Hemodynamic Effects of Hypovolemia in Normal Subjects and Patients with Congestive Heart Failure


SUMMARY

Five young normal subjects (NS) and six middle-aged patients with chronic, low-output, congestive heart failure (HFP) were studied before and after 10 minutes of exposure to hypovolemia induced by negative pressure (30 mm Hg) applied to the lower body. ECG, respirometer, and catheters placed in the subclavian artery and superior vena cava permitted measurements of heart rate (HR), respiration rate, arterial and central venous pressures (CVP), and cardiac output (CO). In the group of NS, systemic vascular resistance (SVR) rose moderately, while CVP fell 4.3 mm Hg; CO, stroke volume (SV), stroke work (SW), and central blood volume (CBV) fell about 20%, whereas blood pressure and HR showed little change. In the group of HFP, control hemodynamic values were generally abnormal. In four patients the response to hypovolemia was similar to that of NS. Two patients with advanced heart failure showed no change or a rise in CO, SV, and SW in the face of a fall in CVP (3.1 and 3.7 mm Hg), no change or a fall in SVR, and a rise in CBV. It is concluded that HFP does not respond to hypovolemia in a consistent manner. Certain patients with advanced failure demonstrated abnormal responses to induced hypovolemia, the causes for which are complex.

Additional Indexing Words: Lower body negative pressure, Myocardial function, Heart failure treatment

ALTHOUGH some aspects of circulatory function are quite consistently abnormal during induced hypovolemia in patients with heart failure,1-4 the response of the heart itself is unsettled. It is clear that the Frank-Starling principle can be demonstrated in acute experimental heart failure in the relatively intact animal with severe myocardial impairment, as well as in the heart-lung preparation.5 6 Attempts to demonstrate this response pattern in patients with heart failure, however, have produced conflicting results.7 8

The recent demonstration, that the application of negative pressure to the lower body (LBNP) provides an effective and practical means to deplete the effective blood volume and lower central venous pressure (CVP).9 10 suggested that this may offer a useful device to re-evaluate the circulatory responses of heart failure patients to induced hypovolemia. This study was designed (1) to compare under controlled environmental and test conditions the hemodynamic responses of normal subjects with those of patients with severe,
chronic, congestive heart failure to moderate hypovolemia and diminished cardiac filling pressure induced by means of LBNP; (2) to study particularly the changes in cardiac performance to evaluate the potential usefulness of LBNP applications as a treatment regimen for chronic heart failure.

**Methods**

Five healthy, young, male volunteers, familiar with vascular catheterization and LBNP exposures, were chosen as normal subjects. Their physical characteristics are presented in table 1.

Six middle-aged patients were selected from the in-patient population at the Marion County General Hospital. Selection criteria were: (1) Chronic, advanced (class III-IV, New York Heart Association criteria), congestive heart failure with low cardiac output. (2) Myocardial impairment as the only cause of heart failure; all patients had ischemic heart disease or hypertensive cardiovascular disease as the etiology of their heart failure. (3) Stable clinical condition. Each patient had been under treatment in the hospital for at least 4 days prior to the day of testing and was considered to be in a stable state. (4) A uniform treatment regimen consisting of digitalis, diuretic agents, low-sodium diet, and restricted activity. (5) No other important intercurrent illness. (6) Willingness to cooperate. Each patient had residual congestion and edema but these were never more than moderate in degree. None had been receiving vasoactive medication (other than digitalis) and none had received recent treatment for hypertension. Their physical and clinical characteristics are presented in table 1.

The LBNP chamber is a steel cylinder closed at one end. The subject lay supine or semisupine in the chamber on a foam-rubber mattress. The open end of the chamber was sealed at the subject's waist. Negative (subatmospheric) pressure was provided by means of a commercial vacuum cleaner. Details of the chamber and LBNP techniques have been described previously. A 10-minute total exposure time was chosen, since earlier studies with this device showed that cardiovascular responses to a chamber pressure change are essentially complete after 5 minutes of exposure. Thirty millimeters of mercury of negative pressure was selected because previous experiments with normal subjects demonstrated that this level of suction provided a moderate degree of hypovolemia, which was well tolerated yet insufficient to cause severe circulatory strain.

