Hemodynamic Studies in Cardiogenic Shock

Treatment with Isoproterenol and Metaraminol


SUMMARY
In 14 subjects with severe cardiogenic shock the characteristic findings before treatment were hypotension, low cardiac output, and increased central venous pressure, with normal values for total peripheral resistance. Oliguria, lactic acidosis, hypocapnia, and hypoxemia also were present. These changes were interpreted as reflecting acute heart failure in association with a peripheral vascular response which was inadequate to maintain normal blood pressure. Isoproterenol caused a decrease in venous pressure and an increase in cardiac output. In most cases this was sufficient to increase blood pressure, despite slight reductions in peripheral vascular resistance. In a few cases, however, the inotropic effect of the drug was so small that the reduction in vascular resistance caused a further fall in arterial pressure. Metaraminol caused elevation of venous pressure, peripheral resistance, and blood pressure at the expense of some reduction of cardiac output. An approach to therapy is discussed in the light of these findings.

Additional Indexing Words:
Myocardial infarction Cardiac output Bacteremic shock Vasoconstrictor drugs

Despite numerous studies the hemodynamic changes associated with cardiogenic shock are still not precisely defined. Whereas there is general agreement that cardiac output and blood pressure are reduced, it has been reported that peripheral resistance may be reduced, increased, or normal. Perhaps largely because of these conflicting reports, there is no agreement on even the principles of therapy.

This report concerns an attempt to define the hemodynamic abnormalities that characterize cardiogenic shock, with careful observation and comparison of the effects of isoproterenol and metaraminol on these abnormalities.

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Methods
The word “shock” is used here solely to denote a clinical syndrome consisting of hypotension, pallor, sweat, and tachycardia. Initially, we studied 25 patients who exhibited these symptoms in severe degree with oliguria. Systolic blood pressure recorded by cuff sphygmomanometer was invariably below 80 mm Hg, though it is important to note that intra-arterial pressure was frequently above this level. In 11 of these patients it became clear that infection or loss of blood was the primary or a contributory cause of shock.

The 14 patients who were the subjects of this present study had suffered myocardial infarction between 7 and 96 hours previously; this diagnosis was based on electrocardiographic and enzymatic changes in all patients and was confirmed by findings at necropsy in 10.

The studies were carried out in the intensive-care area of a cardiorespiratory ward with specially trained nurses. In all cases the electrocardiogram was monitored throughout, and oxygen-enriched mixtures (100% O2 by nasal catheter or 40% O2 in air via tracheal tube) were administered; most of the patients had been given digitals. Central venous pressure (CVP) was measured with a water manometer connected to a
polyethylene catheter inserted via an external jugular or median basilic vein into the superior vena cava or right atrium. Arterial pressure was recorded continuously using a polygraph and pressure transducer (Sanborn no. 267-B) connected to a no. 15 Teflon needle inserted into a radial artery. Pressures were recorded in mm Hg and referred to a level 5 cm below the sternal angle. Cardiac output was measured by the dye-dilution technique, using 1.5 to 3.5 mg of indocyanine green flushed through the central venous catheter with 7 ml of normal saline. Blood was withdrawn through a Sekelj whole-blood cuvette\textsuperscript{12} at a constant rate of 9.89 ml/min and changes in optical density were recorded on a 12-inch potentiometric recorder (Westronics, model ASZ-1). The volume of the sampling system was measured precisely, and the data of Milnor and Jose\textsuperscript{13} were used to correct for that distortion of the curve attributable to the sampling system. Curves were analyzed by use of Dow's formula.\textsuperscript{14}

Systemic vascular-resistance index (SVRI)\textsuperscript{*} was calculated from the formula:

\[
SVRI \text{ (dynes} \cdot \text{sec} \cdot \text{cm}^{-5} / \text{m}^2) = \frac{BP_m - CVP_m \times 80}{\text{Cardiac index (L/min/m}^2)\text{.}}
\]

