A DECREASE in cardiac output (CO) secondary to a reduction in pulmonary vascular surface area may occur in several clinical conditions. For example, certain patients with adult respiratory distress syndrome (ARDS) develop marked pulmonary hypertension caused by a reduction in pulmonary vascular surface area.1,2 Surface area may be reduced as a result of active vasoconstriction, interstitial edema, microembolism, and vascular obliteration.1,2 In another example, pulmonary emboli increase pulmonary vascular resistance (PVR) by mechanical effects, by hypoxic vasospasm, and by release of vasoactive substances.3-5 In both conditions (ARDS and pulmonary emboli) a reduction in pulmonary vascular area results in increased PVR and increased right ventricular afterload. This increases right ventricular stroke work and O₂ consumption, reduces CO, and may affect survival.1,6-8 For example, mortality in patients with acute pulmonary emboli is increased from 6% to greater than 30% if circulatory instability develops.9,10

Despite the above and despite a wide variety of recommendations,5,11-14 few studies have been carried out that systematically investigate the effects of treatment on ventricular performance when CO is significantly reduced because of short-term increase in right ventricular afterload.

Nitroprusside reduces left ventricular filling pressure and pulmonary edema and increases CO and stroke volume in canine low-pressure pulmonary edema.15,16 Similar hemodynamic effects are reported in patients with congestive heart failure and ARDS.17,18 In these clinical and canine studies where PVR was normal or only slightly increased, blood pressure and arterial O₂ tension (Pao₂) fell after nitroprusside administration. In the setting of a marked increase in right ventricular afterload, a fall in blood pressure could significantly reduce the driving pressure for right ventricular perfusion, i.e. blood pressure minus mean right ventricular pressure,19 and impair ventricular performance.

Hydralazine is commonly used to decrease left ventricular afterload and improve cardiac performance in patients with congestive heart failure.20 In patients with left ventricular failure, Pao₂ remains constant with hydralazine and blood pressure may not decrease. Hydralazine has been reported to decrease PVR and to improve ventricular performance in patients with pri-
mary pulmonary hypertension and in patients with pulmonary hypertension secondary to chronic lung disease.

In contrast, results from a recent study demonstrated that while CO increased, PVR did not change when hydralazine was given to five patients with primary pulmonary hypertension. Furthermore, in that study PVR did decrease and CO did not increase with nitroprusside.

A recent study of canine low-pressure pulmonary edema compared, in the same dogs, the short-term cardiopulmonary effects of nitroprusside and hydralazine. Nitroprusside increased CO 17% when blood pressure and systemic vascular resistance (SVR) decreased 21% and 35%, respectively. In contrast, despite a large decrease in SVR with hydralazine, blood pressure remained constant and CO doubled. The constant blood pressure would tend to maintain right ventricular perfusion pressure. In this study, baseline PVR was only slightly increased.

The current study was designed to compare the short-term cardiopulmonary effects of nitroprusside and hydralazine when CO was significantly reduced by a short-term increase in PVR induced by intravenous injection of autologous blood clots. Another objective was to test the hypothesis that in this setting, the short-term cardiopulmonary effects of hydralazine would be more favorable than those of nitroprusside.

**Methods**

Six mongrel dogs (10 to 22 kg) were anesthetized with pentobarbital (30 mg/kg), intubated, and mechanically ventilated (20 ml/kg) in the supine position with 100% O2. Fluid-filled catheters were placed in the femoral artery and left ventricle to monitor appropriate pressures. Under pressure monitoring, a thermostor-tipped Swan-Ganz catheter was inserted through the external jugular vein and positioned in a branch of the pulmonary artery. Two other Swan-Ganz catheters were similarly positioned in the right ventricle and one was withdrawn into the right atrium for injection of saline boluses during determination of CO. The thermal dilution curve was recorded on a separate single-channel recorder and analyzed by computer (Columbus Instruments). All catheters were connected to Statham transducers and outputs were displayed on a 12-channel oscillograph (Electronics for Medicine). Transducers were positioned midway between the front and back of the chest. An intravenous catheter for drug and/or volume infusion was placed in an external jugular vein and a No. 15F cannula was inserted in a femoral vein for injection of autologous blood clots.

