Atypical Response of Intermittent Continuous Murmur of Patent Ductus Arteriosus to Vasoactive Agents, With Particular Reference to the External and Intracardiac Phonocardiography

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A TYPICAL patent ductus arteriosus (atypical PDA) generally indicates the cases without a continuous murmur pathognomonic to this congenital anomaly.1)–21) In this particular group of PDA, which constitutes an approximately 5 per cent of total cases,22)–24) the cause of the lack of typical murmur due to other than pulmonary hypertension is unusual.5),6),9),11)–14),24)–31) On the other hand, it has been believed that a typical murmur is provoked by vasopressor agent in cases of atypical PDA,5),29),32) This is due to the development of the significant aortic-pulmonary pressure gradient by this drug.

This report presents a case of intermittent continuous murmur of proved PDA without pulmonary hypertension and in which amyl nitrite caused attenuation followed by marked intensification of the murmur, whereas vasopressor agent (methoxamine) also caused attenuation or disappearance of the murmur.

CASE REPORT

K. M. (414627), a 20-year-old unmarried female was referred to the phonocardiography because of the murmur. She had a normal birth and development and had no complaints up to the present time. Her history was not contributory except the murmur. A murmur was firstly pointed out early in childhood, and it was not detected at the usual check-up for the entrance to primary school. However, annual physical examination revealed this murmur at the age of 10, and the family was noticed that she has heart disease of probably congenital in origin. Despite this history, the subsequent annual check-up failed to detect the murmur for about 10 years. Lastly, this murmur was again pointed out on the physical examination at the time of the entrance examination of nursery school.

Physical examination revealed no abnormality except the palpatory and auscultatory findings. No signs indicating heart disease were observed by inspection.

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The pulse was regular, normal counting and there was no inequality between four limbs. Blood pressure was 120/80 mm. Hg in the right arm. Chest was flat but had no deformity. Apical impulse was located normally and not heaving, indicating no cardiac enlargement as well as left ventricular hypertrophy. These palpatory findings were ascertained by chest roentgenogram (Fig. 1) and electrocardiogram (Fig. 2). Parasternal lift was not observed, but very slight heaving sensation was appreciated in the left second intercostal space 5 cm. left from the midsternal line, where the mainly late systolic thrill was palpable. No palpatory shock of pulmonic component of the second heart sound was observed.

Auscultation revealed the normal apical first sound, no pathological ejection sound, and the apical third heart sound. The splitting of the second heart sound was not correctly evaluated because of the concomitant loud continuous murmur which was widely transmitted. No Hochsinger's sign was noticed. However, the second sound in the pulmonic area was thought to be slightly accentuated without conclusion that this is due to accentuation of either aortic or pulmonic component. The continuous murmur best heard lateral to the pulmonic area was of grade IV to V/VI and was typical grinding murmur containing both low- and high-pitched components as in usual cases of PDA without pulmonary hypertension, and transmitted to both apical area and left neck. There was faint apical mid-diastolic rumble following the third heart sound. In the right neck, a grade II/VI accidental carotid bruit was noticed, but there was no pathological ejection or regurgitant systolic murmur on the precordium. Of particular interest was the marked change in both intensity and character of the murmur by the change of body position. The above-mentioned auscultatory findings were obtained from the patient in recumbent position, but the murmur was attenuated significantly and became lower pitched in the sitting position. However, several trials failed to cause the complete disappearance of the murmur.

Phonocardiograms revealed the validity of the most part of auscultatory findings. The second sound was proved to be split when both apical area and Erb's point were simultaneously recorded, and the amplitude of the pulmonic component was
not larger than the aortic component, thus the auscultatory incompleteness was complemented. Carotid pulse tracing (Fig. 3, a) also confirmed the usual sequence of splitting. The indirect pulmonary arterial curve (Fig. 3, b), which was recorded by low-frequency pick-up tightly pressed against the point of maximum of palpatory impulse coinciding the point of maximum intensity of the murmur, disclosed that the second component of the second heart sound was pulmonic, because the notch was coincided in time with this component. This low-frequency tracing also showed a series of late systolic and early diastolic tiny vibrations which reflect the thrill caused by the intense murmur. There was an apical ejection systolic murmur followed by systolic component of continuous murmur, and this is not unusual in most of uncomplicated PDA.

Including all the findings of routine examination, the clinical diagnosis of this patient was uncomplicated PDA with small left-to-right shunt. Based on the history, the intermittent disappearance and appearance of the murmur was thought to be the particular anatomical situation of the ductus.

