Effect of Pressor Amines on Experimental Intracardiac Shunts and Valvular Regurgitation*

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INTRODUCTION

The clinical diagnosis of cardiac disease by bedside auscultation can in certain patients tax the most seasoned clinician. Various technics of altering murmurs by the effect of pharmacologic agents on blood flow have been used to separate and identify heart murmurs.14 So too, in the cardiac catheterization laboratory, equivocal hemodynamic data may be obtained even by the most sensitive technics. The direction of flow may vary in balanced shunts and minimal regurgitant flows may be altered in the same individual with different physiologic states. This study is concerned with pharmacologically altering the direction of blood flow in dogs with experimental intracardiac shunts and valvular regurgitation. Indicator dilution curves were recorded as a means of detecting the change in direction and magnitude of flow.

Figure 1: Atrial septal defect demonstrating a rise in systemic pressure, left atrial pressure and increased left-to-right shunting during norepinephrine (Levophed) infusion.

CONTROL

LEVOPHED #1

LEVOPHED #2

FA=82/35
L.A.=5.5

FA=120/55
L.A.=6.0

FA=203/115
L.A.=7.5

FIGURE 1:

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METHODS
Atrial septal defects were created in six dogs under direct vision during inflow occlusion. The technic described by Kay, Thomas and Blalock was used to make ventricular septal defects in six dogs. Patent ductus arteriosus was simulated by a subclavian-pulmonary artery anastomosis in three dogs. Mitral insufficiency was induced in five dogs by the method described.
by Haller and Morrow.7 A dog found to have a congenital ventricular septal defect and valvular pulmonic stenosis was also used in this study. The presence of all defects was confirmed after sacrificing the animals.

Cannulae were placed in the femoral artery and vein, pulmonary artery and vein, and in some cases the right atrium. Pressures were measured with strain gauge transducers and recorded on a multichannel recorder. All dogs were given mepesulfate as an anticoagulant.

Cardiogreen dye was the indicator employed. In the presence of a left-to-right shunt, injections were made in the pulmonary artery. In the dogs with mitral valvular insufficiency, the dye was injected in the left atrium. Blood was sampled from the femoral artery by a constant rate motor driven syringe through a cuvette densitometer. The curves were inscribed on a direct-writing recorder.

Systemic pressure was varied by an intravenous drip containing 4 mg. of norepinephrine (Levophed) in 500 mg. of 5 percent dextrose in water. In addition, several dogs were studied following the intravenous administration of methoxamine hydrochloride (Vasoxyl) in a solution of 20 mg. per 500 ml.

Following the injection of an indicator into the left side of the heart or aorta and recording from a peripheral artery, the absence of a left-to-right shunt or valvular regurgitation is suggested by a curve with a rapid, smooth, uninterrupted downslope reaching the baseline before any evidence of recirculation. In the presence of a left-to-right shunt, whenever the injection is made proximal to the shunt, the downslope of the curve is interrupted by the recirculation of shunted dyed blood.9,10 The larger magnitude of shunt is characterized by a higher break and greater deformity of the downslope of the curve with a lower peak concentration as compared to a normal or lesser shunt curve obtained by the same technic with an equal amount of indicator. Valvular regurgitation is characterized by a smooth prolonged downslope varying directly with the degree of regurgitation.11

**Results**

As noted in Table 1, norepinephrine administration resulted in a rise of systemic arterial pressure and an increase in the left-to-right shunt in all dogs with an atrial

<table>
<thead>
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<th>Defect</th>
<th>Increase</th>
<th>Decrease</th>
<th>No Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septal defect</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td></td>
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<td>Ventricular septal defect, pulmonic stenosis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>2</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

**Figure 4:** Naturally occurring ventricular septal defect with pulmonic stenosis with augmentation of left-to-right shunting with a rise in systemic pressure.
septal defect. The extent of alteration of these dye curves could be correlated with a progressive increase in left atrial mean pressure (Fig. 1).

An equivocal response was noted in the group of dogs with ventricular septal defects. In three of these dogs there was little or no change. Two animals showed a decrease in the apparent left-to-right shunt. However, administration of Vasoxyl in the same animals increased the left-to-right shunt (Fig. 2). One dog showed an increase in shunting while receiving norepinephrine (Fig. 3). In comparison with the rest of this group, this dog had a small ventricular septal defect, and normal right heart pressures.

Naturally occurring pulmonic stenosis and a ventricular septal defect were found in one of the experimental animals. Norepinephrine administration increased the left-to-right shunt as demonstrated by the dilution curves following injection of dye into the pulmonary artery (Fig. 4).

All dogs with subclavian-pulmonary artery anastomosis showed exaggeration of the left-to-right shunt as a consequence of norepinephrine administration (Fig. 5). Trimethaphan camphorsulfonate (Arfonad), on the other hand, lowered the systemic pressure and diminished the shunt. When the shunt was completely closed, norepinephrine failed to alter the contour of the dye dilution curve (Fig. 6).

