Hemodynamic Effects of Nitroprusside and Hydralazine in Experimental Cardiac Tamponade

Noble O. Fowler, M.D., Marjorie Gabel, and John C. Holmes, M.D.

SUMMARY Cardiac tamponade is associated with decreased cardiac output and increased systemic vascular resistance. Thus, vasodilator drugs might lower systemic resistance and increase cardiac output. Three groups of dogs were studied during tamponade. Group I received nitroprusside only; group II received blood transfusion and then nitroprusside; group III received hydralazine.

In group I, nitroprusside lowered right atrial pressure and systemic resistance; cardiac output was unchanged. In group II, transfusion raised right atrial pressure but not cardiac output. Then nitroprusside raised cardiac output significantly. Hydralazine decreased right atrial pressure less than nitroprusside but decreased vascular resistance and raised cardiac output.

Both nitroprusside and hydralazine decreased systemic vascular resistance during tamponade, but only hydralazine raised cardiac output probably because of its lesser effect upon the capacitance vessels. Nitroprusside maintained cardiac output during tamponade despite lowered right atrial pressure but increased cardiac output only after transfusion.

With the last several years, vasodilator drugs have been found capable of increasing cardiac output while lowering cardiac filling pressure in cardiogenic shock and in left ventricular failure in man. Presumably the reduced left ventricular afterload permits the damaged ventricle to maintain or improve stroke volume at the same or lower ventricular filling pressure, thus reducing myocardial oxygen consumption. Some of these drugs may lower cardiac filling pressure also by a dilating action upon the venous capacitance bed. Among the drugs used for this purpose are: nitroglycerin, nitroprusside, isosorbide dinitrate, phenolamine, nitroprusside, hydralazine, and phenoxybenzamine. These agents have been found useful in acute cardiac infarction with cardiogenic shock, chronic heart failure with ischemic heart disease, refractory heart failure of other cause, and in congestive cardiomyopathy. Hemodynamic benefits have also been found in aortic insufficiency and in severe mitral insufficiency.

Cardiac tamponade is a hemodynamic disorder associated with a fall in cardiac stroke volume, decreased cardiac output, a lesser fall in blood pressure, and consequently an increase of systemic vascular resistance. Thus, a drug which tends to lower systemic vascular resistance might increase cardiac stroke volume by improving left ventricular ejection fraction in the face of an unchanged filling pressure of the cardiac ventricles.

Accordingly, we decided to test the hemodynamic effects of sodium nitroprusside and of hydralazine in dogs with experimental cardiac tamponade. Nitroprusside tends to reduce the cardiac filling pressure by dilating the venous capacitance bed; thus we studied the effects of nitroprusside in two groups of animals with tamponade. In the first group, nitroprusside infusion was permitted to decrease cardiac filling pressure as well as systemic vascular resistance. In the second group, cardiac filling pressure was maintained at the original tamponade level by autologous blood transfusion. In a third group, we investigated the hemodynamic effects during tamponade of a vasodilator (hydralazine) which has less effect upon the venous capacitance bed.

These studies demonstrate that nitroprusside decreased systemic vascular resistance and maintained but did not increase cardiac output during tamponade when right atrial pressure was permitted to fall. However, when right atrial pressure was maintained by autologous blood transfusion, nitroprusside significantly increased cardiac output during cardiac tamponade. On the other hand, hydralazine increased cardiac output during tamponade without prior blood transfusion.

Methods

The studies were carried out upon three groups of anesthetized mongrel dogs of either sex, weighing 16.8 to 30.6 kg. Group I comprised six dogs which were given sodium nitroprusside intravenously during cardiac tamponade. Group II animals were transfused with autologous blood during tamponade in order to raise the right atrial pressure by 2 to 5 mm Hg. Two weeks before the study, 400 ml blood was harvested aseptically and another 400 ml seven days before the study. The blood was stored in two plastic blood donor bags containing 1.66 g sodium citrate, and 206 mg citric acid in 63 ml solution, and stored under refrigeration at 5°C. Group III consisted of six dogs which received hydralazine intravenously during cardiac tamponade.