This index represents no more than the ratio of mean arterial pressure to flow, and changes in this ratio are not necessarily attributable to variation in arterial tone. Urine was collected through an indwelling bladder catheter, and its volume was measured hourly. Arterial pH, \(P_{CO_2}\) and \(HCO_3^-\) measurements were made by the technique of Astrup,\textsuperscript{15} and \(O_2\) saturation by the technique of Nahas,\textsuperscript{16} using a Beckman DU spectrophotometer. Arterial blood lactate was measured by the method of Barker and summerson\textsuperscript{17} and pyruvate by the method of friedemann and Haugen.\textsuperscript{18}

The protocol of the study, which was adhered to as closely as possible, was as follows. Samples of arterial blood were taken and initial measurements were made of pressure and output. In some of the patients who had received pressor therapy, this was discontinued for at least 1 hour before initial control values were recorded. In most previous studies of catecholamine therapy in shock, the effect of inadequate venous return, due to hypovolemia or venodilatation, constituted an additional uncontrolled variable. To eliminate this, the protocol required that the central venous pressure be elevated to at least 4 mm Hg in every patient. This was necessary in only one patient (no. 21), who received a transfusion of 800 ml of a plasma expander, polyvinylpyrrolidone (PVP). When control values had been established (table 1), infusion of a solution of isoproterenol (Isuprel) (1 mg in 500 ml of 5\% glucose in water) was commenced at a rate of approximately 10 drops/min. This was increased until either blood pressure or heart rate increased definitely (12 patients). Further observations were made while the infusion was continued for 10 to 45 min, sometimes with different dosages, the maximal dosage rate being approximately 30 drops/min of a double-strength solution. Ten to 20 minutes after stopping the infusion, when heart rate and blood pressure had returned close to control levels, measurements were made again. The study was repeated in comparable fashion in 11 patients, using a solution of metaraminol (Aramine) (100 mg in 500 ml of 5\% glucose in water) at a rate sufficient to raise systolic blood pressure in most patients to between 90 and 110 mm Hg (10 to 30 drops/min).

**Results**

The degree of abnormality present in the patients studied may be judged by comparing the results obtained with normal values. As a first approximation we assumed that the cardiac index, under the conditions of the study, might be expected to vary from 2.5 to 3.9 L/min/m\(^2\). Likewise, using the reported range of arterial pressure in normal subjects, aged 50 to 64 years,\textsuperscript{19} and assuming that mean pressure = diastolic pressure + 1/3 pulse pressure, and that right atrial pressure = 5 mm Hg, the normal range of "driving pressure" (\(BP_m - CVP_m\)) was estimated to be 80 to 120 mm Hg.

As judged by these criteria, the initial control cardiac index invariably was subnormal (mean, 1.57; range, 0.66 to 2.34 L/min/m\(^2\)), and the mean arterial pressure was low (mean, 62 mm Hg; range, 28 to 86 mm Hg) in every instance but one (fig. 1). By contrast, all but two initial values for SVRI fell between isopleths 1,640 and 3,840, and the majority of values probably were within normal range for patients of this age (mean, 2,824; range, 1,860 to 4,880 dynes \(\cdot\) sec \(\cdot\) cm\(^{-5}\) / m\(^2\)).

Initially, 13 of the 14 patients were oliguric...
Physical Data and Initial Control Values on Fourteen Patients

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*Survival.
†After approximately 100 mEq of HCO₃.
‡After infusion of 800 ml of plasma expander (polyvinylpyrrolidone).

(<35 ml of urine/hr), and metabolic acidosis, with elevated values for lactate, was present in eight of the nine patients in whom this was measured (table 1). Despite the inhalation of oxygen-enriched mixtures, significant desaturation was apparent in four of the eight subjects tested.

![Figure 1](http://circ.ahajournals.org/)

The relationship of cardiac index, "driving pressure" (BPm – CVFm), and systemic vascular-resistance index (S.V.R.) at the time of initial observation in 14 patients. The rectangle delineates the approximate range of normality. Broken lines indicate resistance-index isopleths for calculated values of 1,640 and 3,840 dynes • sec • cm⁻²/m².

![Figure 2](http://circ.ahajournals.org/)

The effect of infusion of isoproterenol on cardiac index, "driving pressure," and systemic vascular-resistance index. The rectangle delineates approximate range of normality. Points represent average control values for each patient. Change from control is represented by a separate arrow for each study.