The instrumentation and personnel were essentially the same for the testing of both groups.

**Table 1**

**Physical and Clinical Characteristics of Normal Subjects and Patients with Heart Failure**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age and sex</th>
<th>Wt (kg)/Ht (cm)</th>
<th>Body surface area (m²)</th>
<th>Heart rate and rhythm (beats/min)</th>
<th>Arterial blood pressure (mm Hg)</th>
<th>Clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FB</td>
<td>31 M</td>
<td>96/188</td>
<td>2.18</td>
<td>60 SR</td>
<td>124/74</td>
<td>Normal</td>
</tr>
<tr>
<td>RC</td>
<td>25 M</td>
<td>83/187</td>
<td>2.02</td>
<td>52 SR</td>
<td>118/63</td>
<td>Normal</td>
</tr>
<tr>
<td>AN</td>
<td>28 M</td>
<td>73/177</td>
<td>1.85</td>
<td>55 SR</td>
<td>115/54</td>
<td>History of syncope</td>
</tr>
<tr>
<td>DR</td>
<td>26 M</td>
<td>59/170</td>
<td>1.66</td>
<td>68 SR</td>
<td>111/64</td>
<td>Normal</td>
</tr>
<tr>
<td>JS</td>
<td>26 M</td>
<td>71/182</td>
<td>1.87</td>
<td>58 SR</td>
<td>121/68</td>
<td>Normal</td>
</tr>
<tr>
<td>EA</td>
<td>64 F</td>
<td>78/174</td>
<td>1.91</td>
<td>90 SR</td>
<td>200/100</td>
<td>HCVD, CAD, diabetes mellitus, class III</td>
</tr>
<tr>
<td>CA</td>
<td>60 M</td>
<td>72/165</td>
<td>1.81</td>
<td>90 SR</td>
<td>180/110</td>
<td>HCVD, class IV</td>
</tr>
<tr>
<td>VB</td>
<td>58 F</td>
<td>48/158</td>
<td>1.45</td>
<td>80 AF</td>
<td>150/112</td>
<td>HCVD, CAD, renal disease, class IV</td>
</tr>
<tr>
<td>JB</td>
<td>42 M</td>
<td>75/182</td>
<td>1.91</td>
<td>90 SR</td>
<td>118/85</td>
<td>HCVD, CAD, class III</td>
</tr>
<tr>
<td>MH</td>
<td>57 M</td>
<td>71/159</td>
<td>1.75</td>
<td>85 SR</td>
<td>130/98</td>
<td>HCVD, emphysema, class III</td>
</tr>
<tr>
<td>WT</td>
<td>61 M</td>
<td>81/177</td>
<td>2.06</td>
<td>80 AF</td>
<td>110/60</td>
<td>CAD, class III</td>
</tr>
</tbody>
</table>