The animals were prepared five days before the study with indwelling intrapericardial plastic catheters inserted under pentobarbital sodium anesthesia. On the day of the study the animals were anesthetized with pentobarbital sodium, 30 mg/kg given intravenously, and allowed to breathe spontaneously. During each period of the study the following measurements were made: systemic blood pressure; right atrial pressure; intrapericardial pressure; heart rate; cardiac output; arterial PO2, pCO2, pH and hematocrit; and esophageal temperature by thermocouple. The arterial PO2 was maintained above 60 mm Hg partial pressure by supplemental oxygen if necessary, and the arterial pH was maintained between 7.35 and 7.45 by intravenous injection of 10 mEq NaHCO3 if necessary. These measurements were made by Astrup Blood Gas Analyzer. Pressures were recorded by an 8-channel Grass recorder. Rectal temperatures did not vary more than 1°C. Cardiac output was determined by the indicator-dilution method; we injected 1 ml in-
docyanine green dye into the right atrium and sampled from the aorta.

In the control period cardiac outputs were determined at three minute intervals along with the other variables. Paired cardiac outputs varied no more than 20% and usually no more than 10%. After control cardiac outputs, cardiac tamponade was induced with 0.85% NaCl solution at 37°C until the intrapericardial pressure was raised by 8 to 10 mm Hg from the control level, and until the cardiac output fell at least 25–30%. After five minutes of tamponade, two cardiac outputs were performed at three-minute intervals and the other variables were measured as well.

Group II animals were given autologous blood harvested 7–14 days previously. The blood was warmed to 37°C and infused intravenously at a rate of 100 ml/min so that right atrial pressure increased rapidly by 3 to 5 mm Hg. The infusion was then continued at the slowest rate that would maintain the elevated RAP constant. After 3–5 min of stabilization two cardiac outputs were performed at three-minute intervals. The other variables were measured as well. Then, as the infusion of blood was continued, usually no faster than 16 ml/min, an infusion of nitroprusside intravenously was begun at the dosage of 16 μg/kg/min. After this infusion for four minutes and stabilization of pressures, paired cardiac outputs were measured at three-minute intervals; the other variables were measured as well. The nitroprusside infusion was then stopped and, after 7–10 min, the output measurements were repeated. The blood transfusion was stopped and the right atrial and pericardial pressures were returned to the original tamponade levels by bleeding. After stabilization for 3–5 min, paired cardiac outputs and other variables were measured. Cardiac tamponade was relieved by withdrawal of all of the injected fluid. In all experiments fluid was recovered within 5 ml of the amount injected. After five minutes, paired cardiac outputs and the other variables were measured at three minute intervals.

Group III. The six animals in this group were prepared and studied in the same way as those in group I, except that they received as anesthesia morphine, 3 mg/kg subcutaneously and chloralose, 70 mg/kg intravenously. These animals received hydralazine rather than sodium nitroprusside. After duplicate hemodynamic measurements in a control period, paired measurements were made during tamponade. The animals then received 20 mg hydralazine intravenously as a bolus; hemodynamic measurements were repeated four and eight minutes later. The animals then received another bolus injection of 20 mg hydralazine, followed by hemodynamic measurements four and eight minutes later. The four and eight minute measurements were paired and averaged in data analysis. Then the pericardial fluid was removed and paired hemodynamic measurements were repeated.

Total peripheral resistance in arbitrary units was calculated by dividing the difference between mean blood pressure and right atrial pressure, expressed in mm Hg, by cardiac output, expressed in liters per minute. Mean arterial blood pressure was calculated by adding one-third of the arterial pulse pressure to the diastolic blood pressure.21

**Results**

The results are summarized in tables 1, 2 and 3. Table I shows the results obtained in the six group I animals with cardiac tamponade given sodium nitroprusside, 16 μg/kg/min. These animals did not receive blood transfusion. With cardiac tamponade, right atrial pressure (RAP) and intrapericardial pressure (PP) increased and cardiac output fell significantly. Heart rate increased significantly, and stroke volume fell. Mean blood pressure fell, and total peripheral resistance (TPR) rose significantly. The infusion of sodium nitroprusside was followed by significant decrease in RAP, PP, and mean blood pressure. However, cardiac output showed no change, 95.0 ± 11.8 ml/kg/min vs pre-infusion value of 99 ± 11.5 ml/kg/min; cardiac stroke volume and heart rate also showed no change with nitroprusside, although TPR fell significantly. Following relief of tamponade, cardiac output, blood pressure, and stroke volume returned toward control values.