**Effects of Isoproterenol**

Measurements of hemodynamics before and after the infusion of isoproterenol were compared on 33 occasions in 11 patients. In eight patients the cardiac index was increased during infusion and in most of these the arterial pressure rose simultaneously (fig. 2). In two patients the cardiac index fell slightly during infusion. Systemic vascular-resistance index...
B. P. Central venous Heart Cardiac Blood (mg/100 ml) 

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fell or remained unchanged in all but three cases. In figure 3 the changes in cardiac index are related to changes in venous pressure: the CVP decreased toward normal in all but three patients during infusion, and in another the response was variable.

An attempt was made to determine whether the increased cardiac index which commonly resulted from isoproterenol infusion was due mainly to an increase in stroke volume or in heart rate. One patient (six studies) was excluded because his heart rate was kept constant artificially by electrical pacing. As can be seen in figure 4, the cardiac output increased as a result of increases in both stroke volume and heart rate in most instances, a significant reduction in stroke volume occurring in only one subject. Output of urine increased significantly in three patients, and oliguria persisted during infusion in eight.

**Effects of Metaraminol**

Ten patients were studied before and after the infusion of metaraminol on 14 occasions. Arterial pressure increased in all but one study. This increase was associated usually with a decrease in cardiac index (fig. 5). The cardiac index, however, increased significantly in three patients, and the SVRI decreased slightly in two and remained unchanged in a third. The CVP was elevated further in every case (fig. 6). In nine patients in whom the change in stroke volume could be compared with the change in heart rate, no relationship was apparent (fig. 4). One patient excreted significantly more urine during metaraminol infusion.

**Discussion**

**Control Studies**

Our studies confirm the frequent finding of others that cardiogenic shock is a
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Figure 4

Relationship of percentage changes in heart rate and stroke index during infusion of isoproterenol (Isuprel) and metaraminol (Aramine), respectively. During administration of isoproterenol, increments in cardiac output resulted most commonly from increase in both heart rate and stroke volume. No obvious relationship was demonstrated when metaraminol was given.

Figure 5

The effects of infusion of metaraminol on cardiac index, “driving pressure,” and systemic vascular resistance index. Symbols the same as in figure 2.

Figure 6

Relationship of cardiac index to central venous pressure during infusion of metaraminol. Symbols same as in figure 2.

syndrome characterized by low cardiac output with marked reduction in stroke volume and increased venous pressure. However, the systemic vascular resistance, reported to be markedly elevated in some previous studies, was normal in most of our cases.

The reason for this discrepancy is of some interest. It is unlikely that other investigators studied shock of greater severity than that represented by our series, or that this discrepancy is due to differences in the method of measuring blood pressure; it is almost certainly attributable to the universal use of Hamilton's technique for the determination of cardiac output. The validity of this procedure is well proven in normal dye curves. When the curve is markedly prolonged, however, there may be contamination of the downslope of the primary curve by recirculation of indicator from the coronary sinus, a source of error alluded to in the past but generally ignored. In studies to be reported elsewhere, it could be shown by the simultaneous injection of ascorbic acid and green dye that recirculation to the coronary sinus was sufficiently rapid, relative to the initial transit of dye, to cause contamination of the downslope of the dye curve by recirculated indicator. MacKenzie and associates, who took precautions to reduce the dispersion of the primary curve...
by injecting into the right heart and sampling at the aortic root, reported values comparable to those we obtained with the Dow formula for measurement of curve area. We used this procedure because, being based on measurements of the forward part of the curve alone, it appeared less likely to be in error in the presence of severe shock, and because of its proved ability to determine curve area with considerable accuracy in "normal" curves. Output values derived from the Dow and the Hamilton techniques agree within ±10% in 90% of cases and are within ±18% in all. 

However, when comparison was made between the Dow and Hamilton techniques in the present series of patients, there was a discrepancy in excess of 20% at the time of the first study in 11 of the 14 subjects. The lower values were invariably those calculated by the Hamilton method, and discrepancy was invariably greatest when shock was most severe. Thus, we concluded that reports of markedly increased values of vascular resistance in post-infarction shock probably are due largely to method error in measurement of cardiac output. The characteristic abnormality, as suggested by MacKenzie and associates, is a failure to elevate resistance rather than the presence of excessive resistance.

