The Effect of Increasing Preload on Ventricular Output and Ejection in Man

Limitations of the Frank-Starling Mechanism

DENNIS T. MANGANO, PH.D., M.D., DONALD C. VAN DYKE, M.D., AND ROBERT J. ELLIS, M.D.

SUMMARY The effects of preload augmentation on left ventricular output (Frank-Starling mechanism), ejection fraction, and the relationship between pulmonary wedge pressure and end-diastolic volume were studied in 15 patients immediately after myocardial revascularization. The patients were studied under morphine sulfate anesthesia with the chest temporarily closed. Sequential measurements of radionuclide ejection fraction, thermodilution cardiac output, and systemic and pulmonary arterial pressures were made before and after infusion of 500, 1000, 1250 and 1500 ml of whole blood. Cardiac performance was assessed by means of (1) ventricular function curves (stroke volume and stroke work vs end-diastolic volume); (2) sequential changes in ejection fraction and end-systolic volume; (3) the relationship between pulmonary capillary wedge pressure (PCW) and end-diastolic volume; and (4) changes in estimated wall tension.

Volume transfusion increased the left ventricular end-diastolic volume index (EDVI) from an average control value of 41 ml/m² to 88 ml/m² (after infusion of 1500 ml of whole blood), and increased PCW from 2 mm Hg to 8 mm Hg. Although cardiac index increased (2.1 to 3.6 l/min/m²) and left ventricular stroke work index increased (20 to 38 g-m/m²), the largest increases occurred when EDVI was less than 70 ml/m² and PCW less than 7 mm Hg. Above these values the ventricular function curves were relatively flat. In contrast, ventricular ejection progressively decreased with increasing preload. Ejection fraction decreased from 0.70 to 0.49 and end-systolic volume index increased from 13 ml/m² to 45 ml/m², despite a decreasing systemic vascular resistance.

Thus, in these patients: (1) the Frank-Starling mechanism plays little role in augmentation of stroke volume above a PCW of 7 mm Hg or an EDVI of 70 ml/m²; (2) increases in ventricular output achieved by increasing preload were accompanied by decreases in ventricular ejection fraction; and (3) the filling pressure (volume) associated with maximal ejection fraction was significantly lower than that associated with maximal ventricular output.

STARLING'S LAW of the heart and the associated Frank-Starling mechanism characterize cardiac performance in terms of ventricular function curves.1,2 These curves express the functional consequences of alterations in preload, and serve as the rationale for improvement of cardiac output by volume administration. Studies in animals and man have attempted to define the relationship between ventricular output (stroke work, stroke volume) and filling pressure (end-diastolic, pulmonary wedge, central venous) in normal and disease states.3-11 In patients with significant ventricular dysfunction, the maximal ventricular output is lower than in normal patients and is achieved at higher filling pressures, in some cases 18 mm Hg or more.4,6,11 These results have served as guidelines for volume transfusion therapy in patients with depressed ventricular function.4,6,11 Maximal ventricular work or volume output could be achieved by progressive volume infusion until the "optimal" filling pressure is obtained.

Although progressive increases in filling pressure due to volume loading may increase ventricular output, it is not certain whether other indexes of ventricular function, such as ejection fraction and end-systolic volume, improve as well. If they do, the benefits of volume loading should include improved output and ejection; on the other hand, volume loading may result in diminished ejection fraction and may alter the choice of an optimal filling pressure. These considerations are especially important after cardiopulmonary bypass, when the heart must satisfy the perfusion requirements of the rest of the body as well as maintain adequate ejection to overcome the stresses encountered during cardiac surgery. Accordingly, we determined ventricular function in the immediate postbypass period, and evaluated the effects of increasing filling pressure by volume loading on ejection fraction and end-systolic volume, as well as on ventricular stroke work and stroke volume.

Methods

The protocol for this study was approved by the Committee on Human Research of the University of California, San Francisco, and informed consent was obtained from all patients.

