Effects of Blood Volume Expansion on Left Ventricular Hemodynamics in Man

By V. R. Sanghvi, M.D., F. Khaja, M.D., A. L. Mark, M.D., and J. O. Parker, M.D.

SUMMARY

The hemodynamic effects of acute blood volume expansion with low molecular-weight dextran were studied in 11 normal patients and 18 patients with coronary artery disease free of angina at the time of study and without evidence of heart failure. In the coronary artery disease group 350 ml (range 130–540 ml) was infused at the rate of 26.7 ml/min (range 19–36 ml/min). There was an increase in left ventricular end-diastolic pressure (LVEDP) from 10.3 to 18.7 mm Hg, brachial artery mean pressure (BAm) from 102 to 105 mm Hg, pulse pressure (PP) from 56.7 to 63.2 mm Hg, cardiac index (CI) from 3.1 to 3.8 liters/min/m², stroke index (SI) from 37 to 44 ml/m², and left ventricular stroke-work index (LVSWI) from 46 to 53 g·m/m². There was no change in heart rate. In normal subjects, 387 ml (range 200–480 ml) was infused at the rate of 26.4 ml/min (range 15–37 ml/min). There was an increase in LVEDP from 8.0 to 18.4 mm Hg, PP from 55.5 to 66.8 mm Hg, CI from 3.2 to 4.0 liters/min/m², SI from 38 to 46 ml/m², and LVSWI from 46 to 54 g·m/m². Heart rate and BAm were unchanged. LVEDP increased to abnormal levels in every subject and was associated with small increases in SI and LVSWI. In the absence of myocardial ischemia the challenge of an acute volume did not differentiate left ventricular performance of patients with coronary artery disease from normal subjects.

Additional Indexing Words: Coronary artery disease Dextran Ventricular function

A PPLICABILITY of the Frank-Starling relationship to the intact human heart has been studied intensively over the past several years. Increases in afterload with angiotensin in normal subjects raise left ventricular filling pressure in association with increased stroke work.¹ ² In patients with heart disease, however, the increases in stroke work induce greater elevations of filling pressure. Blood volume expansion with a variety of agents has been utilized to study ventricular function in man, but the results have been variable.⁵–¹⁰ The only report which included information on left ventricular end-diastolic pressure was by Braunwald and associates who were unable to demonstrate a Starling relationship in normal subjects following blood infusion unless sympathetic blockade had been established.⁹ Recently the effects of blood volume expansion with dextran have been studied in patients with acute myocardial infarction, and while left ventricular end-diastolic pressure increased in every patient there were diverse effects on stroke volume.

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and stroke work. Limited data are available on the effects of blood volume expansion on left ventricular hemodynamics in patients with chronic coronary artery disease and in normal subjects. The present study was designed to examine the hemodynamic effects of dextran infusions in such patients.

Methods

Hemodynamic investigations with subsequent selective cinecoronary arteriography and left ventriculography were performed in 28 patients with known or suspected coronary artery disease without clinical evidence of congestive heart failure, cardiomegaly, or ventricular aneurysm. Eight patients had clinical and electrocardiographic evidence of a previous myocardial infarction but none had occurred within 6 months of study. The study was undertaken in each case either definitely to clarify the diagnosis of coronary artery disease or to assist in the selection of suitable candidates for coronary artery surgery. None of the patients was receiving cardiac glycosides or diuretics at the time of study. Informed consent was obtained from each patient, and there were no complications related to the investigation.

The patients ranged in age from 31 to 58 years. All patients were studied in the fasting state, and premedication consisted of 100 mg pentobarbital sodium administered orally 2 hours prior to hemodynamic measurements. Under local anesthesia the right brachial artery and two accompanying veins were isolated. A no. 9 double-lumen or no. 8 single-lumen Courmand catheter was placed with its tip lying in the pulmonary artery. A no. 8 Sones catheter was passed to the left ventricle from the right brachial artery. The left brachial artery was cannulated with a short Teflon catheter by the Seldinger technic.

Control pressures in the right ventricle, pulmonary artery, left ventricle, and brachial artery were recorded at least 15 min after placement of all catheters. The cardiac output was then measured in duplicate by the dye-dilution technic using indocyanine green.

Following these measurements 10% low molecular-weight dextran in 5% dextrose* was infused through the pulmonary arterial catheter using a blood transfusion set. Because of the viscous nature of dextran this was pumped manually. The volume infused ranged from 115 to 540 ml and was administered during a period ranging from 6 to 23 min.

