The Effects of Coronary Artery Disease on Cardiac Function in Nonhypotensive Sepsis

Raymond F. Raper, M.B., B.S.;† and William J. Sibbald, M.D., F.C.C.P.;‡

To assess the effects of coronary artery disease on cardiac function in the presence of sepsis, we compared several hemodynamic indices in two groups of septic patients. Group 1 (n = 69) consisted of patients with nonhypotensive sepsis without coronary artery disease. Group 2 (n = 25) comprised septic patients who had clinical evidence of coronary artery disease. All patients were hemodynamically stable and normotensive at the time of the study. None required inotropic support. While the two groups had similar mean heart rates, mean blood pressures, and biventricular filling pressures, the mean cardiac index was significantly lower in group 2 (3.5 ± 0.9 L/min/m² v.

Human sepsis is characteristically associated with increases in cardiac output and in systemic oxygen delivery and consumption. While recent data have challenged the concept that death from sepsis is inevitably preceded by a failure of this presumably adaptive, hyperdynamic response, it seems likely that any impairment of the ability of septic patients to generate a higher than normal cardiac output is associated with an increased mortality. Where possible, therefore, it is important to identify and correct any factor that might limit the hyperdynamic response usually seen in the presence of systemic sepsis.

Coronary artery disease imposes significant limitations on the hemodynamic response to exercise and probably to acute pulmonary embolus and human sepsis as well. While the effects of coronary artery disease on cardiac function have been studied extensively in the context of exercise, little has been reported about its effects on the hemodynamic response to sepsis. The prevalence of coronary artery disease in Western countries suggests that this might be a major complicating factor in the hemodynamic management of sepsis. Accordingly, we evaluated the effects of coronary artery disease on cardiac function in the presence of sepsis by comparing two groups of septic patients, one of which had clinical evidence of coronary artery disease.

†From the Richard Ivey Critical Care Trauma Centre, Victoria Hospital and the University of Western Ontario, London, Ontario, Canada.
‡Currently Staff Specialist, Intensive Therapy Unit, Royal North Shore Hospital, St. Leonards, NSW, Australia.
‡Supported by the Ontario Heart Foundation, grant AN 1139.

Material and Methods

Patients

Two groups of patients were studied in the context of ongoing management in a multidisciplinary Critical Care Unit (CCU). Group 1 (N = 69) consisted of patients with acute hypoxemic respiratory failure secondary to systemic sepsis. Group 2 (N = 25) was composed of similar septic patients who also demonstrated clinical evidence of coronary artery disease. This study was part of a larger study of the hemodynamic characteristics of critically ill patients, and patient classification was performed retrospectively by one of the authors (W.J.S.) without reference to the hemodynamic data. The diagnosis of systemic sepsis was based on clinical criteria, which required the coexistence of three of the four following features: (1) fever (T>38.5°C), (2) neutrophil leukocytosis (WBC>11 x 10⁹ WBC/cu mm), (3) positive blood cultures, and (4) an inflammatory focus. The source of sepsis varied in both groups, although pulmonary and intra-abdominal sepsis predominated. The presence of coronary artery disease was evaluated using clinical criteria considered to indicate a high probability of coronary artery disease. Diagnostic features included (1) a typical history of angina pectoris or myocardial infarction, (2) ECG evidence of myocardial infarction or ischemia, or (3) the presence of focal wall motion abnormalities on gated cardiac scintigraphy.

All patients were studied soon after admission to the CCU during a period of hemodynamic stability. Intravenous fluid therapy had been previously titrated to achieve a normotensive state, with an adequate match between oxygen delivery and oxygen demand as reflected by serial arterial lactate levels and mixed venous oxygen tensions. Patients requiring inotropic support to achieve this state were not included in this phase of the study. Thus, the effects on myocardial performance of severe or protracted hypotension and exogenous catecholamines have been discounted. Each study consisted of a detailed hemodynamic assessment and ECG-gated cardiac scintigraphy as detailed below.

When assisted ventilation was required, volume-cycled respirators were used, the tidal volume set at 10 to 15 ml/kg and the ventilatory rate set to maintain the arterial CO₂ tension between 37 and 42 mm Hg. All ventilator circuits contained, in parallel, a fresh gas flow circuit to allow spontaneous respiration. Positive end-expiratory pressure (PEEP) was used if the achievement of an arterial O₂ tension greater than 70 mm Hg required an inspired O₂
fraction greater than 0.5. The lowest level of PEEP achieving this goal was applied.

