Cardiac Output Response to Exercise in Patients with Inferior Vena Cava Ligation

By Murray A. Varat, M.D., Noble O. Fowler, M.D., and Robert J. Adolph, M.D.

SUMMARY

Studies were carried out to determine whether hemodynamic alterations may follow inferior vena caval (IVC) ligation. Five patients, aged 29 to 49 years, who had been operated upon 2 to 5 years previously, and five normal controls, aged 39 to 44 years, were studied at rest and during graded submaximal treadmill exercise. There were no significant differences in heart rate, right atrial pressure, brachial arterial pressure, oxygen consumption, or cardiac output between the patients and normals in the supine rest and head-up tilt positions. During treadmill exercise the heart rate and oxygen consumption were comparable in the two groups, but the cardiac output response was definitely diminished in the patient group. This was reflected in the exercise factor, that is, the increase in cardiac output per 100 ml increase in oxygen consumption. The mean exercise factor was 406 ml for the patient group and 726 ml for the controls, a significant difference ($P < 0.001$).

It is concluded that the cardiac output response to upright exercise may be impaired in patients with IVC ligation. Inadequate venous return following IVC ligation may explain the persistent postoperative exertional dyspnea that has been noted in our patients.

Additional Indexing Words:

Exercise factor, Treadmill exercise, Venous return, Dye-dilution cardiac output, Central blood volume

LIGATION of the lower part of the inferior vena cava is a well-accepted treatment for pulmonary embolic disease and is considered the treatment of choice for recurrent pulmonary embolism which has failed to respond to anticoagulant therapy. The operative mortality is low in the absence of underlying heart disease, but in patients with congestive heart failure the immediate postoperative mortality is increased. The recognized long-term complications are leg edema and enlarged superficial veins. Blood flow through the lower inferior vena cava comprises 20 to 35% of the cardiac output at rest and a greater percentage of a larger total cardiac output during leg exercise. Interruption of this flow, therefore, could lead to decreased venous return. Acute occlusion of the inferior vena cava in man and in the experimental animal results in a significant, albeit transient, drop in cardiac output in the resting state. This finding may explain, in part, the increased early postoperative mortality in patients with underlying heart disease.

Chronic interruption of the inferior vena cava may permit an adequate venous return at rest but not during exercise, despite the development of venous collaterals. No studies have been reported on the effect of chronic interruption of the inferior vena cava on
cardiac output response to exercise in man. The only study of the long-term effects of inferior vena caval ligation in man was reported by Ray and Burch,10 and this was concerned solely with local vascular effects. The possibility that an impaired cardiac output response to upright exercise may follow ligation of the inferior vena cava has received almost no consideration. In our experience, however, careful questioning of patients after inferior vena caval ligation has revealed a degree of exertional dyspnea that had not been present preoperatively.

In this study, patients with inferior vena caval ligation underwent several levels of treadmill exercise. Their cardiac output responses at rest, during passive head-up tilting, and during exercise were compared to those of matched controls to determine what, if any, hemodynamic alterations follow inferior vena caval ligation.

Methods

Subjects

Inferior vena caval ligation was performed in 27 patients at the Cincinnati General Hospital from 1961 through 1968. Of these, only seven were found to be still living and free of cardiac disease or recurring pulmonary emboli. One patient refused to be studied, and attempts at cardiac catheterization were unsuccessful in another. This report is based on the results obtained from complete studies in the remaining five patients. Informed consent was obtained from all patients prior to cardiac catheterization.

The clinical characteristics of the patients studied are summarized in table 1. The group consisted of three women and two men, aged 29 to 49 years, who had undergone inferior vena caval ligation from 2 to 5 years previously. In every one of these patients, significant exertional dyspnea appeared postoperatively and has persisted to the present time. Preoperatively, dyspnea had been absent in four patients and minimal in one (H.G.). Three of the five patients had chronic edema and obvious collateral venous patterns in the lower extremities. One of these, patient Q.W., was studied while wearing elastic stockings. There was no evidence of cardiac or pulmonary disease on physical examination, electrocardiograms, or chest roentgenograms. Lung scans with macroaggregated 131I albumin performed within 3 months of the study revealed no significant perfusion defects in four patients. In the fifth patient, Q.W., perfusion was absent or decreased in approximately one third of the total lung volume.

