 2). The maximum changes in the systemic arterial diastolic pressures ranged from +5 mm. Hg to −19 mm. Hg, and averaged −8 mm. Hg (fig. 4).

The ventricular function curves of the patients in group II were generally flatter than those in group I, i.e., larger changes in the left ventricular end-diastolic pressures were associated with smaller changes in the left ventricular stroke work (fig. 5). However, the changes in the left ventricular stroke work and in the left ventricular end-diastolic pressure were directionally similar to those observed in the patients in group I, reductions in the left ventricular stroke work being associated with decreases in the left ventricular end-diastolic pressures in eight of the patients; in one patient (C.De.), the stroke work index remained essentially unchanged in spite of a fall in left ventricular end-diastolic pressure.

Figure 4

The systemic arterial diastolic pressures in the patients in group I (upper panel) and group II (lower panel) plotted against the decreases in the left ventricular end-diastolic pressures (LVED). The control values for the systemic arterial diastolic pressures prior to balloon inflation are shown on the left (0 on the abscissa), and the maximum changes occurring with balloon inflation are indicated by the arrows.

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Discussion

In previous investigations concerned with the effects of impeding the venous return to the heart, right heart filling pressures were measured and correlated with the cardiac output. When phlebotomy was performed, or occluding cuffs on the extremities were inflated, a fall or no change in the cardiac output has been reported to occur in patients without congestive heart failure; in most but not in all instances, these maneuvers resulted in decreases of the right heart filling pressures. In patients with congestive heart failure, a small rise in the cardiac output has usually been observed during these maneuvers, whereas the right heart filling pressures have again responded inconsistently. When hydralazine, Arfonad, or sodium nitrite has been given to reduce venous return, right heart filling pressures diminished both in patients with and without congestive heart failure; the cardiac output tended to diminish in the former group and to increase in patients with congestive heart failure. Some of these studies have been interpreted as indicating that the normal heart operates on an ascending limb of the Starling curve, but the failing heart, being improved by im-
generally resulting in flatter left ventricular function curves in this group than in the patients with normal left ventricles (fig. 5).

There are several possible reasons for the differences between the results of the present investigation and those of previous studies. First, some of the earlier studies were carried out before the development of reasonably accurate methods for the measurement of cardiac output in man. Secondly, many of the patients with heart failure who were the subjects of previous investigations suffered from valvular defects, with variable degrees of regurgitation, or from hypertensive heart disease. In the patients with valvular regurgitation, since only the net forward flow could be measured, total ventricular output was not assessed. It seems possible that in the presence of regurgitant lesions, diminutions in heart size or increases in heart rate induced by diminishing venous return could have reduced the regurgitant stroke volume sufficiently so that total ventricular output might have fallen while the measured forward flow increased. In the patients with left ventricular failure secondary to systemic hypertension, it seems likely that lowering the systemic arterial pressure alone could improve the cardiac output.

Thirdly, it must be emphasized that the earlier studies were carried out before left heart catheterization was available for physiologic studies. With the exception of the investigation by Sobol et al. in which pulmonary artery wedge pressures were recorded, in all of the other investigations right heart filling pressure was estimated or measured, while the great majority of the patients with congestive heart failure who were studied had disease primarily involving the left ventricle. Sarnoff and Berglund have stressed the importance of relating left ventricular function to left heart filling pressures and have pointed out the difficulties that may arise when left ventricular performance is correlated with right heart filling pressures. Furthermore, the use of mean atrial pressure as an index of ventricular end-diastolic pressure, or the use of pulmonary artery wedge

Figure 6
Roentgenogram of the chest in patient S.U., showing generalized cardiomegaly.

peding venous return, operates on a descending limb.

In the present study, in which left ventricular end-diastolic pressure was correlated with alterations in left ventricular function, it was observed that during the steady state following obstruction of systemic venous return to the heart in patients with and without clinical and hemodynamic evidence of impaired left ventricular function, a fall in the left ventricular end-diastolic pressure always occurred which, with a single exception, was accompanied by a reduction in the cardiac output. Furthermore, in all patients without left ventricular disease, and in all but one of the patients with left ventricular disease, the reductions in left ventricular end-diastolic pressure and in the cardiac indices were accompanied by decreases in stroke volume and left ventricular stroke work. It is notable, however, that these reductions in stroke volume and stroke work were less striking in the patients with left ventricular dysfunction,
pressure as an index of left ventricular end-diastolic pressure may be invalid.\textsuperscript{17, 18} Fourthly, the total effect of the drugs employed in some studies to reduce venous return is uncertain. Relatively large changes in aortic pressure occur when Arfonad is administered, and it is possible that this ganglion-blocking agent may also diminish sympathetically mediated stimulation of the myocardium. Thus, the etiology of the changes in cardiac output observed during the administration of this drug may be complex, as was recognized by Sobol et al.\textsuperscript{9} and by Eichna.\textsuperscript{11} Finally, in some of the patients in previous studies, more severe depression of ventricular function may have existed, or the patients may have been studied during a relatively more acute stage of congestive heart failure than the patients reported herein; under such circumstances, it is possible that the left ventricle can indeed be pushed on to a descending limb of the function curve.