M and F represent male and female.
SR and AF, sinus rhythm and atrial fibrillation; HCVD and CAD, hypertensive cardiovascular disease and coronary artery disease. Class represents New York Heart Association classification of heart failure.
Polyethylene catheters (i.d. 1.1 mm) were passed into an adjacent antecubital vein and artery in each subject before each test by a percutaneous technique modified after Seldinger. The tip of the 40-cm long arterial catheter was placed in the subclavian artery and, under fluoroscopic control, the tip of the 70-cm long venous catheter was placed in the superior vena cava. The external ends of the catheters were connected to stopcock manifolds permitting the rapid, sequential measurement of pressures, injection of dye, aspiration of blood samples, and flushing with a dilute solution of heparin-in-saline. Electrocardiographic (ECG) electrodes were placed on each extremity, and a mercury-in-silastic strain gauge was placed across the chest for respirometry. Blood pressures were measured by means of Statham (p23 Db) pressure gauges; mean pressures were obtained electronically. Zero reference for the gauges was set at the mid-chest level. Blood pressure and heart, and respiratory rates were taken over a full respiratory cycle and the average value represents the sample. Lead II of the ECG was monitored throughout each experiment for changes in rate, rhythm and conduction, and P-QRS-T pattern changes. Changes in measured CVP values during LBNP exposures of -30 mm Hg are probably accurate estimations of changes in effective transmural pressure, because this level of suction does not appreciably change esophageal pressure, an index of intrathoracic pressure (unpublished observation). In the evaluation of cardiac function curves, CVP is taken as cardiac filling pressure. The appropriateness of this choice is supported by the fact that it has been the classic site for the measurement of cardiac filling pressure so that comparison can be made with most earlier animal and human studies; catheterization of the left atrium or ventricle, or both, in normal subjects and patients who would not otherwise require catheterization seemed unwarranted; central venous, right and left atrial and ventricular end-diastolic pressures change similarly during induced changes in blood volume.6, 11–16 Although the presence of primary left ventricular failure may alter this relationship, this remains unproved.

Respiration rate was determined from the chest strain-gauge recordings. Cardiac output (CO) was measured by the indicator-dilution technique by means of an injectate of 5 mg of indocyanine green dye, which was flushed from the catheter with approximately 5 ml of saline. Arterial blood was withdrawn at the rate of 25 ml/min through a cuvette densitometer by a constant speed pump. Stroke volume (SV) was calculated by dividing CO by heart rate (HR), and the product of mean systolic arterial pressure and SV represents stroke work (SW). Systemic vascular resistance (SVR) was derived as the product of the quantities (mean arterial blood pressure minus CVP, and 79.9), divided by CO. Central blood volume (CBV) was taken as the product of CO and mean transit time. It has been well established that CBV determinations are subject to error during periods of alterations in blood-flow distribution when arterial samples are obtained from a peripheral site, as was the case in these experiments.17, 18 Since some redistribution of blood flow may have occurred as a compensatory response to hypovolemia, the accuracy of the CBV values reported here is uncertain.

Room temperature remained relatively constant, and chamber temperature rose less than 1° C over the course of each experiment.

The statistical significance of these data was determined by the Student's t-test to compare paired values between control and test periods. Significant P-values (P < 0.05) are denoted in table 2 by an asterisk.

Procedure

Each normal subject and the patients with heart failure fasted and abstained from smoking and unusual exertion before the morning test. To assure adequate hydration, 500 ml of water was drunk 2 hours before arrival at the laboratory. The patients received their usual morning medications. Each subject remained recumbent or semirecumbent in the LBNP chamber for 60 minutes prior to the application of negative pressure. During this time he was instrumented, as described above, and catheter connections and calibrations were carried out. Just prior to the onset of suction, duplicate control recordings were obtained of heart and respiratory rates and arterial and venous pressures, and a dye curve was inscribed; averages of these duplicate measurements represent the control period. The chamber pressure was then lowered to -30 mm Hg (30 mm Hg below the ambient, atmospheric level) and maintained there for 10 minutes. Duplicate recordings were made during the last 3 minutes of the negative-pressure exposure. Following the test procedure, the catheters and other instruments were removed, and the subject was observed for 90 minutes and discharged.

Results

Except for mild, local sensations of saddle pressure and lower abdominal fullness, there were no unusual symptoms in either group. A few patients described easier breathing during the negative-pressure exposures.
Table 2

