Atypical Patent Ductus Arteriosus
The Use of a Vasopressor Agent as a Diagnostic Aid

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Approximately 95 per cent of patients with patent ductus have characteristic machinery murmurs. Five per cent have only systolic murmurs. In such patients, the intravenous or intramuscular administration of a pressor substance, mephentermine, may bring out a continuous murmur. This simple test is a useful adjunct in diagnosis.

In our experience about 95 per cent of patent ducti have the typical machinery murmur, and present no problem in diagnosis. A continuous murmur maximal in the second to third left intercostal space usually means patent ductus arteriosus. Other sites usually indicate other lesions. The typical machinery murmur reflects a systolic and diastolic pressure gradient between the aorta and pulmonary artery with left-to-right shunt in both systole and diastole. The intensity of the murmur may or may not parallel the size of the ductus and the degree of shunt.

It is the atypical 5 per cent of ducti that cause difficulty in diagnosis. The diagnosis of atypical patent ductus can be most rewarding, as a seemingly hopeless and confusing situation may be resolved safely and definitely at the operating table. In atypical patent ductus there may be no murmur, a pulmonic systolic flow murmur, or a late systolic-diastolic murmur overriding the pulmonic second sound having either a late systolic or early diastolic accentuation. Occasionally the murmur of pulmonary insufficiency appears with severe pulmonary hypertension. Atypical murmurs occur chiefly in infancy or when secondary pulmonary hypertension develops.

When atypical murmurs are present, there are several possibilities. The ductus may be extremely small or quite large. In infants and small children with low systemic blood pressures and relatively high pressures in the pulmonary artery, the systolic-diastolic pressure gradients may be quite small, producing turbulence of blood flow in late systole or not at all. When pulmonary hypertension complicates patent ductus, pressure gradients may be reduced or obliterated. Patent ductus, when complicated by additional cardiovascular lesions, most commonly coarctation of the aorta, is usually atypical.

It becomes apparent then that size of the ductus and the pressure relationship between the aorta and the pulmonary artery determine the type of murmur present. Following the suggestion of Bing, we have employed mephentermine sulfate (Wyamine) in doses of 10 to 30 mg. intramuscularly and intravenously to increase cardiac output rapidly and to raise aortic pressure in many patients suspected of atypical patent ductus arteriosus. It produces only minor increases in pulmonary artery pressure. Even in the presence of severe heart disease it safely and effectively raises aortic pressure rapidly, thereby increasing the systolic-diastolic pressure gradient between the aorta and pulmonary artery.

It has a wide margin of safety, since it rarely induces serious ventricular arrhythmias. However, we have observed brief bouts of bigeminal rhythm at the peak of the pressor response in 2 patients, and 1 patient manifested an urticarial reaction.

The atypical murmur in infants below 1 year of age is well illustrated in a 6-month-old girl with an unexplained pulmonic systolic murmur that overrode the pulmonary second sound. After 10 mg. of mephentermine sulfate intramuscularly the typical machinery mur
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mur of patent ductus appeared with changes in aortic pressure (fig. 1). Pulmonary artery pressures in the normal infant following birth are quite high, approximating systemic pressures.\textsuperscript{11} With growth, pulmonary vascular resistance and pressure fall and systemic pressure rises. The typical murmur appears when both a systolic and a diastolic pressure gradient is established.

When the ductus is extremely small, there may be no murmur or only a pulmonary systolic murmur. A 4-year-old, white girl with the typical murmur of patent ductus detected earlier in childhood was referred for surgery. No murmur was audible on admission and only a faint systolic murmur appeared after vigorous exercise. After 15 mg. of mephentermine sulfate intramuscularly the typical machinery murmur appeared, and a small ductus was resected at surgery without the need of cardiac catheterization. Infants have tolerated 10 mg. of mephentermine sulfate intramuscularly without any untoward reaction; in older children 10 mg. intravenously have been well tolerated.

A 21-year-old, white woman was seen with an unexplained pulmonic-systolic murmur. It was a decrescendo blowing pulmonic-systolic murmur with a questionable early diastolic component (fig. 2, \textit{top}). After vigorous exercise the murmur increased in magnitude but remained nondiagnostic. With rapid changes in aortic pressure, the typical continuous murmur of patent ductus appeared (fig. 2, \textit{bottom}).

The inadequacy of exercise in bringing out the continuous murmur in atypical cases is not surprising, since exercise causes no significant change in the mean diastolic blood pressure, either of patients with patent ductus
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BEFORE
VASOPRESSOR AGENT
PULMONIC SYSTOLIC MURMUR  2nd. Lt.

AFTER
VASOPRESSOR AGENT
CONTINUOUS MURMUR APPEARS
FIG. 2. Phonocardiograms and electrocardiograms showing appearance of typical continuous murmur of patent ductus arteriosus after administration of vasopressor agent. Sensitivity 5 in phonocardiograms; paper speed 75 mm./sec.

or of normal control subjects. Rapid elevation in aortic systolic and diastolic pressures by a vasopressor agent increasing turbulence of flow in systole and diastole across the ductus is clearly superior to exercise in atypical cases. This magnitude of increase in the murmur and the appearance of the diastolic component is not attainable by exercise or other physiologic maneuvers (fig. 3).