Dextran administration was terminated when left ventricular end-diastolic pressure rose to approximately twice the control value or when the contents of one bottle (540 ml) had been given. Left ventricular end-diastolic pressure was continuously monitored throughout the infusion period. In seven patients serial measurements of pressures and cardiac output were obtained during the course of the infusion, while in the remaining patients the cardiac output was recorded at the end of the infusion period.

All pressures were measured with P23Db Statham strain gauges from a zero reference level 5 cm below the angle of Louis and were recorded on an Electronics for Medicine DR12 recorder. The systolic and diastolic pressures were recorded over at least two respiratory cycles, and the mean pressures in the brachial and pulmonary artery were obtained electronically. The recording speed was usually 25 mm/sec but was increased to 100 mm/sec for the determination of left ventricular end-diastolic pressure. The point of determination of left ventricular end-diastolic pressure was either at the nadir of the a wave when it was clearly visible or near the peak of R wave of the ECG where the LV pressure pulse showed an abrupt rise. The maximum rate of rise of left ventricular pressure (dP/dt) was obtained by an electronic differentiator. There are theoretic objections to measurement of dP/dt using a fluid-filled catheter and external transducer but direct in vivo comparison with a catheter-tipped transducer at rates of 75-150 beats/min has shown that the two methods of measurement correspond closely up to a value of 2000 mm Hg/sec.

The left ventricular stroke-work index in g-m/m² was calculated using the formula:

\[
\text{LVSWI} = \frac{\text{SI} \times (\text{BAm} - \text{LVEDP}) \times 13.6}{1000}
\]

where SI = stroke index in ml/m², BAm = brachial artery mean pressure in mm Hg, LVEDP = left ventricular end-diastolic pressure in mm Hg.

Following completion of the hemodynamic study left ventriculography and selective coronary arteriography were done in all patients. Seventeen patients had arteriographic evidence of significant coronary artery disease with reduction in luminal diameter of more than 75% in at least one major coronary artery and will be considered as the coronary artery disease (CAD) group. Eight patients including four of these with previous infarctions had focal areas of akinesis in the left ventriculogram, but there were no patients with ventricular aneurysms or gross abnormalities of wall motion on left ventriculography. Left ventriculography was normal in the remaining nine patients with coronary artery disease. Eleven

*Rheomacrodex low molecular weight 40,000, Pharmacia, Uppsala, Sweden.
Table 1

### Statistical Summary of Mean Hemodynamic Data

<table>
<thead>
<tr>
<th>Status</th>
<th>HR (beats/min)</th>
<th>RVEDP (mm Hg)</th>
<th>PAm (mm Hg)</th>
<th>BAml (mm Hg)</th>
<th>PP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>82 ± 14.8</td>
<td>5.0 ± 0.9</td>
<td>15.6 ± 3.2</td>
<td>102 ± 13.6</td>
<td>56.7 ± 16.7</td>
</tr>
<tr>
<td>Infusion</td>
<td>85 ± 11.5</td>
<td>8.3 ± 2.2</td>
<td>22.6 ± 5.1</td>
<td>105 ± 11.7</td>
<td>63.2 ± 15.8</td>
</tr>
<tr>
<td>Dextran</td>
<td>NS</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Infusion</td>
<td>85 ± 11.5</td>
<td>4.8 ± 1.1</td>
<td>13.5 ± 2.5</td>
<td>98 ± 8.1</td>
<td>55.5 ± 9.2</td>
</tr>
<tr>
<td>Control</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood</td>
<td>78 ± 12.7</td>
<td>—</td>
<td>12.8 ± 2.1</td>
<td>95 ± 9.9</td>
<td>59.4 ± 8.6</td>
</tr>
<tr>
<td>Transfusion</td>
<td>81 ± 9.1</td>
<td>—</td>
<td>18.4 ± 2.1</td>
<td>101 ± 9.4</td>
<td>62.8 ± 8.2</td>
</tr>
<tr>
<td>NS</td>
<td>NS</td>
<td>&lt;0.005</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

### Abbreviations:
- HR = heart rate
- RVEDP = right ventricular end-diastolic pressure
- PAm = pulmonary artery mean pressure
- BAml = brachial artery mean pressure
- PP = systemic pulse pressure
- LVEDP = left ventricular end-diastolic pressure
- CI = cardiac index
- SI = stroke index
- RSVWI = right ventricular stroke-work index
- LVSWI = left ventricular stroke-work index
- dP/dt = first derivative of left ventricular pressure pulse
- TTI = modified tension-time index
- P = significance of change between control and infusion periods
- NS = not significant

### Patients

Five additional patients subsequently shown to be free of cardiovascular disease underwent similar hemodynamic studies but rather than dextran they were transfused with 400 ml of whole blood. This had been removed from them 1–2 weeks prior to study and stored in a blood donor bag containing acid-citrate-dextrose at 4°C. Patients had no electrocardiographic, hemodynamic, or arteriographic evidence of heart disease and will be considered as the normal group.