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Central venous pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C T C T</td>
<td>C T</td>
<td>C T</td>
<td>C T</td>
<td>C T</td>
</tr>
<tr>
<td>N FB</td>
<td>60 62 127 123</td>
<td>78 76</td>
<td>93 92</td>
<td>7.0 4.9</td>
<td></td>
</tr>
<tr>
<td>O RC</td>
<td>56 62 120 120</td>
<td>65 73</td>
<td>83 88</td>
<td>5.0 3.0</td>
<td></td>
</tr>
<tr>
<td>R AN</td>
<td>60 62 120 108</td>
<td>60 62</td>
<td>84 81</td>
<td>3.2 -1.8</td>
<td></td>
</tr>
<tr>
<td>M DR</td>
<td>67 70 116 115</td>
<td>63 66</td>
<td>82 78</td>
<td>4.4 -2.5</td>
<td></td>
</tr>
<tr>
<td>A JS</td>
<td>50 56 119 114</td>
<td>60 58</td>
<td>82 79</td>
<td>7.4 2.0</td>
<td></td>
</tr>
<tr>
<td>L Mean</td>
<td>59 62* (2.8)</td>
<td>65 67</td>
<td>85 84</td>
<td>5.4 1.1*</td>
<td></td>
</tr>
<tr>
<td>S (sd)</td>
<td></td>
<td>(1.8) (2.6)</td>
<td>(3.3)</td>
<td>(2.1) (2.7)</td>
<td></td>
</tr>
</tbody>
</table>

C stands for control values and T for t-test values after 7 minutes of LBNP pressure.
*Mean values that differ significantly ($P < 0.05$) from control levels.

Table 2 and figure 1 contain the hemodynamic data from the group of normal subjects. During the suction exposures, changes were quite consistent: HR and systemic vascular resistance rose, but CVP, CO, SV, CBV and SW fell. Although pulse pressure fell slightly, there were no significant changes in blood pressure. Respiratory rates showed no significant change, and there were no subjective or objective signs of hyperventilation. ECG remained unchanged over the course of the test.

The data for the individual patients in the heart failure group are also contained in Table 2 and figure 1. Control values varied widely and differed from the normal owing to the effects of the underlying cardiovascular diseases and the presence of congestive heart failure.
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<table>
<thead>
<tr>
<th>Cardiac output (l/min)</th>
<th>Stroke volume (ml)</th>
<th>Stroke work (g·m)</th>
<th>Systemic vascular resistance (dynes sec/cm²)</th>
<th>Central blood volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C T</td>
<td>C T</td>
<td>C T</td>
<td>C T</td>
<td>C T</td>
</tr>
<tr>
<td>4.1 3.6</td>
<td>68 58</td>
<td>91 81</td>
<td>1660 1912</td>
<td>927 796</td>
</tr>
<tr>
<td>4.9 3.9</td>
<td>84 63</td>
<td>111 85</td>
<td>1275 1751</td>
<td>1661 944</td>
</tr>
<tr>
<td>4.5 3.7</td>
<td>75 61</td>
<td>105 78</td>
<td>1432 1788</td>
<td>1251 1008</td>
</tr>
<tr>
<td>4.9 3.8</td>
<td>73 55</td>
<td>91 68</td>
<td>1252 1633</td>
<td>1340 1044</td>
</tr>
<tr>
<td>4.6 4.0</td>
<td>91 72</td>
<td>115 86</td>
<td>1307 1486</td>
<td>1305 1118</td>
</tr>
<tr>
<td>4.6 3.8*</td>
<td>78 62*</td>
<td>103 80*</td>
<td>1385 1714*</td>
<td>1296 982*</td>
</tr>
<tr>
<td>(0.1)</td>
<td>(4.1) (2.9)</td>
<td>(5.0) (3.2)</td>
<td>(75) (73)</td>
<td>(117) (54)</td>
</tr>
</tbody>
</table>

5.5 3.4               57 47  127 102  1888 2982  2967 2192
2.7 2.8               30 31  64 62  3605 3638  1565 1653
1.4 1.8               14 15  27 27  5689 5069  1104 1543
3.3 2.8               39 32  53 42  2227 2645  1311 1084
3.2 2.5               31 24  47 37  2482 3052  1116 999
4.4 3.6               73 50  111 78  1274 1898  1917 2070
3.4 2.8               41 33  72 58  2861 3214  1663 1590
(0.6) (8.6) (5.4) (15.9) (11.6) (648) (438) (289) (200)

failure. The patients showed greater variability in their responses to the LBNP exposures. There were slight falls in the mean values of CVP, CO, SV, SW, and a rise in SVR; CBV showed little change in contrast to its significant fall in the normal group. Although the directions and magnitudes of most of the individual changes were similar to those in the normal subjects, some changes were inconsistent, so that only the change in CVP was statistically significant. It is notable that two patients, CA and VB, the most severely ill of the group, showed similar response patterns that differed in several respects from the responses of the normal subjects and the other heart failure patients. Their individual

