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Research Article

The hemodynamic effects of isoproterenol infusion, 0.5 µg/kg per min were evaluated in eight intact anesthetized dogs during cardiac tamponade. During tamponade, the mean of pericardial pressures was increased from — 1.5 to 12.5 mm Hg, and the mean of right atrial pressures was increased from 1 to 12.4 mm Hg. Mean cardiac output fell from 144.8 to 44.8 ml/kg per min ($P < 0.001$), and rose to 105.6 ml/kg per min ($P < 0.001$) with isoproterenol. Mean cardiac stroke volume fell from 20.3 to 6.1 ml during tamponade ($P < 0.001$) and rose to 12.1 ml with isoproterenol ($P < 0.001$). The heart rate increased from 193.3 beats/min during tamponade to 217.5 beats/min with isoproterenol ($P < 0.05$). During isoproterenol infusion, the mean right atrial pressure and mean pericardial pressure decreased significantly. With cardiac tamponade, the mean blood pressure fell from 157.5 to 126.1 mm Hg ($P < 0.01$) and did not change significantly with isoproterenol, 11 additional animals were studied with norepinephrine infusion during tamponade. There were no consistent hemodynamic effects with infusions of 0.5 and 1 µg/kg per min. With norepinephrine 2, 5, and 10 µg/kg per min cardiac output rose in some experiments. Isoproterenol infusion increased the cardiac output during tamponade principally by increasing cardiac stroke volume and to a lesser degree by increasing the heart [...]

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Hemodynamic Effects of Isoproterenol and Norepinephrine in Acute Cardiac Tamponade

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ABSTRACT The hemodynamic effects of isoproterenol infusion, 0.5 $\mu\text{g/kg}$ per min were evaluated in eight intact anesthetized dogs during cardiac tamponade. During tamponade, the mean of pericardial pressures was increased from -1.5 to 12.5 mm Hg, and the mean of right atrial pressures was increased from 1 to 12.4 mm Hg. Mean cardiac output fell from 144.8 to 44.8 ml/kg per min ($P < 0.001$), and rose to 105.6 ml/kg per min ($P < 0.001$) with isoproterenol. Mean cardiac stroke volume fell from 20.3 to 6.1 ml during tamponade ($P < 0.001$) and rose to 12.1 ml with isoproterenol ($P < 0.001$). The heart rate increased from 193.3 beats/min during tamponade to 217.5 beats/min with isoproterenol ($P < 0.05$). During isoproterenol infusion, the mean right atrial pressure and mean pericardial pressure decreased significantly. With cardiac tamponade, the mean blood pressure fell from 157.5 to 126.1 mm Hg ($P < 0.01$) and did not change significantly with isoproterenol. 11 additional animals were studied with norepinephrine infusion during tamponade. There were no consistent hemodynamic effects with infusions of 0.5 and 1 $\mu\text{g/kg}$ per min. With norepinephrine 2 , 5 , and 10 $\mu\text{g/kg}$ per min cardiac output rose in some experiments. Isoproterenol infusion increased the cardiac output during tamponade principally by increasing cardiac stroke volume and to a lesser degree by increasing the heart rate. It is postulated that the increased stroke volume resulted from an increased ejection fraction with greater decrease in end-systolic than end-diastolic ventricular volume. These effects are consistent with the known positive inotropic, peripheral vasodilator, and positive chronotropic effects of isoproterenol.