Fifteen men, ages 39–64 years, admitted for coronary artery surgery because of unstable angina (seven patients) and stable progressive angina (eight patients) were studied. Thirteen had one or more myocardial infarctions before admission. None had valvular disease, a history of right- or left-heart failure, or...
evidence of right or left ventricular hypertrophy or
dilation. None had evidence of mitral regurgitation
using left ventriculography. Cardiac catheterization
revealed 90% stenosis of two or more coronary
arteries, ejection fractions of 0.39–0.82 (normal 0.66
± 0.06), left ventricular end-diastolic volume indexes
of 44–107 ml/m² (normal 70 ± 20 ml/m²), pulmo-
rary capillary wedge pressures of 1–14 mm Hg,
and central venous pressures of 0–9 mm Hg.
Medications included isosorbide and nitroglycerin
in all patients, and oral propranolol (40–160 mg four
times per day) in 13 patients. Medications were con-
tinued until 8 hours before surgery.

All patients were premedicated with morphine sul-
fate (10 mg i.m.) and oral diazepam (10 mg).
Anesthesia consisted of morphine sulfate (1.5–3
mg/kg i.v.) and diazepam (0.25–0.50 mg/kg i.v.).
Pancuronium (0.1 mg/kg i.v.) provided muscle relaxa-
tion, and ventilation (with 100% oxygen) was con-
trolled. Hemodynamics were monitored by means of
radial artery and triple-lumen thermodilution pul-
monary artery catheters. All pressure measurements
were recorded on a Gilson polygraph from equi-
sensitive Bell and Howell transducers calibrated with
a mercury manometer. Before each set of mea-
surements, the zero reference point was located 5 cm
posterior to the sternal angle in a direction perpen-
dicular to the frontal plane of the chest.

Ejection fraction was measured from radio-
cardiograms obtained with a coaxial cardiac scintil-
lum probe. The radiocardiogram is a recording of the
amount of a blood-borne bolus of radionuclide in the
heart chambers as a function of time, and is generated
from the first pass of the bolus through the central cir-
culation. Figure 1 shows a typical radiocardiog-
gram from a normal subject and illustrates the method
of measuring ejection fraction directly from the dual
time-activity (strip chart) recording as the difference
between diastolic and systolic counts divided by the
difference between diastolic and background
(baseline) counts.

The probe was positioned over the left ventricle to
record the passage of 1.5 mCi of 99mTc-sodium
eptecheteinate injected into the right atrial orifice of
the thermodilution catheter. The probe incorporates a
central, collimated detector that accepts gamma
photons primarily from the left ventricle, surrounded
by an annular detector collimated for simultaneous
monitoring of background activity around the left ven-
tricle. High-frequency recording of count rate
from within the left ventricle, when corrected for
counts from surrounding structures, provides an ac-
curate measure of left ventricular ejection frac-
tion.

The radionuclide was flushed through the catheter
with the cold solution so that thermodilution cardiac
outputs and radioisotope images were recorded si-
multaneously for all measurements. The position of
the radionuclide probe was not altered throughout the
measurement periods. All measurements were made
at end-expiration. Given stroke volume from ther-
modilution (cardiac output divided by heart rate) and
left ventricular ejection fraction from radio-
cardiography, left ventricular end-diastolic volume can
be calculated as stroke volume divided by ejection frac-
tion. Because regurgitant flow would invalidate this
formula, patients with valvular incompetence were ex-
cluded from the study. In patients with coronary
artery disease without valvular regurgitation, the cor-
relation of end-diastolic volume determined from
cineangiographic and radioisotope images is 0.88.

During cardiopulmonary bypass, cold cardioplegia
was used for myocardial protection. Ischemic arrest
time averaged 51 ± 4 minutes (range 35–74 minutes),
and 3.4 vessels per patient (average) were bypassed.

Cardiopulmonary bypass was discontinued at the
lowest pulmonary capillary wedge pressure to main-
tain a systolic blood pressure greater than 75 mm Hg.
After the administration of protamine, the aortic and
vena cava cannulas were removed, and the sternum
was temporarily reaproximated. Surgery was
stopped, the probe was placed over the left ventricle
and a 5-minute period of hemodynamic stability was
established (systolic blood pressure varying by less
than 10 mm Hg and heart rate varying by less than 5
beats/min). The following values were recorded at
end-expiration: radial artery systolic and diastolic
pressures, heart rate, pulmonary artery systolic and
diastolic, central venous and pulmonary capillary
wedge pressures, radionuclide ejection fraction, and
two thermodilution cardiac outputs (within 10%).