Specific Measurements

Hemodynamic: Patients were hemodynamically monitored with indwelling arterial lines and flow-directed right heart catheters, each of which had been inserted percutaneously before the study. Appropriate positioning of the pulmonary artery catheter was assessed by chest radiography. All pressures were determined at end-expiration using digital and analogue displays coupled to arterial-venous strain gauge pressure transducers (Hewlett Packard). Where appropriate, the pulmonary artery occlusion pressure (PAOP) was corrected for the effect of positive end-expiratory pressure, as previously described. Cardiac output was measured in triplicate by the thermodilution technique using a commercial cardiac output computer (model 5820, Edwards Laboratories). Measurements were averaged and then indexed for body surface area.

Pulmonary: During each reported study blood was drawn anaerobically from both the arterial line and the distal port of the pulmonary artery catheter (mixed venous) into heparinized syringes, which were immediately placed in ice for subsequent blood gas analysis. Blood gas tensions and pH were analyzed using an AME-1 analyzer (Radiometer). Hemoglobin oxygen saturations were calculated from standard nomograms.

Calculated variables: From the measured variables, we calculated the stroke volume index (SVI), the systemic and pulmonary vascular resistance indices (SVRI and PVRI), the left and right ventricular stroke work indices (LVSWI and RVSWI), the systemic oxygen transport index (O_{2}TI), the oxygen consumption index (VO_{2}I), and the oxygen extraction ratio (O_{2}E). Venous admixture (Qs/Qt) was calculated, according to Berggren, on the lowest inspired oxygen concentration required to maintain the arterial oxygen tension greater than 70 mm Hg.

ECG-gated radionuclide angiography: At the time of each hemodynamic study, radionuclide angiography was performed at the patient's bedside, as previously described. We used an ECG-gated equilibrium blood pool technique with the patient in the supine position. Data pertinent to this study were obtained from a modified LAO projection (40° from anterior, 15° caudal tilt). Regions of interest were manually assigned, and, to minimize the right atrial contribution to right ventricular counts, separate systolic and diastolic regions of interest were assigned for the right ventricle as described by Maddahi et al. From the recorded data, right and left ventricular ejection fractions (RV_EF and LV_EF) were calculated by standard techniques. End-diastolic volume indices (EDVI) were subsequently calculated using the formula:

\[
\text{end-diastolic volume index} = \frac{\text{stroke volume index}}{\text{ejection fraction}}
\]

Statistics

All values were expressed as the mean ± SD. Differences between the mean of each variable for the two groups were assessed using Student's t test for unpaired samples. A p value of less than 0.05 was considered significant.

Results

The results are summarized in Table 1. The group 2 patients with coronary artery disease were, on average, older than the group 1 patients. The two groups had similar mean heart rates (HR), mean arterial pressures (MAP), and biventricular filling pressures (PAOP and CVP). Indicators of respiratory dysfunction (Qs/Qt and PEEP level) were also similar for the two groups. However, the group 2 patients had significantly lower mean cardiac index (CI) and O_{2}TI than the group 1 patients. This difference was related entirely to a significantly lower SVI in group 2 (Table 1). There was no statistically significant difference between the in-hospital mortality rates of the two groups.

Systolic Performance

Myocardial systolic function was assessed by performing Frank-Starling analyses of SWI vs EDVI using group mean data (Fig 1). While the mean LVSWI was significantly lower in group 2 than in group 1, this appears to be related to the difference in left ventricular preload between the two groups, since the mean LVEDVI was also significantly lower in group 2. The RVSWI was not significantly lower in group 2 despite the significantly lower mean RVEDVI in that group. Contractile systolic function was further assessed by comparing mean ejection fractions: there were no significant differences in the mean ventricular ejection fractions of the two groups despite the greater afterload (SVRI and PVRI) in group 2.

Diastolic Performance

Biventricular diastolic function was assessed by considering the relationship between the group mean values of ventricular end-diastolic volume and pressure. For both ventricles, the EDVI was significantly lower in group 2 than in group 1 in spite of statistically similar mean filling pressures (Fig 2).

Discussion

In this study we compared several indices of he-
modulatory function in two groups of patients with a clinical diagnosis of hyperdynamic sepsis to ascertain whether coronary artery disease in this context is associated with hemodynamic abnormalities that cannot be attributed to the septic process alone. We found that the patients with coronary artery disease demonstrated significantly lower levels of systemic blood flow and, hence, of oxygen delivery than patients without coronary artery disease. This difference was clearly related to a reduction in stroke volume, which, in turn, was related to reduced biventricular preload. That biventricular end-diastolic volume indices were significantly lower in group 2 than in group 1 in spite of similar measured filling pressures suggests that diastolic ventricular compliance was relatively impaired in the septic patients with coincident coronary artery disease (Fig 2). The similarity in the mortality of the two groups is surprising. The most likely explanation is that the group 1 patients were quantitatively more ill than those in group 2, and this difference diminished the expected increased mortality in the patients with coronary artery disease.