The control group consisted of five volunteers who gave informed consent to the study. There were four firemen, aged 39 to 42 years, and a 44-year-old woman with a past history of iron-deficiency anemia. All were judged to be free of cardiac and pulmonary disease on the basis of a negative history and physical examination and normal chest roentgenograms and electrocardiograms.

Procedures

The subjects were studied in the fasting state and without premedication. Cardiac output was measured by the dye-dilution technic. A radiopaque Teflon catheter with a 2-ml capacity was passed to the junction of the superior vena cava and right atrium under fluoroscopic control. A Courand needle was placed in a brachial artery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date of IVC ligation</th>
<th>Dyspnea</th>
<th>Edema of leg</th>
<th>Collateral venous pattern</th>
<th>Chest x-rays</th>
<th>Electrocardiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.C. 29F</td>
<td>1966</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>J.S. 33F</td>
<td>1967</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>Normal</td>
<td>Nonspecific ST-T wave changes</td>
</tr>
<tr>
<td>H.G. 47F</td>
<td>1964</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Q.W. 42M</td>
<td>1965</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>I.R. 49M</td>
<td>1964</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Normal*</td>
</tr>
</tbody>
</table>

*QRS voltage in leads V5 and V6 near upper limit of normal for age and sex.11

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and the hub firmly secured to the arm. One milliliter (5 mg) of indocyanine green (Cardio-Green*) was slowly injected into the venous catheter and then rapidly flushed with 10 ml of saline. Blood was withdrawn from the brachial artery and through a Gilford densitometer (model 103†) at a constant rate of 38 ml/min. The dye curves obtained were recorded on a Texas Instruments direct writer.‡ The reproductibility of duplicate curves was estimated by an online Lexington Instruments analogue computer (model 303§). At the end of the procedure, the curves were calibrated with the same flow rate and sensitivity settings that were used during the study. A zero point and two calibration points were obtained. The cardiac output and the central blood volume were calculated by the Stewart-Hamilton formula.12 Duplicate cardiac output determinations at each level of exercise agreed within 10% and were averaged.

The heart rate was recorded by telemetry during each cardiac output determination. Right atrial and brachial arterial pressures were obtained in the supine rest and 70° passive head-up tilt positions and recorded on an Electronics for Medicine** photographic recorder, using Statham†‡ P23dB pressure transducers. The gauges were leveled at 12 cm above the table top for the supine position and at the fluoroscopically determined middle of the right atrium for the tilt position. Expired air was collected for 3 min at rest and 1 min during exercise. Aliquots were analyzed for oxygen content according to the method of Scholander.18

Heart rate, right atrial pressure, brachial arterial pressure, oxygen consumption, and cardiac output were measured while the subjects were resting supine and after 4 min in the 70° passive head-up tilt position. The subjects then walked on a treadmill, the speed and grade of which were adjusted to provide varying levels of submaximal exercise. The duration of each exercise period was at least 7 min.

No attempt was made to standardize the work load from one subject to another. Following each exercise period, the subject rested on a chair until his heart rate had returned to its resting value. Heart rate, oxygen consumption, and duplicate cardiac outputs were determined between the fourth and seventh minutes of exercise. The two dye-dilution curves were obtained within the 2 min period that included the determination of oxygen consumption. The response to exercise was measured by relating the increase in cardiac output to an increase in oxygen consumption at a given exercise level over that of the subject while in the resting supine position.

**Results**

The results of hemodynamic studies in the supine and passive head-up tilt positions are presented in table 2. One normal subject who became light-headed during the tilt is not included in these results. The average supine heart rate was 75 beats/min in the patient group and 72 beats/min in the controls. In the tilt position the average heart rate of the patients increased to 72 beats/min and that of the normal subjects to 92 beats/min. The difference in mean heart rate increments between the two groups was of borderline significance (P = 0.05). The right atrial mean pressures were practically identical in both groups, falling from a mean value of 5.5 mm Hg in the supine position to -0.5 mm Hg on tilting. The brachial artery mean pressure did not differ significantly between the two groups in the supine position and fell only slightly with tilt in both. The cardiac index was the same in both the patients and the controls while resting supine, and the fall in cardiac index on tilting was identical (23%) in both groups. The calculated “central” blood volume did not differ significantly between the two groups at rest and fell to a similar degree in both.