INTRODUCTION

In acute cardiac tamponade, diastolic expansion of the ventricles is limited by the available space in the pericardial sac (1). Hence, as intrapericardial pressure

rises, atrial pressure and ventricular diastolic pressure also rise; cardiac stroke volume decreases, and despite partial compensation by tachycardia, cardiac output and blood pressure fall (2), and death may ensue if progressive cardiac tamponade is unchecked. Isoproterenol, a beta sympathetic-stimulating agent, is capable of increasing the cardiac output of the normal heart by augmenting both stroke volume and heart rate (3-5). Isoproterenol is known to increase myocardial contractility, decreasing both end-systolic and end-diastolic volumes of the heart, and to increase the systolic ejection fraction (6), in addition to its positive chronotropic action. Although the heart subjected to acute tamponade cannot ordinarily increase its output by greater diastolic filling, it seemed likely that isoproterenol, by increasing heart rate and cardiac stroke volume, might increase cardiac output in acute tamponade. Since isoproterenol tends to decrease systemic vascular resistance, we decided also to study the effects of norepinephrine, a positive inotropic agent that tends to increase systemic vascular resistance.

METHODS

The studies were made upon mongrel dogs weighing from 17.7 to 28.6 kg and anesthetized with pentobarbital sodium, 30 mg/kg body weight. The animals were supported in the supine posture, and vertical midchest position used as a zero reference point. Aortic, right atrial, and intrapericardial pressures were measured simultaneously via Cournand catheters placed by fluoroscopy; Statham P24DB or P23BB transducers and a four-channel Sanborn direct-writing oscillograph were used for pressure measurements. Cardiac outputs were measured by the Stewart-Hamilton principle. Indocyanine green dye in 2.5 mg amounts was injected into the right atrium and sampled from the aortic arch; dye concentrations were read from a Gilford densitometer recording as blood was withdrawn at a constant rate with a Colson syringe. The apparatus was calibrated with the same lot of dye in concentrations of 5 and 10 mg/liter contained in the same animal's blood. The pericardial sac was cannulated in the closed chest animal by passage of a Brockenbrough catheter and needle through the right atrial wall under fluoroscopy. The position of the catheter tip was established

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by fluoroscopic observation during injection of from 2 to 3 ml of 75% Hypaque. Experiments were acceptable only if the saline solution injected into the pericardial sac to produce tamponade could be completely recovered (or within 8 ml), and if the position of the catheter tip and the intact state of the parietal pericardium were confirmed by autopsy of the animal at the conclusion of the experiment. Heart rate was measured from the phasic blood pressure recording. Cardiac stroke volume was estimated by dividing the cardiac output, expressed in ml/min, by the heart rate. Total peripheral resistance was expressed in arbitrary units, obtained by dividing mean aortic pressure (mm Hg) by cardiac output, expressed in liters/min.

After control measurements of pressures and cardiac output, cardiac tamponade was induced by serial injections of 20-ml amounts of physiologic saline, warmed to 37°C, into the pericardial sac, until the right atrial pressure was 9-14 mm Hg. Measurements of pressure and cardiac output were then repeated. The animal then received into the femoral vein either an infusion of isoproterenol, 0.5 µg/kg per min or an infusion of an equal volume of physiologic saline solution for the same period of time. A Harvard constant infusion pump was used to control the infusion rate. After 3 min, measurements of pressures and cardiac output were repeated and the infusion was discontinued. Then, after 5 min, a second infusion of either isoproterenol or saline solution, whichever was not used first, was given for the same period of time. Then cardiac output and pressure measurements were repeated. The order of the observations was randomized, so that some animals received isoproterenol first, and others saline first. Then the second infusion was halted and after another 5 min cardiac output and pressure measurements were made. Then the saline solution was aspirated from the pericardial sac and cardiac output and pressure measurements were again made. Hence, measurements of cardiac output and pressures were made in six periods: control, tamponade, tamponade plus isoproterenol, tamponade plus saline infusion, tamponade, and control. The mean values obtained from the eight animals for each period were

compared for statistically significant differences by means of the student *t* test (7).

In order to study the hemodynamic effects during tamponade of a sympathomimetic amine that increases cardiac contractility and also increases peripheral resistance, 11 additional animals were studied during an infusion of norepinephrine. These 11 animals were studied in a fashion identical with those receiving isoproterenol. Five animals received norepinephrine, 0.5 µg/kg per min during tamponade; three received norepinephrine, 1 µg/kg per min and 2 µg/kg per min, and three received norepinephrine, 5 µg/kg per min and 10 µg/kg per min.