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**Figure 2**

Relation between changes in central venous pressure and changes in cardiac output, stroke volume and stroke work during lower-body negative pressure exposure. Closed circles connected by dashed lines represent patients C.A. and V.B.
data are denoted by closed circles connected by dashed lines in the figures. There were no important ECG changes, no significant changes in respiration rates, and no evidence of hyperventilation in the heart-failure group.

Figure 2 displays the relationships between CVP and three indices of cardiac performance, CO, SV, and SW. The spread in the response patterns in the HF group is in contrast to the essential consistency of the normal subjects. Again, the two sickest subjects behaved differently, showing no significant change or a rise in CO, SV, and SW in the face of a fall in CVP.

Discussion

The amount of blood impounded in the lower body and lost from the effective blood volume during LBNP exposures of this degree and duration is uncertain. Musgrave measured plethysmographically the change in the volume of blood in both legs during 5 minutes of negative-pressure exposure at 40 mm Hg and found that an average of 614 ml had been pooled. Gauer and associates proposed that there is a relationship between the change in the central venous pressure and the diminution in the effective blood volume that can be expressed by the statement: CVP can be expected to fall 0.49 ± 0.12 cm H$_2$O per kilogram of body weight per milliliter of blood volume loss. With use of this formula, it can be estimated that in our group of normal subjects an average of 873 ml of blood was lost from the central circulation during the 10-minute exposures. Comparison of the pulse and blood pressure changes found in the normal subjects during these LBNP exposures with the changes reported from bleeding studies suggests that over 10 ml per kilogram of body weight (over 760 ml) had been removed from the effective blood volume in the normal subjects.

The circulatory changes induced by LBNP in the heart failure patients seem sufficient to conclude that a significant degree of hypovolemia had been induced, but the amount of blood sequestered from the central circula-

tion in this group cannot be estimated with accuracy for three prime reasons: (1) The amount of blood impounded in the lower body may not be equal in the two groups because of the altered vascular and extravascular compliance in patients with heart failure due to congestion and edema and altered neurohumeral activity; (2) because of the increased total blood volume usually associated with heart failure, an equal volume of sequestered blood may not represent an equivalent decrement in effective blood volume and may thus provide a lesser circulatory stress; (3) the cardiovascular system in heart failure patients may respond differently to an equivalent degree of hypovolemia because of the altered activity of the sympathetic nervous system and levels of vasoactive hormones, the administration of drugs affecting the circulation, and local-tissue metabolic changes due to inadequate perfusion.

It is notable that in the present study the magnitudes of the changes of individual values for many of the measured factors in the heart failure patients were similar to those in normal subjects; mean differences from control values were not significant because a few of the individual changes were discrepant and at times divergent. Figure 1 demonstrates the general consistency of the changes in the normal group and the variability of the heart failure patients. CVP fell uniformly and was the only measured factor that changed consistently in this group. Four of the patients with milder degrees of heart failure (class III) showed changes in the other measured factors that were generally similar to the normal patterns, whereas the two patients with advanced failure usually changed similarly and often exhibited a different type of response.

The normal subjects showed consistently a large (270 ml mean) fall in central blood volume during LBNP exposure. Three of the heart-failure patients showed a similar change; the other three demonstrated a rise. LBNP may have produced only an insignificant hypovolemia in these patients, the CBV rise being attributed to random measurement.
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error. However, other hemodynamic changes are evidence that a significant fall in effective blood volume had occurred, and the CBV rise in one patient was striking and well beyond ordinary measurement error. Although an enhanced peripheral venoconstrictive response to hypovolemia could explain the increased CBV, this has never been demonstrated in heart failure. The rise may also be ascribed to an erroneous measurement of mean transit time due to a redistribution of blood flow. The information at hand is not sufficient to discriminate among these possibilities.