Though the clinical diagnosis was thought to be hundred per cent correct, the functional test using vasoactive drugs was performed to observe the response of the murmur in this particular case. Prior to the test, it was suspected that amyl nitrite will attenuate the murmur, whereas methoxamine augment it. As shown in Fig. 4, amyl nitrite test resulted in definite attenuation, particularly of the diastolic component, of the murmur as in usual case (around 15 to 40 sec.). However, an unusually loud murmur appeared as soon as the tachycardia tended to subside thereafter. On the other hand, intravenous administration of methoxamine (0.1 mg./Kg.,
Table I. Cardiac Catheterization Data

<table>
<thead>
<tr>
<th>Location</th>
<th>Pressure</th>
<th>Oxygen Content</th>
<th>Other Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. PA</td>
<td>14/8 mm. Hg</td>
<td>11.4 vol %</td>
<td>Oxygen Capacity 15.2 vol.%</td>
</tr>
<tr>
<td>L. PA</td>
<td></td>
<td>11.7</td>
<td>Oxygen Saturation 93.4%</td>
</tr>
<tr>
<td>Main PA</td>
<td></td>
<td>13.2</td>
<td>Oxygen Consumption 218 ml/min.</td>
</tr>
<tr>
<td>RV (outflow)</td>
<td>16/0-2</td>
<td>11.0</td>
<td>Systemic Blood Flow 7.8 L/min.</td>
</tr>
<tr>
<td>RV (inflow)</td>
<td></td>
<td>11.2</td>
<td>Pulm. Blood Flow 7.8 L/min.</td>
</tr>
<tr>
<td>RA</td>
<td>a = 5, v = 3</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>SVC</td>
<td></td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td></td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>A. Fem.</td>
<td>114/55</td>
<td>14.4</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 5, a.
Fig. 5, b.
within 23 sec.), contrary to our expectation, caused the definite decrease in loudness of the murmur. Because of the peculiarity of the murmur, the patient was advised for further detailed examinations. Cardiac catheterization disclosed the normal pressure levels in both systemic and pulmonary circuits, and the catheter was introduced into aorta via ductus. Thus, the clinical diagnosis was confirmed, though the oxygen analysis failed to disclose the left-to-right shunt (Table I). The continuous murmur was present throughout the procedure except when catheter was in the ductus.

Intracardiac phonocardiography was undertaken subsequently using portable phonocardiograph and barium-titanate phonocatheter*. The murmur in the ductus was mainly late systolic in time and was variable in shape from beat to beat. The withdrawal of the catheter from ductus to main pulmonary artery disclosed sudden appearance of loud murmur (Fig. 5, a), which was transmitted poorly to both right and left pulmonary arteries and not backward. Again the precordial murmur was greatly attenuated when the phonocatheter was placed in the ductus.

The functional phonocardiography using methoxamine was performed as mentioned previously. The phonocatheter was placed in the main pulmonary artery just on the opposite side faced to ductus, where the intense continuous murmur was recorded. Prior to the intravenous administration of methoxamine (same dose as in the previous test), the precordial murmur was continuous and was accompanied by thrill. Methoxamine caused marked systemic hypertension (from 120/60 to 165/85 mm. Hg, 1 min. after injection) and reflex bradycardia. The continuous murmur was more strikingly diminished than the previous test, and the early to mid-diastolic component of the murmur almost completely disappeared (Fig. 5, b). Late systolic component remained but with lesser intensity. Late diastolic murmur of lesser amplitude was constantly observed during subsequent 3 to 4 min. Then the murmur gradually restored the continuous character. Blood pressure was returned to the control level 7 min. after injection. However, precordial auscultation could not reveal any continuous murmur up to the 15 min. after injection (cf. Fig. 5, b), and the full development of this murmur on the precordium took about 30 min. after the maximum effect of methoxamine (last tracing of Fig. 5, b). There was no change in patient's condition during the catheterization and the functional phonocardiography. No change of body position was permitted during the procedure.