RESULTS

Eight animals had acceptable studies with isoproterenol. The saline solution aspirated from the pericardial sac to relieve tamponade was either clear or slightly blood-tinged, hence there was no evidence of hemodynamically significant bleeding into the pericardial space. The volumes of saline solution required to produce tamponade were 80-260 ml, with a range of 4.9 to 11.0 ml/kg body weight.

The results in the animals receiving isoproterenol, 0.5 µg/kg per min and in those receiving norepinephrine, 0.5 µg/kg per min are shown in Tables I and II. In the animals receiving isoproterenol, 0.5 µg/kg per min, the control cardiac outputs averaged 144.8 ml/kg per min (Table I), and fell significantly during tamponade ($P < 0.001$) to 44.8 ml/kg per min, and rose significantly during isoproterenol ($P < 0.001$) to 105.6 ml/kg per min. The cardiac outputs were virtually identical during the two tamponade periods with no infusion, and the one tamponade period during saline infusion. The increase of cardiac output was due princi-

TABLE I
Hemodynamic Effects of Isoproterenol in Experimental Cardiac Tamponade (Eight Animals)

	Control before tamponade	Tamponade	Isoproterenol during tamponade	Tamponade	Saline	Control after tamponade
Cardiac output, ml/kg per min	144.8 ± 18.5*	44.8 ± 4.7	105.6 ± 12.9	44.6 ± 3.9	46.7 ± 4.8	155.9 ± 13.2
Heart rate, beats/min	181.9 ± 10.6	193.3 ± 8.9	217.5 ± 7.8	198.9 ± 10.5	196.5 ± 10.8	170.3 ± 6.8
Right atrial pressure, mm Hg	1.0 ± 0.035	12.4 ± 0.61	9.0 ± 0.94	11.7 ± 0.71	11.7 ± 0.39	1.2 ± 0.39
Intrapericardial pressure, mm Hg	-1.5 ± 0.37	12.5 ± 0.79	8.6 ± 0.94	12.15 ± 0.41	12.3 ± 0.49	-1.7 ± 0.44
Cardiac stroke volume, ml	20.3 ± 2.7	6.1 ± 0.8	12.1 ± 1.6	5.9 ± 0.7	6.2 ± 0.9	23.6 ± 2.1
Blood pressure, mm Hg	157.5 ± 5.9	126.1 ± 8.6	122.1 ± 8.7	129.4 ± 7.7	129.3 ± 8.6	159.8 ± 8.2
Total peripheral resistance	49.6 ± 7.3	117.2 ± 13.6	51.2 ± 6.0	122.8 ± 11.9	122.1 ± 12.9	44.6 ± 5.5

* Mean ± SE.

TABLE II
Hemodynamic Effects of Norepinephrine 0.5 µg/kg per min in Experimental Cardiac Tamponade (Five Animals)

	Control before tamponade	Tamponade	Norepinephrine during tamponade	Tamponade	Saline infusion	Control after tamponade
Cardiac output, <i>ml/kg per min</i>	165.8 ±19.7*	41.4 ±3.6	45.9 ±2.7	45.6 ±2.6	52.1 ±5.1	153.4 ±11.4
Heart rate, <i>beats/min</i>	167 ±16.1	163.8 ±11.2	168.4 ±10.3	157.2 ±10.9	156.6 ±12.2	134.0 ±14.0
Right atrial pressure, <i>mm Hg</i>	0.7 ±0.32	10.6 ±0.70	10.1 ±0.33	9.1 ±0.63	9.1 ±0.63	0.2 ±0.21
Intrapericardial pressure, <i>mm Hg</i>	0.1 ±0.33	12.9 ±0.86	12.1 ±0.79	11.6 ±0.86	11.7 ±0.91	-1.7 ±0.67
Cardiac stroke volume, <i>ml</i>	18.8 ±1.2	4.8 ±0.2	5.2 ±0.1	5.5 ±0.2	6.3 ±0.5	22.1 ±1.1
Mean arterial blood pressure, <i>mm Hg</i>	146.8 ±14.7	85.5 ±21.0	103.9 ±19.0	98.0 ±18.4	103 ±17.1	163 ±16.4
Total peripheral resistance	50.2 ±9.2	109.2 ±26.5	118.1 ±18.6	116.1 ±24.0	110.8 ±23.7	58.6 ±9.6