Several basic mechanisms could be of importance in considering the hemodynamic responses to reduced venous return in the patients without impaired left ventricular function. It has been shown in the isolated papillary muscle contracting isotonically that the work performed is dependent both on the preload, which is analogous to the end-diastolic fiber length in the intact ventricle, and on the afterload, which is analogous to the aortic diastolic pressure in the intact organism.\textsuperscript{19} It has also been clearly demonstrated by Sarnoff and his associates\textsuperscript{20} in the isolated, metabolically supported dog heart that when blood is progressively infused, the stroke volume and stroke work are functions of the left ventricular end-diastolic pressure, provided aortic pressure, heart rate, and the catecholamine background remain constant;\textsuperscript{20} under these conditions, in contrast to those existing with the standard heart-lung preparation,\textsuperscript{1, 2} a descending limb of the left ventricular function curve cannot be readily demonstrated.\textsuperscript{16} Similarly, a descending limb was never seen in a series of closed-chest, unanesthetized dogs subjected to large infusions of whole blood.\textsuperscript{21} In addition, it has been demonstrated experimentally that the left ventricle responds to changes in aortic pressure within a certain range with little or no alteration in the left ventricular end-diastolic pressure or stroke volume.\textsuperscript{22, 23} It therefore seems unlikely that the relatively small reductions in the aortic diastolic pressures that occurred in this investigation (fig. 4) were directly responsible for the observed decreases in the left ventricular end-diastolic pressures that took place; thus, the concomitant reductions of left ventricular end-diastolic pressure, cardiac output, stroke volume and work observed in this study suggest that the performance of the ventricle was a function of its end-diastolic pressure. These data provide further evidence for the applicability of Starling's law to the nonfailing left ventricle of man, and suggest that in patients without congestive heart failure the left ventricle operates on the ascending limb of a Starling curve.

When considering the responses of the patients with impaired left ventricular function, it is pertinent to recall that a decrease in the external work and power of isolated heart muscle preparations can readily be shown when the resting length is stretched beyond a critical level.\textsuperscript{19} Similarly, in the unsupported canine heart-lung preparation, in which ventricular performance is considered to be impaired, left ventricular stroke volume and left ventricular stroke work diminish when filling pressure is raised beyond an optimum point.\textsuperscript{2, 3} In addition, in depressed hearts, the stroke volume and left ventricular end-diastolic pressure are no longer independent of the aortic pressure, and elevating aortic pressure causes a fall in the left ventricular stroke volume and stroke work and a rise in left ventricular end-diastolic pressure.\textsuperscript{22, 23} Similarly, it has recently been shown that, when aortic pressure is increased by the infusion of angiotensin, in some patients with impaired left ventricular function the elevation of left ventricular end-diastolic pressure that ensues is accompanied by a fall in the left ventricular stroke volume and stroke work.\textsuperscript{24} It appears, then, both from experimental and clinical studies, that a descending limb of the Starling
curve can be readily demonstrated when an additional work load is imposed on a heart with impaired function.

It was therefore anticipated that if the left ventricle of a patient with cardiac dysfunction were operating on a descending limb of the ventricular function curve under relatively basal conditions, improvement in ventricular performance (elevation of cardiac output, stroke volume, minute work or stroke work) would result from reduction of the existing left ventricular end-diastolic pressure. The results of the present investigation indicate that this was not the case in any of the nine patients studied, even though in some of them the ventricular end-diastolic pressures were strikingly elevated and the hearts were greatly enlarged (fig. 6). Indeed, the reductions in the left ventricular end-diastolic pressures that occurred in these patients were almost invariably associated with falls in stroke volume and stroke work. In these patients, as in those with normal left ventricles, relatively small and variable changes in the aortic diastolic pressures occurred (fig. 4). It therefore appears that, when venous return is impeded, the Starling relationship applies to the depressed human left ventricle in a manner qualitatively similar to that observed in patients without left ventricular disease. However, while the nonfailing ventricle is on a steeply ascending limb of the Starling curve, the failing ventricle is on a flattened, depressed curve. It is appreciated that the reduction in heart size, which probably accompanied inflation of the balloon, would favorably influence the relationship between ventricular wall tension and intraventricular pressure through the operation of Laplace's law,²⁴,²⁶ and would thereby tend to lower the heart's oxygen requirements and improve cardiac efficiency; nevertheless, in the patients with heart failure reported herein, the external performance of the left ventricle did not improve when ventricular end-diastolic pressure was reduced, and it is suggested from these and previous studies²⁴ that a descending limb of the left ventricle's Starling curve may become apparent only with the imposition of an added work load.

Summary

The acute circulatory responses to impeding venous return to the heart by the inflation of a balloon in the inferior vena cava were determined in 14 patients undergoing left heart catheterization. In the five patients without clinical or hemodynamic evidence of impaired left ventricular function, left ventricular end-diastolic pressure fell, and the decrease was accompanied by reductions in the cardiac index, left ventricular stroke volume, and left ventricular stroke work. In nine patients with impaired left ventricular function, directionally similar responses were noted, although the left ventricular function curves relating left ventricular end-diastolic pressure to left ventricular stroke work were generally flatter and lower than those in the patients without left ventricular disease. In none of the patients did a significant increase in cardiac index, stroke volume, or left ventricular stroke work occur during inflation of the balloon. It is concluded that the Starling relationship appears to operate in a directionally similar manner both in the normal and the depressed human left ventricle, and that the left ventricles of patients with impaired function are not on a descending limb of the curve. However, a descending limb of the left ventricular Starling curve may become apparent when an additional work load is imposed on the diseased ventricle.

Addendum

Since this paper was submitted, M. A. Sackner et al. have published a paper (Am. J. Cardiol. 13: 782, 1964) in which the effects of restricting venous return on circulatory dynamics were studied in patients with and without heart failure. Although no patients with severe failure were studied, no evidence for a descending limb of the Starling curve was found in patients considered to have mild or moderate degrees of heart failure.

References


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Circulation. 1964;30:719-727
doi: 10.1161/01.CIR.30.5.719

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