During the control period the cardiac index averaged 3.19 liters/min/m² in the normal subjects and rose to 4.01 liters/min/m² (P < 0.001) following infusion. In the CAD group these values were 3.09 and (P < 0.001).

### Results

Table 1 shows the mean values of the pertinent parameters for both groups and their statistical significance.

### Dextran Infusion

The heart rates were similar in each group during the control period, and there was no change following infusion (fig. 1). The brachial artery mean pressure was similar in both groups during the control period and did not change significantly with infusion in the normal subjects. In the CAD group, this pressure increased from 102 to 105 mm Hg following infusion (P < 0.01) (fig. 1). Following infusion the pulse pressure in the CAD group increased from 56.7 to 63.2 mm Hg (P < 0.01), and in the normal subjects it increased from 55.5 to 66.8 mm Hg (P < 0.01). During the control period the cardiac index averaged 3.19 liters/min/m² in the normal subjects and rose to 4.01 liters/min/m² (P < 0.001) following infusion. In the CAD group these values were 3.09 and

![Figure 1](http://circ.ahajournals.org/)
### BLOOD VOLUME EXPANSION

<table>
<thead>
<tr>
<th>LVEDP (mm Hg)</th>
<th>CI (liters/min/m²)</th>
<th>SI (mL/m²)</th>
<th>RVSWI (g/m²)</th>
<th>LVSWI (g/m²)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>TTI (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.4 ± 3.3</td>
<td>3.1 ± 0.6</td>
<td>37.4 ± 8.1</td>
<td>4.4 ± 1.8</td>
<td>47.1 ± 13.6</td>
<td>1973 ± 984</td>
<td>1128 ± 250</td>
</tr>
<tr>
<td>19.3 ± 3.0</td>
<td>3.8 ± 0.8</td>
<td>44.7 ± 9.0</td>
<td>8.1 ± 2.8</td>
<td>52.4 ± 14.1</td>
<td>2082 ± 921</td>
<td>1208 ± 226</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>NS</td>
<td>&lt;0.005</td>
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</table>

### Dextran infusion - CAD (n = 17)

<table>
<thead>
<tr>
<th>LVEDP (mm Hg)</th>
<th>CI (liters/min/m²)</th>
<th>SI (mL/m²)</th>
<th>RVSWI (g/m²)</th>
<th>LVSWI (g/m²)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>TTI (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0 ± 3.0</td>
<td>3.2 ± 0.2</td>
<td>37.9 ± 4.4</td>
<td>4.0 ± 1.2</td>
<td>46.3 ± 5.5</td>
<td>1938 ± 604</td>
<td>1153 ± 202</td>
</tr>
<tr>
<td>18.4 ± 3.2</td>
<td>4.0 ± 0.4</td>
<td>45.7 ± 4.8</td>
<td>7.1 ± 3.0</td>
<td>52.1 ± 7.4</td>
<td>2231 ± 615</td>
<td>1250 ± 164</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.02</td>
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</tbody>
</table>

### Dextran infusion - normal (n = 11)

<table>
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<tr>
<th>LVEDP (mm Hg)</th>
<th>CI (liters/min/m²)</th>
<th>SI (mL/m²)</th>
<th>RVSWI (g/m²)</th>
<th>LVSWI (g/m²)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>TTI (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2 ± 1.5</td>
<td>3.2 ± 0.6</td>
<td>42.3 ± 9.7</td>
<td>—</td>
<td>49.0 ± 11.7</td>
<td>1628 ± 551</td>
<td>1025 ± 276</td>
</tr>
<tr>
<td>16.2 ± 1.1</td>
<td>3.6 ± 0.5</td>
<td>44.6 ± 6.8</td>
<td>—</td>
<td>51.9 ± 8.7</td>
<td>1698 ± 549</td>
<td>1113 ± 177</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