Table 2 shows the results in the eight group II animals with cardiac tamponade given sodium nitroprusside intravenously after right atrial pressure was raised by 3 to 5 mm Hg by transfusion of the animal's previously harvested

| Table 1. Hemodynamic Data—Dogs with Cardiac Tamponade Receiving Sodium Nitroprusside |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Cardiac output (ml/kg/min)      | Control         | Tamponade       | Nitroprusside infusion | After nitroprusside | Remove tamponade |
| Heart rate (beats/min)          | 162.0 ± 15.1    | 215.3 ± 6.1**   | 199.0 ± 10.3           | 191.0 ± 9.3       | 147.5 ± 15.6**  |
| Stroke volume (ml/kg)           | 1.06 ± 0.11     | 0.45 ± 0.05***  | 0.47 ± 0.03            | 0.48 ± 0.04**     | 1.06 ± 0.03***  |
| Right atrial pressure (mm Hg)   | -1.8 ± 0.7      | 7.8 ± 0.8***    | 3.8 ± 0.5***           | 5.2 ± 0.6*        | -2.0 ± 0.5      |
| Intrapericardial pressure (mm Hg)| -3.2 ± 0.9      | 6.9 ± 0.6***    | 3.8 ± 0.7***           | 4.8 ± 0.3         | -4.2 ± 0.7      |
| Mean blood pressure (mm Hg)     | 138.0 ± 3.7     | 133.3 ± 7.8     | 92.7 ± 7.8***          | 105.7 ± 7.2*      | 133.5 ± 5.5***  |
| Total peripheral resistance (arbitrary units) | 43.3 ± 7.68     | 63.5 ± 7.92***  | 45.7 ± 5.07**          | 53.4 ± 5.42†      | 41.6 ± 3.6***   |

**NOTE:** 1) ** vs control (P <0.01); *** vs control (P <0.001).
2) ** vs tamponade (P <0.01); *** vs tamponade (P <0.001).
3) ** vs control (P <0.01); * vs nitroprusside (P <0.05); † vs nitroprusside (P <0.01).
4) ** vs nitroprusside (P <0.01); *** vs after nitroprusside (P <0.001).
blood. As in group I, cardiac tamponade was associated with tachycardia, a fall in mean blood pressure and decrease in cardiac output and stroke volume, along with increase of right atrial and intrapericardial pressure and TPR. With autologous blood transfusion, the RAP and PP rose significantly. However, cardiac output and stroke volume demonstrated no change. The infusion of sodium nitroprusside decreased RAP and PP. Cardiac output, heart rate and stroke volume each rose significantly. TPR fell significantly. When sodium nitroprusside was stopped, these variables returned toward their previous levels with the following significant changes: cardiac output and heart rate rose and TPR, blood pressure, RAP and PP rose. Removal of blood in order to return RAP to the pre-infusion value was not associated with hemodynamic changes. Relief of tamponade was followed by changes similar to those seen in group I, except that stroke volume was significantly higher than the control value. Left ventricular end-diastolic pressures were measured by a Millar catheter in four animals. The changes were very much like those in right atrial pressure. Control pressures averaged $-0.8$ mm Hg; during tamponade they averaged $7.9$ mm Hg; after blood transfusion, the mean left ventricular end-diastolic pressure was $13.5$ mm Hg, and after nitroprusside the average fell to $7.3$ mm Hg.

Group III. The initial heart rates were slower than in groups I and II owing to the morphine-chloralose anesthesia (table 3). The hemodynamic changes after cardiac tamponade were similar to those described in groups I and II. The bolus intravenous injection of 20 mg hydralazine was followed by a significant decline in RAP, PP, mean BP and systemic vascular resistance with a significant rise in cardiac output and in stroke volume. Heart rate was unchanged. Further changes in the same direction were seen after a second 20 mg bolus of hydralazine. Control mean RAP during tamponade in the nitroprusside group ($7.8$ mm Hg) was not significantly different from that in the hydralazine group ($9.7$ mm Hg). However, the mean RAP after the first dose of hydralazine ($7.8$ mm Hg) was significantly greater than that after nitroprusside ($3.8$ mm Hg), $P < 0.01$. The mean RAP ($6.6$ mm Hg) after the second dose of hydralazine was also significantly greater than after nitroprusside, $P < 0.05$.

After relief of tamponade, the mean blood pressure, systemic resistance and RAP were significantly lower than during the control period. Cardiac output and heart rate were significantly greater than during the control period.

Systemic vascular resistances were not different during tamponade in group I (nitroprusside — $63.5$ U) and in group III (hydralazine — $53.6$ U) animals. After the first dose of hydralazine, the mean systemic vascular resistance was lower after hydralazine ($33.4$ U) than after nitroprusside ($45.7$ U) but not significantly so. After the second dose of hydralazine, the mean systemic vascular resistance was lower after hydralazine ($27.7$ units) than after nitroprusside ($45.7$ units), $P = 0.02$.