After these control measurements, progressive volume
loading was begun. A total of 1500 ml of whole blood
was transfused into a peripheral vein over 30 minutes.
The hemodynamic measurements were repeated after
infusion of 500, 1000, 1250 and 1500 ml.

No pharmacologic agent was given and no
respiratory adjustment was made for 15 minutes
before or during the measurement period.

Data were analyzed using two-way analysis of
variance comparing hemodynamics at each volume

![Figure 1](http://circ.ahajournals.org/attachment/2017/09/19/20170915140404/Figure1.jpg)

**Figure 1.** A typical radiocardiogram obtained from a coaxial probe system with time-activity curves from the left ventricle (central port) and background (annular detector). EF = ejection fraction.
transfusion state with the one immediately preceding. (The control hemodynamics were compared with the 500-ml values, the 500-ml values with the 1000-ml values, and so forth.) In addition, the control values were compared with the 1500-ml values using a paired t test.

**Results**

Figure 2 demonstrates the effects of acute volume loading in one patient. Infusion of 1500 ml of whole blood over 30 minutes significantly (p < 0.05, paired t test) increased end-diastolic volume, and wedge pressure increased from 4 mm Hg to 8 mm Hg. Ventricular output and work both increased. However, ejection fraction progressively decreased, and end-systolic volume rose from 13 to 59 ml/m². No significant change occurred in either systemic vascular resistance or heart rate.

Table 1 summarizes the changes in hemodynamics for all 15 patients. Significant (p < 0.05, paired t test) increases in indexes of ventricular output (cardiac index, stroke work index and blood pressure) were accompanied by decreases in ejection fraction and associated increases in the end-systolic volume index, despite a decreased systemic vascular resistance. Pulmonary capillary wedge pressure and end-diastolic volume increased; PCW increased by approximately 1 mm Hg for each 16-ml increase in end-diastolic volume. For purposes of discussion, an estimate of the left ventricular wall tension at the start of systole (T) was computed from the Laplace relationship. Here, wall thickness is unknown, and T = P × R, where P represents mean systolic blood pressure and the radius (R) is derived from EDV (EDV = 4/3 πR³). Significant increases in T were found in all patients.

In table 2, a comparison of the preoperative catheterization findings with the intraoperative volume loading results is shown for each patient. In most cases the preoperative ejection fraction, pulmonary wedge pressure and left ventricular end-diastolic volume were near the intraoperative ranges. In patient 9, the values for ejection fraction differed significantly. This patient suffered an acute myocardial infarction while on cardiopulmonary bypass.

Ventricular function curves for the 15 patients are shown in figures 3A and 3B. For most patients, the ascending limbs of the stroke volume and end-diastolic volume index curves were not particularly steep (slopes generally less than 0.6), even over the lower range of end-diastolic volumes. These curves flattened at end-diastolic volumes of 70 ml/m² or

<table>
<thead>
<tr>
<th>EDVI (ml/m²)</th>
<th>PCW (mm Hg)</th>
<th>BP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>SVR (dyn-sec/cm²)</th>
<th>CI (ml/min/m²)</th>
<th>SVI (ml/m²)</th>
<th>SWI (g-m/m²)</th>
<th>EF</th>
<th>ESVI (ml/m²)</th>
<th>T (cm dyn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>2.3</td>
<td>88 ± 4</td>
<td>88</td>
<td>1258</td>
<td>2.1</td>
<td>28</td>
<td>20</td>
<td>0.70</td>
<td>13</td>
<td>227</td>
</tr>
<tr>
<td>±3</td>
<td>±0.6</td>
<td>52 ± 2</td>
<td>±5</td>
<td>±1</td>
<td>±0.1</td>
<td>±2</td>
<td>±1</td>
<td>±0.04</td>
<td>±2</td>
<td>±11</td>
</tr>
<tr>
<td>After 1500-ml transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>7.6</td>
<td>113 ± 7</td>
<td>83</td>
<td>1024</td>
<td>3.6</td>
<td>42</td>
<td>38</td>
<td>0.49</td>
<td>47</td>
<td>371</td>
</tr>
<tr>
<td>±6</td>
<td>±0.9</td>
<td>60 ± 4</td>
<td>±4</td>
<td>±8</td>
<td>±0.1</td>
<td>±2</td>
<td>±4</td>
<td>±0.04</td>
<td>±5</td>
<td>±25</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Statistical analysis by paired t test. All changes were significant (p < 0.05), except for heart rate and systemic vascular resistance.