* Mean of five experiments ±SE.

pally to a rise of cardiac stroke volume (Table I), and only slightly to an increase of heart rate (Table I). The average cardiac stroke volume fell significantly from 20.3 to 6.1 ml during tamponade ($P < 0.001$) and rose significantly during isoproterenol ($P < 0.001$) to 12.1 ml. The heart rate rose, but not significantly, during tamponade from a mean of 181.9 to 193.3 beats/min ($P > 0.3$). During isoproterenol the mean heart rate rose significantly to 217.5 beats/min ($P < 0.05$).

In the control period intrapericardial pressure was subatmospheric in each animal with an average of -1.5 mm Hg. During tamponade mean intrapericardial pressure rose significantly to 12.5 mm Hg ($P < 0.001$), and during isoproterenol fell significantly to 8.6 mm Hg ($P < 0.01$) (Table I), with a return to the previous tamponade level after discontinuing isoproterenol. Right atrial pressure changes followed the intrapericardial pressure closely (Table I). The control mean right atrial pressure was 1 mm Hg, with a significant rise to 12.4 mm Hg during tamponade ($P < 0.001$) and a significant fall to 9 mm Hg during isoproterenol ($P < 0.01$). During tamponade the mean systemic blood pressure fell significantly from an average of 157.5 to 126.1 mm Hg ($P < 0.01$) (Table I). There was no significant change in the mean aortic blood pressure (122.1 mm Hg) during isoproterenol ($P > 0.2$). The total peripheral resistance rose strikingly during tamponade from a mean of 49.6 arbitrary units to 117.2 units ($P < 0.001$). During isoproterenol the total peripheral resistance fell significantly to 51.2 units ($P < 0.001$).

During saline infusion, the hemodynamic measurements were essentially unchanged from the two tamponade periods with no infusion (Table I).

In contrast to the changes observed during isoproterenol, the infusion of 0.5 µg/kg per min norepinephrine produced little consistent hemodynamic effect in five animals studied during cardiac tamponade, as shown in Table II. In the control period, mean cardiac output was 165.8 ml/kg per min, falling to 41.4 ml/kg per min during tamponade, and was essentially unchanged at 45.9 ml/kg per min during norepinephrine. Heart rate averaged 167 beats/min during the control period, 163.8 beats/min during tamponade, and 168.4 beats/min when norepinephrine was infused during cardiac tamponade. Mean right atrial pressure was 0.7 mm Hg in the control period, 10.6 mm Hg during tamponade, and 10.1 mm Hg when norepinephrine was infused during tamponade. Mean intrapericardial pressure rose from 0.1 to 12.9 mm Hg during tamponade, and was not changed (12.1 mm Hg) by norepinephrine infusion during tamponade. Cardiac stroke volumes averaged 18.8 ml in the control period, 4.8 ml during tamponade, and were essentially unchanged when norepinephrine was infused (5.2 ml). Mean arterial blood pressures averaged 146.8 mm Hg in the control period, falling to 85.5 mm Hg with tamponade. There was a rise in mean blood pressure with norepinephrine to an average of 103.9 mm Hg but this was not significantly different from that during saline infusion (103 mm Hg).

Total peripheral resistance, as in the animals receiv-

ing isoproterenol, rose during tamponade; there was a slight but not significant increase during norepinephrine infusion (Table II).