### Blood transfusion - normal (n = 5)

<table>
<thead>
<tr>
<th>LVEDP (mm Hg)</th>
<th>CI (liters/min/m²)</th>
<th>SI (mL/m²)</th>
<th>RVSWI (g/m²)</th>
<th>LVSWI (g/m²)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>TTI (units)</th>
</tr>
</thead>
</table>
| 3.76 liters/min/m², respectively (P < 0.001) (fig. 2). The stroke index during the control period averaged 37.9 mL/m² in the normal group and rose to 45.7 mL/m² following infusion (P < 0.001) (fig. 2). In the CAD group this rose from 37.4 to 44.7 mL/m² (P < 0.001). Left ventricular end-diastolic pressure during the control period averaged 8.0 mm Hg in the normal group and 10.4 mm Hg in the patients with coronary artery disease. Following infusion this pressure rose to abnormal levels in every patient and averaged 18.4 mm Hg in the normal group (P < 0.001) and 19.3 mm Hg in the CAD group (P < 0.001) (fig. 3). The right ventricular end-diastolic pressure in the control group (P < 0.001) (fig. 3). The right ventricular end-diastolic pressure (LVEDP) increased significantly to abnormal levels in both groups of patients following dextran infusion. SEM = standard error of the mean.

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period averaged 4.8 mm Hg in the normal group and 5.0 mm Hg in the CAD group. Following infusion this rose to 9.6 and 8.3 mm Hg in the two groups, respectively. Left ventricular stroke-work index averaged 46.3 g-m/m² in the normal group and rose to 52.1 g-m/m² (P < 0.02) following infusion. In the patients with coronary artery disease this rose from 47.1 to 52.4 g-m/m² (P < 0.02) (fig. 4). The left ventricular dP/dt was similar during the control period and did not change significantly in either group following the infusion. The arterial hematocrit decreased 4 vol % following dextran infusion in both groups of patients (P < 0.001). When the hemodynamic parameters in the control period were compared in the two groups there were no significant differences. This was also true in the postinfusion period.

**Blood Transfusion**

The mean hemodynamic data for the five additional normal subjects infused with blood are shown in Table 1.

As with the dextran infusion, the heart rate and brachial artery mean pressure did not change significantly following blood transfusion. The brachial artery pulse pressure averaged 59.4 mm Hg in the control period and rose to 62.8 mm Hg at the completion of the transfusion. The cardiac index and stroke index increased from 3.20 liters/min/m² and 42.3 ml/m² to 3.61 liters/min/m² and 44.6 ml/m², respectively. Left ventricular end-diastolic pressure increased in every patient following blood transfusion. The average value increased from 8.2 to 16.2 mm Hg. Left ventricular stroke-work index increased from 49.0 g-m/m² in the control period to 51.9 g-m/m² following transfusion.

**Discussion**

The hemodynamic effects of rapid blood volume expansion with saline, glucose, albumin, blood, and dextran have been studied in man. Most of these studies have shown increases in right atrial or pulmonary artery pressure, but limited data on left ventricular pressure are available. In normal subjects Warren and associates using infusions of saline showed significant increases in right atrial pressures with no change in cardiac output; however, with albumin infusions they reported increases in right atrial pressure with minimal change in cardiac output. Schnabel and co-workers infused distilled water, glucose in water, and saline, in normal subjects in volumes sufficient to increase blood volume by 8.4%, but found no significant increase in cardiac output or right atrial pressure. Using dextran, however, the same infusion volume induced a significant increase in right heart filling pressures and cardiac output. Fleming and Bloom using large infusions of dextran (1000-1500 ml) reported significant increases in right atrial, pulmonary arterial, and pulmonary capillary pressures.
wedge pressures. The cardiac output was usually increased, but this was not consistently associated with any pressure change in the venous or pulmonary system. McMichael and Sharpey-Schafer infused saline in normal subjects and found increases in both cardiac output and right atrial pressures. The variability in the hemodynamic response in these studies may in part be related to differences in experimental procedures, such as the rate and volume of infusion, the type of infusate, and the temporal relationship of hemodynamic observations to the infusion period.