Abbreviations: EDVI = end-diastolic volume index; PCW = pulmonary capillary wedge pressure; BP = blood pressure; HR = heart rate; SVR = systemic vascular resistance; CI = cardiac index; SWI = stroke work index; EF = ejection fraction; ESVI = end-systolic volume index; T = estimate of left ventricular wall tension.
TABLE 2. Comparison of Preoperative and Intraoperative Findings in the 15 Patients

<table>
<thead>
<tr>
<th>Preoperative catheterization findings</th>
<th>Intraoperative volume loading findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt</td>
<td>EF</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>2</td>
<td>0.67</td>
</tr>
<tr>
<td>3</td>
<td>0.39</td>
</tr>
<tr>
<td>4</td>
<td>0.80</td>
</tr>
<tr>
<td>5</td>
<td>0.82</td>
</tr>
<tr>
<td>6</td>
<td>0.70</td>
</tr>
<tr>
<td>7</td>
<td>0.60</td>
</tr>
<tr>
<td>8</td>
<td>0.62</td>
</tr>
<tr>
<td>9</td>
<td>0.72</td>
</tr>
<tr>
<td>10</td>
<td>0.62</td>
</tr>
<tr>
<td>11</td>
<td>0.60</td>
</tr>
<tr>
<td>12</td>
<td>0.82</td>
</tr>
<tr>
<td>13</td>
<td>0.81</td>
</tr>
<tr>
<td>14</td>
<td>0.79</td>
</tr>
<tr>
<td>15</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Refers to the change from the control value to the 1500-ml value.

Abbreviations: EF = ejection fraction; LVEDV = left ventricular end-diastolic volume; PCW = pulmonary capillary wedge pressure.

greater. The ascending limbs of the stroke work and end-diastolic volume index curves were steeper. However, in at least half of these patients a relative flattening can be appreciated at end-diastolic volumes exceeding 70 ml/m².

Figure 3C shows the relationship between the ejection fraction and the end-diastolic volume index. In nine of the 15 patients, the ejection fraction monotonically decreased as the end-diastolic volume index increased. In six patients, an initial increase in ejection fraction preceded its progressive decrease. The average decrease in ejection fraction was 30% (range 9–63%). The average decrease in ejection fraction was 0.30 for each 50 ml/m² increase in the end-diastolic volume index.

The relationship between cardiac index and ejection fraction is shown in figure 4. At each level of infusion (control, 500, 1000, 1250, and 1500 ml), the end-diastolic volume index, pulmonary wedge pressure, ejection fraction and cardiac index were averaged and the standard errors were obtained. The scales of end-diastolic volume-index and pulmonary wedge pressure were chosen such that the normal range of pulmonary wedge pressure (0–12 mm Hg, or 12 mm Hg) corresponded to the normal range of the end-diastolic volume index (50–90 ml/m², or 40 ml/m²). As infusion progressively increased these two measurements, it also increased cardiac index and decreased ejection fraction.