To induce formation of autologous blood clots, 1000 IU of thrombin (Parke-Davis) was added to 100 to 150 ml of blood that had been withdrawn into a glass beaker. After approximately 30 min the clot was removed from the beaker and cut into cubes approximately 1 cc in size. Clots were placed in a 60 ml catheter-tipped syringe and suspended in normal saline. Six percent dextran was infused as required (range 30 to 70 ml) to raise left ventricular end-diastolic pressure (LVEDP) to approximately 5 mm Hg. After steady-state conditions were maintained for approximately 10 min (stable CO, blood pressure, and mean pulmonary arterial pressure [PAP]), baseline measurements of CO, heart rate, PAP, blood pressure, left ventricular pressure, and right ventricular pressure were obtained during a 3 sec period of arrested ventilation at functional residual capacity. Immediately afterward, arterial and mixed venous blood samples were collected for analysis of PO2, PCO2, and pH by a Corning blood gas analyzer (Model 165/2). Small volumes (1 to 2 ml) of clotted blood were then injected through the femoral catheter into the venous circulation. Clots were injected slowly to allow for stabilization of pressures between injections. Arterial blood gases were frequently sampled, pH was maintained above 7.25 by treatment of metabolic acidosis with intravenous sodium bicarbonate (range 10 to 40 ml), and PacO2 was maintained between 30 and 40 mm Hg by adjusting ventilatory rate. During placement of the catheter and administration of clots to increase PVR, anesthesia was maintained with intravenous doses of pentobarbital (25 mg injected over 30 to 60 sec) given as required. There was a transient, small reduction in blood pressure with each injection, which recovered within 1 to 2 min. Repeated injection of blood clots over 1 to 2 hr results in an initial increase, then a gradual sustained decrease in CO.

When CO had been reduced to 60% of baseline and hemodynamic values were stable on consecutive measurements 10 min apart, heparin (100 IU/kg iv) was administered to terminate clot propagation. After another 10 min period, values were again measured and, if stable, were recorded as control values (control 1).

Dogs were then given nitroprusside by infusion, titrated to one of the following end points: CO increased to 80% of control, blood pressure decreased approximately 30%, or heart rate increased approximately 30%. Heart rate and blood pressure were continuously recorded and measurements of CO were frequently repeated. Heart rate and blood pressure were prospec-
Table 1 (Continued)

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<thead>
<tr>
<th>PACO₂ (mm Hg)</th>
<th>PCO₂ (mm Hg)</th>
<th>pH</th>
<th>PACO₂ (mm Hg)</th>
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<td>7.28±0.03</td>
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<tr>
<td>489±87</td>
<td>452±54</td>
<td>378±164</td>
<td>408±118</td>
</tr>
</tbody>
</table>

Results

Table 1 illustrates the hemodynamic effects of increased PVR after intravenous administration of blood clots (compare baseline with control 1). Note that CO and stroke volume were markedly depressed (p < .01), while heart rate, PAP, PVR, SVR (p < .01), and RVEDP (p < .05) were increased. Corresponding to the fall in CO, mixed venous O₂ tension (PvO₂) decreased (p < .01). Blood pressure and LVEDP were not affected.

By a two-way ANOVA, measurements obtained during control periods (control 1, 2, and 3) were not significantly different. This indicated that the preparations were stable over a period ranging from 75 to 120 min after administration of clots. To compare the effects of drugs, control 1 and control 3 were used and control 2 was disregarded.

Table 1 shows that both nitroprusside and hydralazine reduced RVEDP and LVEDP from control values (p < .05) and that the degree of reduction was similar for both drugs. Filling pressures decreased in each instance with therapy and the change was always at least 1 mm Hg. Despite a similar reduction in ventricular filling pressures, hydralazine significantly increased (p < .05) CO and stroke volume by 108% and 88%, respectively. Corresponding to the change in CO, Pvo₂ increased (p < .05) with hydralazine. While blood pressure and PAP remained constant, SVR and PVR decreased (p < .01). Systemic resistance fell 46%, from 102 to 55 mm Hg/1/min with hydralazine and PVR decreased 40%. Nitroprusside, on the other hand, did not increase CO and caused a 33% fall (p < .01) in blood pressure. Mean PAP and PVR were unchanged with nitroprusside, and although SVR decreased (p < .01) 32%, this change was less marked than that with hydralazine (p < .05).

Note that values for arterial pH and Paco₂ were similar in all conditions. Mean Pao₂ decreased with nitroprusside and increased with hydralazine. Values for arterial O₂ increased in each instance with hydralazine, but because of variability this change was not significant.

Discussion

The current study was designed to investigate the short-term cardiopulmonary effects of nitroprusside and hydralazine in a canine preparation of increased PVR and reduced CO. One objective was to test the hypothesis that when right ventricular afterload is significantly elevated, acute cardiopulmonary effects of hydralazine would be more favorable than those of nitroprusside.

We emphasize at the outset that our study is experimental in nature and that an artificial method was used...
for increasing PVR. The study was performed in anesthetized dogs, in which a short-term increase in PVR decreased CO; the effects of drugs in this preparation might be quite different from those in the unanesthetized human when the resting CO is not decreased. It is also possible that some of the drug effects were mediated through the sympathetic and parasympathetic nervous system; if so, these effects could be different in patients.