**Discussion**

In cardiac tamponade, diastolic filling of the ventricles is reduced. Systemic arterial blood pressure is maintained but
Table 1. Hemodynamic Effects of Hydralazine During Cardiac Tamponade

<table>
<thead>
<tr>
<th></th>
<th>(1) Control</th>
<th>(2) Tamponade</th>
<th>(3) Hydralazine infusion</th>
<th>(4) Hydralazine infusion</th>
<th>(5) Removal of tamponade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (ml/kg/min)</td>
<td>122.1 ± 13.3</td>
<td>79.1 ± 11.9</td>
<td>108.9 ± 19.0**</td>
<td>133.9 ± 19.3***</td>
<td>223.3 ± 30.8**</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>79.5 ± 12.6</td>
<td>217.5 ± 6.9</td>
<td>218 ± 7.4</td>
<td>213.8 ± 7.0</td>
<td>180.0 ± 16.7**</td>
</tr>
<tr>
<td>Stroke volume (mg/kg)</td>
<td>1.66 ± 0.22</td>
<td>0.37 ± 0.06***</td>
<td>0.48 ± 0.07**</td>
<td>0.59 ± 0.08**</td>
<td>1.23 ± 0.10**</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>0.32 ± 0.98</td>
<td>9.7 ± 1.03</td>
<td>7.8 ± 0.88***</td>
<td>6.6 ± 0.95**</td>
<td>-3.0 ± 0.68***</td>
</tr>
<tr>
<td>Intrapericardial pressure (mm Hg)</td>
<td>-2.4 ± 0.77</td>
<td>9.9 ± 1.13</td>
<td>8.0 ± 1.04***</td>
<td>6.7 ± 1.05**</td>
<td>-4.4 ± 1.0**</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>127.8 ± 3.2</td>
<td>106.8 ± 8.1*</td>
<td>88.8 ± 4.9**</td>
<td>81.5 ± 2.1*</td>
<td>99.5 ± 5.4**</td>
</tr>
<tr>
<td>Total peripheral resistance (arbitrary units)</td>
<td>46.4 ± 4.05</td>
<td>55.6 ± 5.79†</td>
<td>33.4 ± 2.8***</td>
<td>27.7 ± 3.10**</td>
<td>21.3 ± 3.39***</td>
</tr>
</tbody>
</table>

NOTE: 1) * vs removal of tamponade (P = NS).
2) † vs control (P = NS); ** vs control (P <0.05); *** vs control (P <0.001).
3) ** vs tamponade (P <0.001); *** vs tamponade (P <0.01); **** vs tamponade (P <0.001).
4) * vs tamponade (P <0.05); ** vs tamponade (P <0.01); *** vs tamponade (P <0.001).
5) ** vs control (P <0.01); * vs control (P = NS).

at a reduced level by increased systemic arterial resistance; cardiac stroke volume is reduced but to some degree maintained by increased systolic ejection.22 Cardiac output tends to be reduced but to some degree is maintained by tachycardia. The beta adrenergic nervous system is important in maintaining cardiac output by increasing ventricular systolic ejection.22 Although atrial pressures and ventricular diastolic pressures are increased in cardiac tamponade, cardiac filling pressure or effective transmural pressure is decreased because of the elevated intrapericardial pressure.23 Cooper et al. were able to raise the blood pressure of dogs with acute tamponade by saline infusion.24 Although the blood pressure rose moderately with blood transfusion in our animals, cardiac output did not rise. In Cooper’s study the tamponade was more severe and the hematocrit was decreased by hemodilution; these factors may explain the different results in our investigation.

It is probable that nitroprusside infusion, given to decrease left ventricular afterload in the present study, did not increase cardiac stroke volume and cardiac output in the nontransfused animals of Group I because the right atrial pressure fell. When cardiac tamponade is induced the compliance of the heart is altered and it is difficult to determine preload from atrial or ventricular diastolic pressure. However, certain qualitative statements are possible. Since there was no loss of pericardial fluid and since there is no reason to believe that nitroprusside altered pericardial compliance, the pronounced fall in pericardial pressure must mean that there is less diastolic filling of the heart after nitroprusside. Left ventricular diastolic pressure was very close to right atrial pressure during cardiac tamponade.