Three animals received norepinephrine 1 $\mu\text{g/kg}$ per min and 2 $\mu\text{g/kg}$ per min.¹ Although arterial blood pressure rose, there was no significant change in cardiac output at the lower infusion rate. In the same animals, norepinephrine, 2 $\mu\text{g/kg}$ per min, increased cardiac output and stroke volume in only one of three dogs, and right atrial pressure and intrapericardial pressure did not change significantly. When norepinephrine was infused at the rate of 5 and 10 $\mu\text{g/kg}$ per min, blood pressure increased at each infusion rate in each of the three animals. In animal No. 14-67, cardiac output increased primarily through an increased heart rate, stroke volume remaining essentially unchanged at each infusion rate. In animal No. 14-68, the cardiac output increased at each infusion rate, as a result of a modest increase in both cardiac rate and stroke volume. In animal No. 14-69, there was no significant change in cardiac output during either infusion of norepinephrine.

Because of the inconsistent hemodynamic effects of even large doses of norepinephrine during tamponade, the potency of the same lot was tested by rapid injection of 1 $\mu\text{g/kg}$ norepinephrine intravenously in five intact anesthetized dogs without tamponade. Systemic systolic blood pressure promptly rose 49 to 86 mm Hg in each instance.

DISCUSSION

In these experiments the hemodynamic effects of cardiac tamponade were comparable to those reported in previous investigations (2); cardiac output and stroke volume fell; heart rate rose; blood pressure decreased; and peripheral resistance rose. Isaacs, Berglund, and Sarnoff (1) concluded that the circulatory effects of cardiac tamponade resulted not from pressure on the great veins, and not from impaired cardiac contractility, but from limited diastolic filling of the ventricles, since ventricular function curves were normal when related to transmural ventricular diastolic pressure. Ferguson, Bristow, Mintz, and Rapaport (8) and O'Rourke and associates (9) found that despite a reduced end-diastolic volume in tamponade, the end-systolic volume was unchanged and hence the ejection fraction was reduced.

In both animal and human experiments, isoproterenol can be shown to reduce end-systolic and end-diastolic cardiac volume, to increase systolic ejection fraction, to increase heart rate, and to decrease peripheral resistance

(3-5). These changes occur despite a decrease of central venous pressure (10). Each of these effects might be expected to improve cardiac output in acute cardiac tamponade. In the present experiments, increased cardiac stroke volume was more important in the increase of cardiac output during tamponade than was tachycardia. Since diastolic filling of the ventricles presumably could not be increased without raising the atrial pressure, it is logical to assume that cardiac stroke volume was elevated by increase of systolic ejection fraction and a reduction of end-systolic volume. Some reduction of end-diastolic volume also probably occurred. These concepts were supported by the significant decreases of intrapericardial pressure and right atrial pressure observed when isoproterenol was administered during cardiac tamponade. The difference between mean right atrial pressure and intrapericardial pressure did not increase with isoproterenol; hence, the increased cardiac stroke volume was due to an increased contractility rather than to increased effective filling pressure.

In these studies, norepinephrine, 0.5 $\mu\text{g/kg}$ per min, failed to increase cardiac rate or stroke volume during tamponade, and caused but slight increase in mean blood pressure or peripheral resistance. An inconsistent increase of cardiac output occurred with 2, 5, and 10 $\mu\text{g/kg}$ per min norepinephrine. Norepinephrine, like epinephrine and isoproterenol, increases the force of myocardial contraction (cardiac beta sympathetic-stimulating effect) in animals and in man (11, 12), but ordinarily, unlike isoproterenol, decreases heart rate, increases peripheral resistance (peripheral alpha-receptor-stimulating effect), and leaves cardiac output unchanged or slightly decreased in intact man (13). The failure to increase cardiac output during cardiac tamponade with doses that were effective when isoproterenol was used may well be related to the failure to decrease peripheral resistance and the lack of consistent increase in heart rate. The positive inotropic effect of norepinephrine did not result in a consistent increase of cardiac output, although norepinephrine may increase cardiac output in hemorrhagic shock (14), where central venous pressure is low, rather than increased as it is in tamponade. Even though norepinephrine, 5 $\mu\text{g/kg}$ per min, increased heart rate in five of six experiments, cardiac output rose significantly in only three of these five animals, lending further support to the importance of inotropic rather than chronotropic influences in increasing the cardiac output during tamponade. The increase of heart rate at these high doses may have been related to a preponderance of the beta receptor effect of norepinephrine. In addition, the pentobarbital anesthesia has atropine-like effects (15). Atropine is known to block the aortic arch and carotid sinus buffer nerves; in man, norepinephrine infused after atropine may increase both heart rate and cardiac output (16).