**DISCUSSION**

As it has been precisely described by Leatham33 and subsequently been accepted widely, the continuous murmur is a kind of regurgitant murmur which is caused by communication between high- and low-pressure areas. In case of PDA, the former is aorta and the latter pulmonary artery. This hemodynamic interpretation of the murmur clearly explains the cases with atypical non-continuous murmur, in which the aorto-pulmonary pressure gradient is not apparent due to pulmonary hypertension including Eisen-

* The sensor was mounted at the tip of Courand catheter of #6.
menger reaction, association of other anomaly (coarctation, ventricular septal defect and other complicated anomalies, congestive heart failure, and physiological developmental stage in infancy. These as well as the genesis of intermittent murmur and complete disappearance in cases of subacute bacterial endocarditis were all reviewed in detail in the previous publication.

Intermittent continuous murmur in simple PDA unassociated with pulmonary hypertension was reported in detail with phonocardiographic confirmation by Shapiro et al., Keith and Sagarminaga, and Hyrske et al., in recent years. However, no adult case was reported except case 1 of Fiehring et al., and no intracardiac phonocardiographic exploration was attempted at the time of the absence of the precordial murmur. Previous authors attempted to examine the unusual character of the murmur by various maneuvers, but vasopressor agent was not administered to provoke the murmur.

Using mephentermine sulfate (Wyamine), Crevasse and Logue have attempted to provoke a typical continuous murmur in 4 (or probably more) cases of atypical PDA, in which at least one case (4-year-old, girl) is probably the case under discussion. This method is quite reasonable whenever the aorto-pulmonary pressure gradient is sine qua non of the appearance of ductus murmur. Our previous work also demonstrated 4 cases of atypical PDA, in which one case had a history of intermittent murmur (Fig. 2 of the paper), showed a typical machinery murmur by intravenous administration of methoxamine. However, the unusual attenuation or disappearance of the murmur by this vasopressor drug in the present case is not explained only by the aorto-pulmonary pressure gradient, but another mechanism should be considered. The unusual augmentation of the murmur subsequent to the typical response to amyl nitrite inhalation also remains to be clarified. Unfortunately, however, no angiocardiographic study and also surgical exploration were permitted, then, the exact cause of these unusual auscultatory as well as phonocardiographic findings remains within a limit of speculation. However, the valve or veil-like structure inside of the ductus observed by Keith and Sagarminaga and Hyrske et al. seems unlikely in our case, because the artificial systemic hypertension failed to augment the murmur. Most likely, the situation may be similar to the observation of Shapiro et al., who presumed the acute angulation of ductus which could be obliterated by slight shifts in mediastinal structures. Our case may have similar anatomy. Attenuation or disappearance of the murmur after methoxamine administration may be explained by the obliteration of the ductus caused by the shift of the cardiac base, because this drug causes the increase in the ventricular volume, both systolic and diastolic. The unusual “rebound” phenomenon caused
by amyl nitrite inhalation may also be interpreted by the similar mechanism. As the intracardiac phonocardiography in PDA has showed the louder murmur in the left than the right pulmonary artery,41–43 the ductal opening is usually located slightly left to the bifurcation of main pulmonary artery. The murmur in both pulmonary arteries in our case, however, was not so loud as in main pulmonary artery and was of equal intensity. Such a fact may further confirm the slightly abnormal opening of the ductus and this may be easily bent to obliterate by the volume change of the heart. Active contraction of the muscular wall of ductus,44 which may be potentiated by methoxamine, seems to have no importance in our case, because of the variability of murmur by body position.

As Hyrske et al.11 discussed, the discovery of atypical PDA with intermittent disappearance of the continuous murmur is essentially the matter of choice. However, it should be stressed that the absence of “precordial” continuous murmur does not necessarily indicate that no shunt is present in such a case. As shown in the intracardiac and extracardiac phonocardiograms in Fig. 5, discrepancy may exist, where the murmur is present in the pulmonary artery but it is silent over the chest wall. The same circumstance was recently demonstrated by Moghadam et al.,23 who recorded continuous murmur inside pulmonary artery in 9 out of 10 infants with large PDA associated with congestive heart failure. Thus the value of intracardiac phonocardiography has to be emphasized as the one of the routine clinical diagnostic tools.

Summary

A 20-year-old female with proved patent ductus arteriosus of insignificant left-to-right shunt and intermittent continuous murmur was reported. Once auscultation and phonocardiography revealed a typical continuous murmur, but this was responded unusually by amyl nitrite and methoxamine. Amyl nitrite inhalation initially caused usual response (attenuation of the murmur), but it was followed by unusual intensification. Intravenous administration of methoxamine caused, contrary to the expectation, decrease (first test) or disappearance (second test) of the murmur. The cause of these unusual findings is discussed.

References