The results of studies at supine rest and during the various exercise levels in all 10 subjects are presented in table 3. The mean oxygen consumption at rest was 142 ml/min/m² in the patients and 129 ml/min/m² in the control subjects, an insignificant difference (P > 0.2). On the treadmill, all subjects more than doubled their resting oxygen consumption. In addition, the heart rate increased substantially with exercise in every case but one. In patient I.R., a former prizefighter who is presently employed as a heavy laborer, the heart rate at the lowest exercise level was 59 beats/min, giving the very high stroke volume

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*Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.
+Gilford Instruments Laboratory, Oberlin, Ohio.
‡Texas Instruments, Inc., Houston, Texas.
§Lexington Instruments Corporation, Waltham, Massachusetts.
**Electronics for Medicine, Inc., White Plains, New York.
†‡Statham Instruments, Inc., Los Angeles, California.

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### Table 2

**Hemodynamics at Rest in the Supine and 70° Passive Head-up Tilt Positions**

<table>
<thead>
<tr>
<th>Patients or subjects</th>
<th>Position</th>
<th>Heart rate (beats/min)</th>
<th>Mean pressure (mm Hg)</th>
<th>Cardiac index (L/min/m²)</th>
<th>Central blood volume (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arterial</td>
<td>Right atrial</td>
<td></td>
</tr>
<tr>
<td>E.C.</td>
<td>Supine</td>
<td>77</td>
<td>82</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>29F</td>
<td>Tilt</td>
<td>83</td>
<td>90</td>
<td>-1</td>
<td>2.6</td>
</tr>
<tr>
<td>J.S.</td>
<td>Supine</td>
<td>69</td>
<td>102</td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>33F</td>
<td>Tilt</td>
<td>71</td>
<td>96</td>
<td></td>
<td>2.2</td>
</tr>
<tr>
<td>H.G.</td>
<td>Supine</td>
<td>88</td>
<td>104</td>
<td>6</td>
<td>2.9</td>
</tr>
<tr>
<td>47F</td>
<td>Tilt</td>
<td>102</td>
<td>98</td>
<td>5</td>
<td>2.0</td>
</tr>
<tr>
<td>Q.W.</td>
<td>Supine</td>
<td>83</td>
<td>130</td>
<td>6</td>
<td>3.5</td>
</tr>
<tr>
<td>42M</td>
<td>Tilt</td>
<td>98</td>
<td>130</td>
<td>-3</td>
<td>2.5</td>
</tr>
<tr>
<td>I.R.</td>
<td>Supine</td>
<td>56</td>
<td>108</td>
<td>8</td>
<td>2.4</td>
</tr>
<tr>
<td>49M</td>
<td>Tilt</td>
<td>56</td>
<td>108</td>
<td>-2</td>
<td>2.0</td>
</tr>
<tr>
<td>Mean supine</td>
<td></td>
<td>75</td>
<td>105</td>
<td>5.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Mean tilt</td>
<td></td>
<td>82</td>
<td>104</td>
<td>-0.3</td>
<td>2.2</td>
</tr>
<tr>
<td>% change (supine to tilt)</td>
<td>10</td>
<td>-1</td>
<td>-106</td>
<td>-23</td>
<td>-26</td>
</tr>
</tbody>
</table>

**Normal subjects**

| M.H.                 | Supine   | 62                     | 97       | 5           | 2.5                     | 909                         |
| 43F                  | Tilt     | 85                     | 88       | -1          | 1.8                     | 646                         |
| M.F.                 | Supine   | 87                     | 107      | 5           | 2.8                     | 902                         |
| 42M                  | Tilt     | 110                    | 110      | -1          | 2.5                     | 869                         |
| E.K.                 | Supine   | 65                     | 6        |             | 3.2                     | 960                         |
| 41M                  | Tilt     | 75                     | 6        |             | 2.5                     | 869                         |
| W.M.                 | Supine   | 72                     | 93       | 5           | 2.3                     | 768                         |
| 41M                  | Tilt     | 98                     | 90       | 2           | 1.6                     | 557                         |
| R.R.                 | Supine   | 70                     |          |             | 3.8                     | 1421                        |
| 39M                  |          |                        |          |             |                         |                              |
| Mean supine*         |          | 72                     | 99       | 5.3         | 2.6                     | 860                         |
| Mean tilt*           |          | 92                     | 96       | -0.5        | 2.0                     | 691                         |
| % change (supine to tilt) | 29       | -3                    | -109     | -23         | -20                     |                              |

*Average for 3 patients only.

of 163 ml/beat. These results are included, however, because the oxygen consumption and cardiac output values at this exercise level are not discordant with the results obtained at higher exercise levels.