¹ The tabulated results obtained in animals receiving norepinephrine, 1 $\mu\text{g/kg}$ per min.; 2 $\mu\text{g/kg}$ per min.; 5 $\mu\text{g/kg}$ per min, and 10 $\mu\text{g/kg}$ per min have been omitted. These tables may be obtained by writing to Dr. N. O. Fowler, Cardiac Research Laboratory H-3, Cincinnati General Hospital, Cincinnati, Ohio 45229.

The relatively insignificant effect of the lower doses of norepinephrine upon arterial blood pressure and total peripheral resistance may have been related to nearly maximal sympathetic nerve stimulation and catecholamine release attendant upon the low blood pressure and reduced cardiac output accompanying acute cardiac tamponade.

In acute cardiac tamponade, restoration of more nearly normal circulatory dynamics is most readily achieved by aspiration of liquid from the pericardial sac, thus relieving tamponade. However, in some instances, this procedure cannot be carried out promptly. Cooper, Stead, and Warren (17), Blalock and Ravitch (18), and Isaacs and coworkers (1) demonstrated that intravenous infusions may increase the systemic arterial blood pressure in man or animals with acute tamponade. However, this procedure is not always useful (19), especially with severe tamponade (1). The present study demonstrates that isoproterenol infusion is an additional means of providing temporary increase of cardiac output in acute cardiac tamponade. The animals used in these studies had normal myocardial function initially. This condition does not always occur in cardiac tamponade in man but is probably frequently present, especially when tamponade follows trauma. The results are consonant with those described by Kuno (20) in experiments performed with the heart-lung preparation and reported in 1917. Adrenaline, 100 μ g, added to the venous reservoir, increased blood pressure and cardiac output and lowered venous pressure during cardiac tamponade in these preparations. In Kuno's experiments, the increased cardiac output produced by adrenaline must have been related to positive inotropic and chronotropic effects, since peripheral resistance could not change appreciably. The increased cardiac stroke volume observed with isoproterenol infusion during cardiac tamponade may well be related to the positive inotropic effects of isoproterenol. However, the decreased total peripheral resistance produced by isoproterenol is probably significant in permitting or augmenting this inotropic action, as suggested by the lesser cardiac output response to norepinephrine.

It would be desirable to study the effect of a pure vasodilator upon the hemodynamics of cardiac tamponade. In an abstract, we reported that in dogs given phenoxybenzamine, a consistent increase of stroke volume, heart rate, and cardiac output occurred during tamponade.² However, phenoxybenzamine is known to increase plasma vasopressor activity in cats (21), and to produce positive inotropic and chronotropic effects on the heart of intact dogs (22). These effects are not found in the isolated rabbit heart (22), and are presumably related to adrenal and sympathetic catecholamine

² Holmes, J. C., and N. O. Fowler. Sympathetic stimulation and blockade in acute cardiac tamponade. Submitted for publication.

release by direct stimulation, or to a reflex sympatho-adrenal effect from blood pressure reduction. Hence, the use of phenoxybenzamine did not achieve the desired separation between the vasodilator and positive inotropic influences upon cardiac dynamics during experimental cardiac tamponade.

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