The reason for this inadequate elevation of vascular resistance is unknown. There seems little doubt that hypotension may occur in association with pyrexia in some patients who have suffered infarction; and even though pyrexia rarely accompanies clinical shock, occurring only once in our series (patient 21), there may well be a release of substances with a vasodilator action from the infarcted muscle. Likewise, hypoxia and acidosis, both common in our subjects (table 1) and well-recognized in recent studies might diminish the normal vasoconstrictor response.

Effects of Therapy

The clinical appearance of these patients before treatment was characterized by all of the features of acute heart failure, with elevation of CVP, low cardiac output, oliguria, and lactic acidosis, and in most cases the picture was further complicated by their failure to develop a sufficient degree of vasoconstriction to maintain normal arterial pressure. Although they did not expectorate frothy sputum, it is probable that there was a degree of pulmonary edema as well, as evidenced by the presence of hypoxemia and hypocapnia.

Therapeutic measures to correct the acidosis and hypoxia are not hard to devise. It is uncertain, however, whether priority should next be given to the restoration of cardiac output or blood pressure. Significant elevation of blood pressure by use of purely vasoconstrictor drugs, such as methoxamine hydrochloride, may be expected to result in further depression of cardiac output in patients with cardiogenic shock. This may be less apparent with the use of norepinephrine or metaraminol, which combine a powerful inotropic action with a peripheral vasoconstrictor effect. We chose to contrast the effects of metaraminol with those of isoproterenol, a drug which exerts powerful chronotropic and inotropic action and causes a small degree of peripheral vasodilatation. This drug has produced satisfactory results in experimental coronary shock in dogs and in patients with various forms of noncardiogenic shock.

The effects of these two drugs given consecutively to 10 subjects are depicted in figure 7. In most instances, isoproterenol caused
an increase in output sufficient to elevate arterial pressure despite some reduction in resistance. There was a simultaneous decrease in CVP (fig. 3) which, if paralleled by changes in left atrial pressure, might reflect improvement in ventricular function. We considered these effects favorable. In three instances, however, there was no increase in output to offset the decrease in resistance, and blood pressure fell. We considered this to be an adverse effect. By contrast, metaraminol usually caused elevation of blood pressure at the expense of a decrease in cardiac output, an effect which has been reported by others. The desirability of this effect is open to debate. Although further compromise of peripheral flow aggravates oliguria and acidosis, it may be that in these subjects the increased coronary perfusion pressure is of greater importance to survival.

Although the duration of these observations was brief, our experience with prolonged use of isoproterenol for several days at a time does not suggest that tachyphylaxis develops, and no experimental evidence could be found to suggest that its administration might of itself cause contraction of blood volume. The results obtained in cardiogenic shock are sufficiently encouraging to justify its further trial. Three precautions must be strictly observed during its administration. Ventricular filling must be adequate, as reflected by CVP. Continuous electrocardiographic monitoring is essential, to detect increased ventricular excitability, which we have observed in several patients not reported here. Finally, when the myocardium is so depressed that the isotropic response is absent or small, isoproterenol may effect only some reduction in peripheral resistance. The consequent fall in blood pressure may be disastrous, and for this reason continuous monitoring of blood pressure also is essential.

References
15. Astrup, F.: A simple electrometric technique for the determination of carbon dioxide tension in blood and plasma, total content of carbon.
CARDIOGENIC SHOCK

On Learning in Medicine

To the experimenter immersed in his research, and to the clinician struggling with the load of experience and the needs of his patients, it may seem unpractical to concern ourselves with the theory of medical knowledge. On the other hand, it is perhaps the lack of rational doctrine and a general interest in the problems of method that has made medicine the scene of so much disunited and contradictory effort, and helped to put it down from its historical position as the mother and the nurse of science.—WILFRED TROTTER: The Collected Papers of Wilfred Trotter. London, Oxford University Press, 1941, p. 127.
Hemodynamic Studies in Cardiogenic Shock: Treatment with Isoproterenol and Metaraminol

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