Repeat injections of pulmonary emboli increased PVR so that despite elevated RVEDP, CO and stroke volume fell. In contrast to its effects when PVR is normal or only slightly increased,16-18 nitroprusside did not increase CO despite a 33% reduction in blood pressure. Although it is possible that a larger dose of nitroprusside might have increased CO, we consider it unlikely for several reasons. First, there was a large decrease in SVR with nitroprusside, and when PVR is normal, CO usually increases when systemic resistance and blood pressure decrease.19,20 Second, despite the large decrease in SVR, PVR remained constant with nitroprusside, indicating the absence of a significant effect on the pulmonary vasculature. Finally, despite a larger fall in blood pressure with nitroprusside in a similar study, there was no increase in CO.20 In that study, two dogs developed frank right ventricular failure when blood pressure fell during nitroprusside infusion; that is, CO and stroke volume fell despite an increase in RVEDP. In the presence of pulmonary hypertension, a decrease in blood pressure could significantly reduce the driving pressure for right ventricular perfusion (mean blood pressure minus mean right ventricular pressure) so that right ventricular performance could deteriorate because of ischemia.19 Accordingly, it is conceivable that the failure of CO to increase with nitroprusside in the current study is explained by the decrease in blood pressure and a decrease in right ventricular perfusion.

In contrast to nitroprusside, hydralazine maintained blood pressure, and despite similar reductions in biventricular filling pressures, there was a marked increase in CO and stroke volume. Similar results are reported when hydralazine is given to patients with congestive heart failure, patients with primary and secondary pulmonary hypertension, and dogs with oleic acid pulmonary edema.17,20-22 In our study, hydralazine most likely improved ventricular performance because it reduced the resistance impeding right and left ventricular ejection. Despite constant PAP and blood pressure, a decrease in resistance to ejection would allow increased shortening so that stroke volume would increase secondary to a reduction in end-systolic volume.27 However, an increased inotropic state with hydralazine cannot be ruled out.28 Although it is possible that some of the short-term cardiopulmonary effects seen with hydralazine were in part due to prior treatment with nitroprusside, for the following reasons we consider this possibility unlikely. The half-life of nitroprusside is only a few minutes29 and posthydralazine measurements were obtained approximately 45 min after nitroprusside had been discontinued. Moreover, short-term effects of hydralazine were assessed approximately 40 min after all measured variables had returned to baseline, i.e., approximately 40 min after measured effects of nitroprusside had disappeared.

Previous studies have compared short-term cardiopulmonary effects of nitroprusside and hydralazine. Pierpont et al.17 compared the effects of both drugs in patients with left ventricular failure. Although both nitroprusside and hydralazine increased cardiac index to a similar degree, only nitroprusside significantly reduced mean blood pressure, mean PAP, and PVR. Franciosa et al.30 reported similar but not identical effects in patients with left ventricular failure; the increase in CO was similar with both drugs and although blood pressure decreased with each agent, the change was greater with nitroprusside. Furthermore, while both nitroprusside and hydralazine decreased PVR, only nitroprusside significantly reduced PAP. In contrast, only hydralazine increased CO and decreased PVR in the current study. Despite the large decrease in SVR with hydralazine, blood pressure remained constant because flow increased. In addition, PAP did not decrease with nitroprusside despite a large fall in blood pressure. The different effects of the two drugs on PVR may be partially explained by the increase in flow with hydralazine. A higher flow might recruit pulmonary vasculature and decrease resistance. It is also possible that in this preparation hydralazine is a more effective pulmonary vasodilator. The differences between our results and those of previous studies17,30 may be explained by the experimental conditions, i.e., unanesthetized patients with left ventricular failure vs anesthetized, ventilated dogs with a short-term increase in PVR.

Despite the potential importance of increased RV afterload on cardiac performance, few studies have investigated the effects of treatment when CO is reduced because of a short-term increase in PVR. Our results demonstrate that in a canine preparation of pulmonary emboli (blood clot), short-term cardiopulmonary effects of hydralazine may be more favorable than those of nitroprusside when a decrease in CO complicates an increase in PVR.
LITERATURE INVESTIGATION—HEMODYNAMICS AND VENTRICULAR FUNCTION

References

8. McIntyre KM, Sahama AA: Hemodynamic and ventricular responses to pulmonary embolism. Prog Cardiovasc Dis 17: 175, 1974
Effects of hydralazine and nitroprusside on cardiopulmonary function when a decrease in cardiac output complicates a short-term increase in pulmonary vascular resistance.

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