Transfusion of whole blood prior to nitroprusside resulted in a rise in right atrial and in left ventricular diastolic pressure, which undoubtedly was due to increased diastolic size of the heart. Then, when nitroprusside was given, the right atrial and left ventricular diastolic pressures returned to their original values during tamponade. Thus, in all probability cardiac chamber size and preload were maintained and the effect of decreased afterload in increasing cardiac output could be demonstrated. The hearts of animals after nitroprusside were undoubtedly functioning on different Frank-Starling curves owing to the reduced afterload, thus yielding a higher stroke volume for a given filling pressure. Blood transfusion in group II animals permitted a higher filling pressure than was seen after nitroprusside in group I animals, thus producing a higher stroke volume.

Nitroprusside infusion decreased right atrial mean pressure from 7.8 to 3.8 mm Hg in group I dogs (untransfused), and by the same amount, from 11.8 to 7.8 mm Hg in group II dogs (transfused). In group I, the 4 mm Hg fall in atrial pressure was associated with no change in cardiac output, whereas in group II the 4 mm Hg fall in atrial pressure was associated with a rise in cardiac output. This difference may be explained by the assumption that the left ventricular function curve was different after nitroprusside owing to a decrease in systemic vascular resistance. Thus, after nitroprusside, the left ventricular output was greater than before at a given atrial pressure, owing to decreased left ventricular afterload. The slope of the ventricular function curve after nitroprusside was thus different than that before nitroprusside, where raising atrial pressure during tamponade had little effect on cardiac output.

An additional possible effect of nitroprusside in augmenting left ventricular stroke volume and output must be considered. An increase of apparent left ventricular compliance might permit a larger end-diastolic volume than expected from atrial pressures, thus yielding a greater cardiac output than anticipated from the degree of fall in pericardial and right atrial pressure after nitroprusside. Left ventricular diastolic filling thus might be augmented during tamponade if a decrease of pulmonary vascular resistance had led to a decrease in right ventricular volume. We cannot comment further upon these possibilities since ventricular dimensions were not measured in our experiments.

Nitroprusside has been found not to demonstrate a positive cardiac inotropic effect11 on isolated papillary muscle. Although the blood pressure fall produced by nitroprusside may reflexly increase cardiac sympathetic stimulation to cause a positive inotropic effect,13 this was not evidenced by increased cardiac output during nitroprusside infusion in our group I animals.

Hydralazine decreases systemic vascular resistance like nitroprusside but differs from nitroprusside in having less effect on the venous or capacitance vessels.14 In the present

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study, hydralazine infusion lowered right atrial pressure during tamponade significantly less than did nitroprusside. Peripheral vascular resistance during tamponade tended to be decreased more by hydralazine than by nitroprusside. Thus, cardiac diastolic size, judged from the lesser fall in atrial and intrapericardial pressures, was probably greater during tamponade after hydralazine than after nitroprusside. Hence, cardiac output and stroke volume could increase as the result of the decrease in systemic vascular resistance after hydralazine but not after nitroprusside. It is possible that the effect upon resistance vessels was greater after hydralazine than after nitroprusside in our studies. The increased cardiac output after hydralazine, after tamponade was relieved, is to be expected because of the reduction of left ventricular output impedance and as a reflex effect of the blood pressure fall upon the sympatho-adrenal system mediated through baroreceptors. Hydralazine is not believed to have a positive cardiac inotropic effect in the usual blood concentrations, although such an effect may be found when high concentrations are present in the coronary circulation.25

The effect of vasodilators upon the cardiac output during tamponade depends upon the interplay of several mechanisms. Reduction of venous return alone would be expected to decrease cardiac output; the fact that nitroprusside fails to do so indicates that the decrease in systemic resistance has enabled the left ventricle to pump more effectively and on a different Frank-Starling curve. Since the drug nitroprusside may alter ventricular compliance, ventricular preload cannot be judged accurately from the changes in atrial and intrapericardial pressures. Hydralazine increased cardiac output during tamponade because of its greater effect on systemic vascular resistance and lesser effect on the venous capacitance bed. It is possible that baroreceptor mediated sympatho-adrenal stimulation may also raise cardiac output after hydralazine. We found that isoproterenol, which also decreases atrial pressure in cardiac tamponade, increases cardiac output strikingly. With this beta adrenergic agent, not only is there arterial vasodilation, but there is a positive cardiac inotropic effect which can increase ventricular systolic ejection. We have used none of these agents during cardiac tamponade in man; such investigations remain for the future.

References
Hemodynamic effects of nitroprusside and hydralazine in experimental cardiac tamponade.
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