The relationship between pulmonary capillary wedge pressure and end-diastolic volume index is shown in figure 5. We discerned four patterns: (1) In eight of the 15 patients, pulmonary capillary wedge pressure increased progressively with end-diastolic volume index, with an average slope of approximately 10 mm Hg per 50 ml/m². (2) In two patients, the slope was higher (approximately 20 mm Hg per 50 ml/m²). One of these patients (indicated by filled square) had an ejection fraction of 0.76 immediately before bypass and 0.31 immediately after bypass. Evidence of an acute anterolateral myocardial infarction (ECG, CPK-M bands, ⁹⁹mTc pyrophosphate uptake) was found and was assumed to occur during bypass. The second patient (indicated by asterisk) had to be placed
back on bypass because of difficulty with the anastomosis of the left anterior descending coronary artery graft. After this, the volume infusion protocol was performed. (3) In two patients, the pulmonary wedge pressure did not change significantly (less than 3 mm Hg) until an end-diastolic volume index of 55 ml/m² was reached. (4) In three patients, pulmonary capillary wedge pressure increased by 5 mm Hg or less over a large (> 50 ml/m²) range of end-diastolic volume index. We could not correlate these findings with preoperative angiographic ejection fraction, age, number of vessels bypassed or ischemic time.

Discussion

In this study, ventricular function curves showed myocardial depression over normal ranges of left ventricular end-diastolic volumes and pulmonary capillary wedge pressures. In most patients, the ascending limb of the stroke volume curve had a shallow slope, even over the lower range of end-diastolic volumes. In approximately half of the patients, the same was true for the stroke work curves. The stroke volume and stroke work curves both flattened at end-diastolic volumes greater than 70 ml/m². Because these relationships have not been described before, comparisons with other results cannot be made. However, data relating ventricular output to filling pressure in patients without cardiac disease and in patients with congestive heart failure and acute myocardial infarction are available. These results suggest that our ventricular function curves are depressed compared with normal curves, and that our ventricular outputs are similar to those in patients with acute myocardial infarction and congestive heart failure. However, our results diverge from results after infarction or failure because the ascending limb in our studies flattened at normal rather than high values of pulmonary capillary wedge pressure. Several factors may explain these findings. First, four patients had ventricular dyssynergy, and one had a depressed ejection fraction (0.39) preoperatively. Second, the effects of cardioplegic arrest and cardiopulmonary bypass may have reduced myocardial performance. Comparison with the preoperative catheterization data (table 2) reveals that at nearly equivalent end-diastolic volumes, the intraoperative ejection fraction appears to be decreased. Although comparative afterload data are not available, it appears that myocardial performance may be reduced after bypass. Third, pericardial excision before the study may have altered both diastolic compliance and systolic performance.

Fourth, the pulmonary capillary wedge pressure may not reflect the left atrial “kick” component to the end-diastolic pressure, and therefore may underestimate the end-diastolic pressure. One factor that probably did not play a role in terminating the ascent of the ventricular function curve is the anesthetic. Morphine sulfate plus oxygen does not depress contractility at the doses used in this study.

Ejection fraction decreased with volume loading in all patients. In nine patients, ejection fraction progressively decreased as end-diastolic volume increased from control values. In the remaining six patients, a small initial increase in ejection fraction preceded its progressive decrease. Although ejection fraction is affected by changes in preload and afterload, it is a useful indicator of ventricular systolic performance and contractility. Studies in animals and man using ventriculography, echocardiography, and ultrasonic techniques indicate that ejection fraction either increases or remains unchanged as end-diastolic volume increases. However, increases in afterload...
consistently decrease ejection fraction. In our study, ejection fraction progressively decreased despite an increase in end-diastolic volume and a decrease in systemic vascular resistance.

There are two explanations for these results. First, myocardial contractility may have decreased with volume loading. There is evidence that in the control state the patients were relatively hypovolemic (table 2). Thus, contractility may have been enhanced during the early volume loading periods. This is difficult to establish because no direct measurements of contractility were made. However, progressive volume loading increased the rate of rise of the radial artery pressure tracing in all patients. Although this may be a weak index of ventricular contractility, it weighs against the hypothesis that contractility progressively decreased. Second, although systemic vascular resistance either did not change or decreased with volume loading, ventricular afterload may have increased as end-diastolic volume increased (Laplace relationship). To illustrate this effect, we estimated the wall tension at end-systole. The relationships between ejection fraction, systemic vascular resistance, and \( T \) are shown in figure 6. A direct, rather than an inverse, relationship exists between ejection fraction and systemic vascular resistance. However, \( T \) increased by 63% with volume loading, and its relationship with ejection fraction is an inverse one. Thus, changes in \( T \), and not systemic vascular resistance, may have contributed to the decrease in ejection fraction with volume loading. The Laplace effect may play an important role in these patients.