In figure 4 is the phonocardiogram of a 5-year-old, Negro boy with coarctation, aortic stenosis, and heart failure. Intermittently, in the background, was a suggestion of the murmur of patent ductus. After 15 mg. of mephentermine intravenously the typical murmur of patent ductus clearly appeared (fig. 4). A large 12-mm. ductus was subsequently ligated with repair of the coarctation. There was only a 20-mm. systolic pressure gradient across the aortic valve. It is not unusual to find a "silent" patent ductus at surgery or necropsy examinations, particularly in association with coarctation of the aorta. In Abbott's autopsy series none of the 21 cases of patent ductus associated with coarctation was diagnosed clinically. The ductus is usually extremely small, may communicate at or distal to the coarctation site, or may be associated with pulmonary hypertension, which accounts for its atypical nature. When cardiac enlargement or heart failure is out of proportion to the clinical degree of coarctation, a large atypical patent ductus or endocardial fibroelastosis is usually present.

DISCUSSION

We have employed mephentermine sulfate in a patient with pulmonary hypertension associated with patent ductus, when a shunt could not be demonstrated by cardiac catheterization, but the murmur was demonstrated by this technic and the ductus was resected. Rapid alterations in aortic pressure by vasopressor agents should increase the left-to-right shunt in atypical patent ductus and make the shunt more readily detectable by simultaneous cardiac catheterization. We are currently investigating this problem, but clinically the appearance of the continuous murmur after vasopressor agents is so unequivocal that fur-
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Fig. 3. Appearance of typical continuous murmur of patent ductus arteriosus after administration of vasopressor agent. Sensitivity 5 in phonocardiograms.

We have produced the typical continuous murmur by this method in approximately 12 patients with atypical murmurs that were confirmed at operation. Furthermore, we have examined the effects of mephentermine on all common congenital and acquired cardiovascular lesions and the auscultatory and phonocardiographic results are quite different and not easily confused with those produced in atypical patent ductus. There have been no errors to date and the hazard, discomfort, expense, and time of cardiac catheterization have been avoided.

One can formulate the total auscultatory spectrum of this anomaly. In infants with small or absent pressure gradients no murmur, a pulmonary systolic flow murmur, or late systolic murmur overriding the second sound may be present. As the child develops, pulmonary vascular resistance falls, and systemic pressure rises, a large gradient in systole and diastole is created and the well-recognized continuous murmur appears. If the ductus is large or there are intrinsic changes in the pulmonary vessels, pulmonary hypertension may ensue. As the pulmonary artery pressure rises, the gradient lessens and reversion to atypical systolic murmurs occurs. When the pulmonary artery and aortic pressures become equal, murmurs may disappear. If the pulmonary arterial hypertension is great or the pulmonary artery dilatation distorts the pulmonic valve, the diastolic murmur of semilunar insufficiency of the pulmonic valve appears. Differential cyanosis or additional systolic murmurs appear as the pulmonary artery pressure exceeds aortic pressure and a right-to-left shunt appears. Patent ductus arteriosus associated with coarctation, or when very small or quite large, may be atypical.

Mephentermine sulfate is an effective and safe agent in rapidly raising aortic pressure.
and increasing the systolic-diastolic pressure gradients between the aorta and pulmonary artery. Turbulence of blood flow in both systole and diastole is increased by this pressure alteration and the continuous murmur appears in atypical cases related to ductus size or small gradients across the ductus related to relative or of acquired hypertension in the pulmonary circuit.

**Summary**

About 5 per cent of patients with patent ductus arteriosus have atypical murmurs. There may be no murmur, a pulmonic systolic flow murmur, or a late systolic murmur over-riding the second sound. The size of the ductus and the pressure relationships between the aorta and pulmonary artery dictate the type of murmur present with this entity. Mephentermine sulfate is a safe and effective agent in rapidly raising aortic pressure and thereby creating or widening the pressure gradient between the aorta and pulmonary artery, producing the typical machinery murmur in atypical cases.

**References**

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Urine flow on a background of a maintained water load was increased during steroid administration. These effects were independent of intake and renal output of sodium. During salt restriction there was an increase in maximal urine flow and free water clearance. Sometimes the increase in water excretion was observed with a simultaneous small increase in sodium excretion. It was also noted that there was a gain in body weight and an increase in total solute excretion in some cases. The increase in glomerular filtration rate (GFR) was small after steroids and not parallel with the increase in maximal urine flow. GFR was increased by single intravenous infusions of hydrocortisone, but the increase in diuretic response to an increased intake of water was not always observed. Renal tubular water reabsorption was decreased by the steroids under consideration. It has been suggested that the additional free water is provided by a redistribution of solute reabsorption between proximal and distal tubules or by a change in tubular permeability to water.
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