Sepsis in the human is usually associated with an increase in cardiac output and, hence, in oxygen transport. This increase in oxygen transport subserves the increased peripheral demand for oxygen that is generated by the septic process. Not surprisingly, an inability to augment oxygen transport in the presence of sepsis has been associated with a relatively poor prognosis. Coronary artery disease has clearly been associated with an impaired ability to increase oxygen transport suitably in response to exercise. While little has been reported of the hemodynamic effects of coronary artery disease in the context of sepsis, some limitation of the hyperdynamic response to sepsis would not be unexpected.

In the current study we indeed found that patients with coronary artery disease have lower levels of cardiac output and oxygen transport than a similar group of patients without coronary artery disease. This was so in spite of fluid resuscitation to similar filling pressures and in spite of statistically similar oxygen consumption indices. The lower oxygen transport in the patients with coronary artery disease was due entirely to a reduction in stroke volume, since there was no difference in the mean heart rate or the arterial oxygen content of the two groups.

The lower SVI in the group 2 patients appears to have resulted largely from differences in biventricular preload. In spite of statistically similar right and left ventricular end-diastolic filling pressures, the end-diastolic volume indices of both ventricles were significantly lower in the group 2 patients with coronary artery disease. This implies a difference in diastolic compliance between the two groups. Since only a single-point pressure-volume analysis is available for
each patient, no conclusion regarding the slopes of the ventricular pressure-volume curves can be drawn. Nevertheless, these data indicate that the modulus of chamber stiffness of both ventricles of the group 2 patients was increased since the average pressure-volume curve of this group was left-shifted relative to the group 1 patients without coronary artery disease (Fig 2).

That coronary artery disease might be associated with impaired diastolic compliance is not surprising. Acute myocardial ischemia has been previously reported to reduce diastolic compliance\(^1\) as has myocardial infarction.\(^2\) In fact, several recent publications have indicated that diastolic functional abnormalities are more sensitive indicators of the presence of myocardial ischemia than are systolic functional parameters.\(^3\) The importance of this study is that in the presence of sepsis, coronary artery disease was associated with a clinically significant abnormality of biventricular compliance, which resulted in reduced ventricular preload and, ultimately, in reduced oxygen transport. Since blood oxygen contents in this study were assessed from calculated rather than measured oxygen saturations, it is possible, although unlikely, that a systematic difference in hemoglobin saturation curves between the two groups may negate the observed differences in oxygen transport. This would not, however, negate the observed differences in cardiac function.

The limited assessment of myocardial contractility in this study did not suggest that systolic dynamics were impaired by coronary artery disease. Biventricular afterload, as reflected by the appropriate vascular resistance indices, was higher in the group 2 patients, yet biventricular ejection fractions were not different. The maintenance of biventricular ejection fractions in this group of patients despite a relative increase in biventricular afterload and a relative decrease in biventricular preload indicates that contractile function was certainly not reduced when compared with the septic patients without coronary artery disease. Frank-Starling analyses of stroke work index end-diastolic volume index (Fig 2) likewise indicated no major difference in contractile function between the two study groups. Clearly, coronary artery disease may be associated with impaired contractile function. Thus, it seems highly likely that the exclusion of patients requiring inotropic agents from this study masked this effect. This exclusion has also discounted the effects of exogenous catecholamines on diastolic myocardial function.

It seems most likely that the difference in ventricular compliance between the two groups is related to the presence of coronary artery disease. Other factors that might influence diastolic function, including heart rate and ejection and coronary perfusion pressures,\(^4\) were similar for the two groups. Both PEEP\(^5\) and pulmonary hypertension\(^6\) may affect left ventricular compliance adversely, but these values were not different in the two groups. The patients with coronary artery disease were somewhat older than the patients without. It has been suggested that age alone may affect diastolic myocardial function,\(^7\) although this aspect was not directly assessed in that study. Age alone, however, is not usually associated with reduced ventricular preload\(^8\) and this variable alone would not fully account for the observed differences.

Apart, perhaps, from coronary angiography, there is no truly specific parameter for the diagnosis of coronary artery disease. Especially in the critically ill, history may be unavailable or unreliable. Electrocardiographic abnormalities may be nonspecific and may occur in the absence of coronary artery disease.\(^9\) Whatever their specificity, the common clinical indicators employed in this study to identify patients with coronary artery disease clearly identify a subgroup of septic patients with impaired myocardial compliance. The clinical significance of this finding is that patients with coronary artery disease may benefit from fluid resuscitation to higher filling pressures or from the use of compliance-altering agents that might enable an increase in ventricular preload and hence in cardiac output.

References

10 Calvin JE, Driedger AA, Sibbald WJ. An assessment of myocardial function in human sepsis utilizing ECG gated cardiac

Plan to Attend
54th Annual Scientific Assembly
Anaheim
October 3-7, 1988