Experiments to evaluate the Frank-Starling relationship in man have produced conflicting results. Rapaport’s and Taquini’s groups, reporting on diminished venous return and cardiac filling pressure in normal subjects and patients with heart failure by means of tilting and bleeding, found in the normal subjects the expected fall in SV and CO, with a rise in HR; in contrast, patients with heart failure showed little or no change in any of these performance factors. An apparent descending limb on the cardiac function curve was demonstrated consistently in patients with congestive heart failure by McMichael and Sharpey-Schafer, who used venous occlusion cuffs on the extremities to impound blood peripherally, and by Howarth and co-workers, using venesection. When a diminished filling pressure was created by means of drug-induced vasodilation, CO was found to fall in the normal group but rise in heart-failure patients. Other studies in heart failure patients, with use of extremity occlusion cuffs and bleeding and intermittent positive-pressure breathing to diminish venous return, demonstrated a variable response in cardiac output without any consistent relationship to changes in right ventricular end-diastolic pressure. More recent investigations with balloon-occlusion of the inferior vena cava to diminish venous return and filling pressure demonstrated that patients with heart failure have abnormal filling-pressure cardiac-performance curves but not a descending limb. These inconsistent results may be due in part to (1) dissimilar methods used to produce hypovolemia and diminish venous return—in some patients in previous studies the induced hypovolemia was insufficient to cause an appreciable change in any of the measured circulatory variables, including filling pressure; (2) heterogeneous patient populations with variations in the degree and duration of heart failure and the kind of heart involvement; (3) inconsistent administration of cardiac and vasoactive drugs; and (4) the presence of important intercurrent conditions or disease that may alter cardiovascular responses.

In this study, in spite of attempts to control these experimental and test conditions, cardiac performance indices showed important variability in the HF group (fig. 2). The two patients with advanced heart failure exhibited a different response, with little change or rise in SV, CO, and SW in the face of a fall in CVP. This response pattern cannot be attributed to an altered afterload since there was no clear relationship between performance indices and the small diastolic blood pressure changes observed. Although these changes can be interpreted as demonstrating a descending limb on the Frank-Starling curve, this is not a unique explanation. Alteration in neurohumoral activity may have affected the condition of the myocardium and “shifted” these patients to another of the family of performance curves that Sarnoff found in the laboratory animal. As has been emphasized recently, if a descending limb is present in the human heart, it must be an inherently unstable condition requiring the intervention of auxiliary inotropic mechanisms and/or alterations in the peripheral circulation as auxiliary governors of the performance of the heart. Another factor that may be important is the decrease in chamber size, which probably accompanies depletion of the effective blood volume; a more favorable ventricular tension-pressure relationship will diminish myocardial oxygen consumption and tend to improve the efficiency of the heart. Finally, perhaps filling pressure was actually unchanged in these two patients, and the low
CVP measurements were caused by a diminished intrathoracic pressure due to apparent hyperventilation. This explanation seems unlikely since very vigorous hyperventilation, which is required to produce a significant fall in intrathoracic pressure, was never observed, and unpublished experiments in this laboratory showed that hyperventilation (as measured by blood gas changes) is not found during LBNP exposures until hypovolemia is extreme and syncope imminent. Because of the complexities of clinical experimentation, it seems impossible to sort out these effects at present.

This range of reactions to a diminished venous return and filling pressure may explain the occasional successes but passing popularity of earlier attempts to treat chronic congestive heart failure with hypovolemia produced by means of phlebotomy and inferior vena cava ligation. It is of interest that LBNP was used for the treatment of heart failure a century ago with some success. There seems little reason to expect that hypovolemia produced by any means will provide an effective treatment regimen for most cases of chronic heart failure, although it may prove helpful in the occasional patient with very advanced failure.

Acknowledgment
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