Of the five dogs with mitral insufficiency, two showed increase in mitral regurgitation as noted by prolongation of the descending limb of the dye curve. In three dogs, the response was minimal (Fig. 7). Two of these dogs were then given an intravenous infusion of Vasoxyl with marked exaggeration of the degree of insufficiency.

**DISCUSSION**

Norepinephrine has been demonstrated to raise systemic resistance and left ventricular pressure with a similar but lesser degree of rise in pressure in the pulmonary circulation.¹ The latter effect is secondary

![Figure 5](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21394/)
in part to pulmonary vasoconstriction but mainly to a rise in left ventricular end-diastolic and left atrial pressure.\textsuperscript{13,34} The overall effect is an increase in the pressure gradient between the systemic and pulmonary circuits and other low pressure areas in the heart. One might assume, therefore, that flow through a communication between the left and right side of the heart would be accentuated by the administration of a pressor agent. This was demonstrated in each of the shunts when the pressor agent was methoxamine. Norepinephrine produced similar results except in some of the ventricular septal defects. One may surmise that the differential response to these drugs is attributed to the positive inotropic effect of norepinephrine with an augmentation of effective forward flow. In addition, it has been shown\textsuperscript{15} that norepinephrine results in a shortening of the duration of ventricular systole during which a predominant part of left-to-right ventricular shunting would occur. An additional factor that cannot be evaluated in the experimental preparation is the behavior of a defect with a full thickness muscular rim which may participate in ventricular contraction with a narrowing of the defect during systole. It is of interest that the naturally occurring defect in the membranous septum of one animal responded with the anticipated augmentation of shunting during norepinephrine infusion. Methoxamine, on the other hand, has solely a pressor effect and shunting was exaggerated in every case.

Experimental and clinical studies by Braunwald and associates\textsuperscript{16} showed that in mitral insufficiency administration of norepinephrine is followed by an exaggerated elevation of the mean left atrial pressure. This observation was confirmed in this study. However, there was an inconstant relationship to regurgitant flow as measured by indicator dilution curves. When methoxamine was administered, there was increased mitral insufficiency. Norepinephrine, on the other hand, did not have as great or constant an effect as in the dogs with ventricular septal defects. This apparent disparity is attributable to the positive inotropic effect of norepinephrine. In an experimental preparation that simulated mitral valvular regurgitation, Ross and coworkers\textsuperscript{17} demonstrated the role of norepi-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{No evidence of shunting after elevation of systemic pressure with a closed aortic-subclavian artery communication. Suggestion of increased forward flow by the smaller area under the dilution curve after Levophed administration.}
\end{figure}
nephine in stimulating an initial fall in left atrial pressure, a rise in systemic output and a decrease in regurgitant flow. Ultimately, with increasing dosage, the pressor effect would be expected to predominate and exaggerate the degree of regurgitant flow. An important difference from acquired disease in the human is the diminutive size of the dog's left atrium with a different pressure-volume relationship so that there may be significant elevation of left atrial pressure, with minimal increase in regurgitant flow. In humans, however, the larger left atrium may not respond in the same fashion. If the pressure-volume relationship of the atrium were such that large increments of volume would be reflected by little change of pressure, then the study of the change of dilution curves during administration of vasopressors would be more sensitive than a change in pressures in detecting small degrees of regurgitation.

**Summary**

Experimental atrial septal defects, aortic-pulmonary communications, ventricular septal defects and mitral insufficiency were created in dogs. Arterial indicator dilution curves were recorded before, during, and after the administration of norepinephrine and methoxamine. Alteration of the curves suggests an increase in left-to-right shunting in dogs with atrial septal defects and aortico-pulmonary communication.

An inconsistent response followed administration of norepinephrine to dogs with ventricular septal defects and mitral regurgitation. When methoxamine was infused, dogs with ventricular septal defects showed an apparent increase in the left-to-right shunt, and animals with mitral valvular insufficiency had an increase in re-
The findings support the clinical observations of changing murmurs under these circumstances and may be applied during cardiac catheterization studies.

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Resumen
Se produjeron intercomunicaciones auriculares, aortocapulmonares, interventriculares e insuficiencia mitral en perros. Se obtuvieron curvas indicadoras de dilución arterial antes, durante y después de la administración de noradrenalina y metoxamina. La alteración de las curvas sugiere un aumento del paso de izquierda a derecha en los perros con defecto del septum aórtico y en el aortocapulmonar.

Una respuesta inconstante se observó después de la administración de noradrenalina en los perros con intercomunicación ventricular y regurgitación mitral. Cuando se infundió metoxamina los perros con paso en el tabique ventricular mostraron un aumento aparente del paso de izquierda a derecha y los animales con insuficiencia mitral tuvieron un aumento en la regurgitación.

Estos hallazgos apoyan la observación clínica de los soplos cambiantes bajo estas circunstancias y pueden tener aplicación durante estudios por la cateterización cardíaca.

Zusammenfassung


References

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