Although the variations in treadmill speed and grade precluded a precise comparison, there was a similarity in the values for oxygen consumption at roughly equivalent work loads between the patients and the controls. The cardiac index response to exercise, on the other hand, was definitely less in the patients than in the controls, when identical or similar work loads were compared. This was reflected in the exercise factor, that is, the increase in cardiac output per minute per 100-ml increase in oxygen consumption (table 3). The values at any given exercise level were compared to those at supine rest. The mean exercise factor in the group of patients with inferior vena caval ligation was a 406-ml increase in cardiac output per 100-ml increase in oxygen consumption, with a range of 280 to 493 ml (fig. 1). In the normal controls the mean value was 726 ml with a range of 569 to 822 ml. The difference in exercise factors between the two groups is highly significant ($P < 0.001$). The central blood volume increased with exercise.
in three of the patients and in all of the normal subjects (table 3). The increase in central blood volume with exercise is expressed as a function of the increase in oxygen consumption. The mean increase in the patient group was 42 ml/100 ml increase in oxygen consumption and in the control group was 98 ml. This difference in central blood volume increments is statistically significant ($P < 0.001$).
Exercise factors in patients and normals expressed as the increase in cardiac output (in \(\text{ml/min}/100\ \text{ml/min} \)) increase in oxygen consumption from the resting supine values to a given exercise level. Dots indicate individual determinations, the top of the bars indicate mean values, and the short horizontal lines indicate 1 standard deviation.

Discussion

There are no reported studies of the response of cardiac output to chronic interruption of the lower inferior vena cava. Chronic experiments in dogs and long-term follow-up of patients with inferior vena caval ligation have been mainly concerned with the peripheral vascular effects of the procedure. These have demonstrated that increased venous pressure below the ligation site persists for many years. Systemic hemodynamic effects have been studied acutely in the dog by several investigators. They have shown that immediately following occlusion of the lower inferior vena cava the cardiac output decreases by 20 to 47% below control levels but that it returns to normal within an hour despite maintenance of the occlusion. In man, Ross and Braunwald and Sackner and associates have similarly demonstrated an immediate fall in output as well as in ventricular filling pressure in patients with and without congestive heart failure. In these studies, however, the occluding balloon was located above the level of the renal veins.

In their study cited earlier, Ray and Burch remarked on the apparent absence of serious disturbances in patients with inferior vena caval ligation. A review of the literature confirms that systemic alterations secondary to this procedure have not previously been considered. A partial justification for this viewpoint is suggested by the normal hemodynamics obtained at rest in the present study. There was no difference in mean arterial pressure, mean right atrial pressure, cardiac index, and calculated central blood volume between the patients and the normal controls in the supine position. In the head-up tilt position, these variables decreased by virtually an identical amount in both groups. On the basis of these data, it appears that vascular reflexes and collateral blood flow are adequate to maintain normal filling pressure and cardiac output at rest.

These mechanisms are inadequate, however, to produce a normal cardiac output response to upright exercise. Inspection of the data reveals that the rise in cardiac output with treadmill exercise was less in patients with inferior vena caval ligation than in normal controls. Oxygen consumption, on the other hand, was similar in both groups. The result is a significantly \((P < 0.001)\) decreased exercise factor in the patient group.

The exercise factor as an indicator of cardiac output response is particularly suitable for use in patients with inferior vena caval ligation. Leg pain on prolonged walking is a common complaint following inferior vena caval ligation. It was present to some degree in every patient in this study. It was therefore considered unlikely that they would be able to reach the intense exercise required to measure maximal work load, maximal oxygen intake, or cardiac output at a low pulmonary arterial saturation. The exercise factor reflects changes in oxygen consumption and cardiac output rather than absolute values. It allows the use of submaximal exercise and

**Figure 1**

Exercise factors in patients and normals expressed as the increase in cardiac output (in \(\text{ml/min}/100\ \text{ml/min} \)) increase in oxygen consumption from the resting supine values to a given exercise level. Dots indicate individual determinations, the top of the bars indicate mean values, and the short horizontal lines indicate 1 standard deviation.
obviates the need to standardize the work load.