Frye and Braunwald studied the Starling relationship in normal man by inducing hypervolemia with blood transfusions. In contrast to the present study where relatively small volumes of dextran produced significant increases in cardiac index, stroke index, and left ventricular stroke-work index, infusion of 1500 ml in their studies produced no significant change in cardiac output, stroke volume, or stroke work. No data regarding ventricular filling pressures were reported, but these findings were attributed to peripheral pooling due to autonomic regulation with failure of central blood volume and ventricular volume to increase. Following sympathetic blockade with trimethaphan an identical infusion volume increased central blood volume significantly, and cardiac output, stroke volume, and stroke work increased dramatically. In later studies Braunwald, Frahm, and Ross showed increases in left ventricular end-diastolic pressure, cardiac output, and stroke work following infusion of blood after similar ganglionic blockade, thus demonstrating the Starling relationship. Data on left ventricular end-diastolic pressure following infusion, before ganglionic blockade, were, however, not presented. Peripheral pooling, preventing an increase in ventricular volume, does not appear to be a factor in our study as left ventricular end-diastolic pressure increased in every patient during blood volume expansion, suggesting an increase in left ventricular volume and myocardial fiber length. In spite of this, only moderate increases in cardiac output and left ventricular stroke work were observed in normal subjects and in patients with coronary artery disease (fig. 5).

Analysis of left ventricular function relating stroke work or stroke index to left ventricular end-diastolic pressure in this study demonstrates the presence of the Frank-Starling relationship in the intact human heart when preload is increased by volume expansion. However, the rise in filling pressures appear out of proportion to the observed increase in cardiac output which gives a relatively flat ventricular function curve (figs. 5, 6). Several explanations for this finding can be considered. It is possible that the patients with coronary artery disease responded in this fashion because of impaired ventricular function due to myocardial fibrosis or from ischemia induced by the volume load. However, since the normal subjects showed a similar response and there was no clinical or electrocardiographic evidence of ischemia during the infusion, this explanation is unlikely. Dextran may alter left ventricular compliance so that the observed changes in filling

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**Figure 5**

Left ventricular function curve drawn by relating left ventricular stroke-work index (LVSWI) to left ventricular end-diastolic pressure (LVEDP) before and following dextran infusion. The ventricular function curve appeared relatively flat and is similar in the two groups of patients.
pressures do not accurately reflect changes in left ventricular volume, but there is no information available regarding this effect of dextran. Dextran may have a direct depressant effect on the heart. Although there is limited information on the effect of dextran on left ventricular function, recent studies in patients with acute myocardial infarction have shown striking increases in stroke volume and stroke work in some patients as filling pressures are increased by dextran infusions. The ventricular pressure-volume relationships could be altered by the pericardium. The pericardial distensibility, however, is such that the changes induced in left ventricular volume by small infusions would not be expected to alter the pressure-volume relationships of the left ventricle. Pericardial limitation also seems unlikely in the absence of equal diastolic pressures in the right and left ventricles. The similarity of the hemodynamic response to dextran and blood infusions in our study supports the hypothesis that the alterations in left ventricular filling pressures are related to the blood volume expansion and not due to the properties of the infusate.

The method used for calculation of left ventricular stroke-work index also flattens the ventricular function curve. The subtraction of left ventricular end-diastolic pressure from the brachial artery mean pressure reduces stroke work at higher filling pressures. If this correction factor were not used, the ventricular function curves relating stroke work to left ventricular end-diastolic pressure are steeper and similar to ventricular function curves drawn from Braunwald's data during volume expansion after ganglionic blockade (fig. 7). It thus appears that volume expansion even without ganglionic blockade can demonstrate the Frank-Starling relationship in intact man.

The relatively flat ventricular function curves could represent the withdrawal of sympathetic drive to the heart secondary to baroreceptor stimulation. Although mean brachial arterial pressure did not change with blood or dextran infusion there was an increase in pulse pressure. This change could increase baroreceptor stimulation and reduce sympathetic activity to the heart. One
might expect a reduction of heart rate in this situation but this did not occur. This could be related to dominance of parasympathetic tone in the resting state or to other reflex mechanisms.\textsuperscript{18}

It is evident that the challenge of an acute volume load does not differentiate left ventricular performance in patients with coronary artery disease from normal subjects. This is true, however, only in the absence of myocardial ischemia at the time of the infusion, as ischemia is known to be associated with depression of left ventricular function.\textsuperscript{14, 19, 20}

The demonstration of marked changes in both right and left ventricular filling pressures with small volume infusions stresses the importance of careful fluid administration, particularly in patients with a low cardiac reserve.

**Acknowledgments**

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**References**

1. Ross J Jr, Braunwald E: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. Circulation 29: 739, 1964


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