Comparison of the ventricular function curve results with the ejection fraction curve results (fig. 4) reveals that increasing filling pressure by volume loading increases ventricular output; however, ejection fraction decreases and end-systolic volume increases over the range of normal pulmonary capillary wedge pressures and end-diastolic volumes. We hypothesize that the ejection fraction at any end-diastolic volume is the slope of the line drawn from the origin to a point on the stroke volume ventricular function curve at that end-diastolic volume (ejection fraction equals stroke volume divided by end-diastolic volume). Along the flat portion of the ventricular function curve, stroke volume is relatively constant; thus, the ejection fraction (slope) will decrease as end-diastolic volume increases. In our patients, these curves were flat over the normal ranges of end-diastolic volume, and the ejection fraction decreased over these ranges. The ejection fraction and ventricular function curve results are therefore consistent. Based on this interpretation, ejection fraction can be considered as a characterization of the Starling curve, and as such, is an index of the effectiveness of the Starling mechanism. As ejection fraction decreases, a comparatively larger increase in end-diastolic volume is needed to effect the same increase in stroke volume. With further decreases in ejection fraction, use of the Starling mechanism to increase cardiac output is less effective.

In our patients, such a situation exists over the normal ranges of pulmonary wedge pressures and end-diastolic volumes. Though volume loading increased cardiac output, it resulted in a disproportionately increased end-diastolic volume.

The relationship between pulmonary capillary wedge pressure and end-diastolic volume was not consistent in this series of patients, as was suggested in our previous study. It appears that significant biologic variability exists. A pulmonary capillary wedge pressure of 4 mm Hg could be associated with an end-diastolic volume index of 25–110 ml/m². These inconsistencies may be explained by differences in pulmonary, atrial and ventricular diastolic compliance. Steep curves occurred in the two patients who had difficulty during cardiopulmonary bypass (fig. 5, filled square and asterisk). In contrast, the slopes of such curves were relatively flat in the three patients who presented without evidence of preoperative ventricular distension. Pulmonary capillary wedge pressure was a rather insensitive indicator of end-diastolic volume in these three patients.

In conclusion, our results suggest that increasing filling pressure by volume loading has associated benefits and costs. Volume loading from relatively low to normal filling pressures increases ventricular stroke work and stroke volume, but it also increases \( T \). In addition, maximizing ventricular output by increasing filling pressure is associated with a reduction in ejection fraction. Progressive decreases in ejection fraction indicate a decrease in the effectiveness of the Starling mechanism over normal ranges of pulmonary capillary wedge pressure and end-diastolic volume.

Based on the results of this study, we recognize the

**FIGURE 6.** Relationship between ejection fraction and systemic vascular resistance (SVR) (left) and estimated wall tension (\( T \)) (right).
limitations of the Starling mechanism even over normal ranges of filling pressures in this group of patients, and therefore caution against discontinuation from cardiopulmonary bypass at high filling pressures.

Acknowledgment

The authors thank Dr. Robert Hickey of the Veterans Administration Hospital, San Francisco, and Dr. Kaku Chatterjee of the University of California, San Francisco, for advice and encouragement, and Dr. Hal Anger of the Donner Laboratory of Medical Physics, University of California, Berkeley, for providing the coaxial cardiac scintillation probe used in these studies.

References

   (translated by Chapman CB, Wasserman E) Am Heart J 58: 282, 467, 1959
The effect of increasing preload on ventricular output and ejection in man. Limitations of the Frank-Starling Mechanism.
D T Mangano, D C Van Dyke and R J Ellis

Circulation. 1980;62:535-541
doi: 10.1161/01.CIR.62.3.535

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/62/3/535.citation