Many authors,17,18 utilizing various types and intensities of exercise and both major methods of cardiac output determination, have measured normal exercise response by relating the change in cardiac output to the change in oxygen consumption. The exercise factors derived from these studies lie within a relatively narrow range (an increase in cardiac output of approximately 500 to 800 ml per 100 ml increase in oxygen consumption over the resting supine values). In the present study the range of exercise factors in 11 determinations in normals was 569 to 822 ml. Further evidence for the stability of this parameter is provided in reports of patients with mild to moderate cardiac disease whose exercise factors lie within the normal range.19,20 Moreover, the exercise factor does not appear to be influenced by training.21

The values for central blood volume both at rest and on exercise in the control group are not unlike those obtained by Marshall and Shepherd22 in normals undergoing treadmill exercise. The increase in central blood volume with exercise, when related to the increase in oxygen consumption, was significantly (P < 0.001) less in the patients with inferior vena caval ligation than in the normal subjects. This decreased central blood volume response to exercise in patients with inferior venal caval ligation is dissimilar to that expected in patients with cardiac disease. Yu and associates23 found that the increase in central blood volume with exercise was greater than normal in patients with cardiac disease in general and with heart failure in particular. No definite comparison between our patients and theirs is possible, since in their study exercise was performed in the supine position and a different central blood volume compartment was measured. An exhaustive review of the literature reveals no studies in patients with cardiac disease, which duplicates the conditions of the present study. The subnormal central blood volume response to exercise in our patients is consistent with the concept that a mechanism different from that of heart disease underlies their subnormal cardiac output response.

The demonstrated decreased response of cardiac output to exercise in patients with inferior vena caval ligation is most likely related to the procedure itself or to the disease that prompted it (that is, pulmonary embolism). The tendency of pulmonary thromboemboli to resolve completely in patients without underlying disease24 does not completely insure that the patients studied were free of pulmonary vascular obstruction. Pulmonary artery pressure was not measured during exercise. The measurement seemed unjustified in both the patients and the normal subjects because of the danger of provoking serious arrhythmias or perforating the heart or pulmonary artery. However, none of the patients had any clinical evidence of increased pulmonary artery pressure at rest. Normal pulmonary perfusion scans confirmed the absence of significant obstruction to blood flow in the larger arteries in four patients. In the fifth patient, Q.W., perfusion was absent or decreased in approximately one third of the total lung volume. The significance of this is unclear, however, since he has not had any episodes suggestive of pulmonary embolism since 1965, has no clinical evidence of pulmonary hypertension, and had a normal resting right atrial pressure.

The cardiac output response to exercise is probably not influenced by mild degrees of pulmonary hypertension. Staněk and associates25 studied six patients with mild pulmonary hypertension secondary to pulmonary parenchymal disease. In these patients the average pulmonary arterial mean pressure was 23 mm Hg at rest and 36 mm Hg during exercise. The average exercise factor was 720 ml, almost identical to that found in the control group in the present study. In the same study, Staněk and associates also found a normal cardiac output response to exercise following pneumonectomy. Pulmonary vascular obstruction does not appear to be a factor in the diminished cardiac output response to exercise seen in the patient group in the present study.
The results obtained in this study are perhaps best explained by the vascular changes secondary to inferior vena caval ligation. In normal human subjects, Grossman and associates, using differential PAH concentrations, found that blood flow through the inferior vena cava represents 28 to 36% of the total cardiac output in the resting supine position. Vena caval flow during exercise was studied by Nielsen and Fabricius using differential oxygen contents, and by Pannier and associates, using an isotope-dilution method. If we use their figures, blood flow in the lower part of the inferior vena cava represented 20 to 30% of the total cardiac output at rest and approximately 45% during supine leg exercise. During leg exercise, therefore, blood flow through the lower part of the inferior vena cava increases both absolutely and in relation to the total cardiac output. The collateral circulation that becomes operative following inferior vena caval ligation is probably capable of handling blood flow at rest. However, it is possible that venous return during exercise may be limited by a maximal cross-sectional area of the collateral channels. Moreover, venous return is further hampered by the superficial location of the collateral vessels, which are thus not affected by the pumping action of the leg muscles. The overall result is an inadequate venous return to the heart during exercise, with a consequent reduction in cardiac output.

The results obtained suggest that there are chronic systemic sequelae to ligation of the inferior vena cava, manifested by a decreased cardiac output response to treadmill exercise. This long-term effect should be taken into account when selecting patients for ligation.

Acknowledgment
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