Physiologic Studies of Paroxysmal Hyperpnea in Cyanotic Congenital Heart Disease

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Paroxysmal hyperpnea occurs in younger children with cyanotic congenital heart disease with decreased pulmonary blood flow. These episodes, also called hypoxic spells or blue spells, are characterized by increasing cyanosis in spite of an increased rate and depth of respiration. Gradual dulling of the sensorium may progress to unconsciousness.1

The patients subject to paroxysmal hyperpnea have in common an inadequate pulmonary blood flow and a right-to-left shunt. Any increase in systemic venous return, in the face of a fixed or even diminished pulmonary blood flow, would result in an increase in right-to-left shunting and a further lowering of arterial saturation. Hyperpnea in normal subjects results in increased cardiac output,2 3 and in dogs there is evidence that hyperpnea causes an increase in pulmonary vascular resistance.4

We have studied four children with tetralogy of Fallot subject to paroxysmal hyperpnea utilizing an isothermal catheter flowmeter to study the effects of normal inspiratory effort on flow in the vena cavae. In one of these patients, arterial blood gases and pH were obtained in the waking and sleeping states.

Methods

Mellander and Rushmer's5 device for heating a coil of wire in proximity to a thermistor mounted on a catheter was modified by Katsura et al.6

...who heated the thermistor directly. We have developed this further, using a transistorized, balanced bridge circuit with a rapid response time.7 The temperature of the thermistor is maintained at a constant, pre-set temperature; flow of blood at normal body temperature cools and bead slightly, requiring increased electrical current to maintain the thermistor temperature. A voltage proportional to the required current is recorded. The response time depends almost entirely upon the physical characteristics of the thermistor bead and its exposure to the blood stream.

Although it is theoretically possible to quantify flow with the isothermal thermistor flowmeter, it is necessary to fix the diameter of the vessel, with the catheter tip in its exact center. The catheters used in our studies were not fixed, and we made no attempt to draw quantitative inferences.

In addition to the recording of vena caval flow, respiration with a pneumograph, arterial saturation with an earpiece oximeter, and arterial and caval pressures were recorded.

The four patients ranged in age from 1 month to 3 years. The experimental studies were performed during the course of a routine diagnostic study. The three older children were studied under Demerol-Phenergan-Thorazine sedation.

In one child of 1 year, surgical intervention was required. The day prior to surgery a polyethylene cannula was placed in the radial artery at the wrist, under local anesthesia. Blood was drawn during sleep, after a quiet night, and 45 minutes after waking, while the patient was lying quietly. The PO2, PCO2, and pH were determined with a Beckman 160 Gas Analyzer, with appropriate temperature corrections.

Results

Figures 1 and 2 are representative records obtained from two patients during quiet breathing. The patient in the first figure, more severely limited, had an arterial saturation of 68 per cent. Definite, low-amplitude respiratory fluctuations in the arterial saturation may be seen superimposed upon the cardiac pulsations. Flow in the inferior vena cava (in this case, at the upper abdominal...
Figure 1

Record obtained during cardiac catheterization of an 18-month-old girl with moderately severe tetralogy of Fallot. Arterial saturation recorded by a Wood's earpiece oximeter, and inferior vena caval flow with an isothermal thermistor flowmeter. The heaviest vertical lines are 1 second apart.

Figure 2

Record obtained from a 2-year-old girl, mildly limited, with tetralogy of Fallot.
level) increased sharply with inspiration, 20 to 40 msec. after onset of inspiration. The ratio of pulmonary to systemic blood flow was 1:4, which means that 75 per cent of the left ventricular output was derived from the systemic venous return.

The patient in figure 2 had less severe limitations, although she had had definite paroxysmal hyperpnea. Her arterial saturation was 96 per cent during catheterization, under sedation. Although greater amplification was used to record her arterial saturation, there are no perceptible respiratory or cardiac fluctuations in saturation.

Flow patterns in the superior vena cava were very similar to the flow in the inferior vena cava.

Blood gas and pH values in one patient are given in table 1, during sleep and quiet waking. There is a definite fall, upon waking, in arterial pO₂, pH and oxygen saturation, and an increase in pCO₂ and bicarbonate. (This is in contrast to the normal changes with waking; a fall in pCO₂ and an increase in pH and arterial saturation.)

Discussion

The flowmeter studies in our patients with tetralogy confirm the pumping effect of respiration on flow in the venae cavae previously demonstrated in acute animal experiments by Brecher. Arterial saturation fluctuates with respiration in the patients with more severely limited pulmonary blood flow. Both observations indicate that hyperpnea would have an appreciable effect on the patient with cyanotic congenital heart disease and diminished pulmonary blood flow, and earlier work has indicated that the effects are undesirable.

Van Lingen and Whidborne demonstrated that voluntary hyperventilation in older patients with tetralogy of Fallot produced a consistent fall in arterial saturation, whereas hyperventilation in the normal subject produces an increase in arterial saturation. These findings are consistent with, although not precisely comparable to, the results in our patient asleep and awake (table 1). In the normal subject, sleep is attended by a very prompt reduction in ventilation, a fall in oxygen saturation, and a rise in pCO₂.

Returning from the sleeping to the waking state reverses the relationship as the patient increases ventilation. In our subject with tetralogy of Fallot, waking increased the pCO₂ and lowered the arterial saturation by 8 per cent.

A comparable situation occurs with exercise in the patients with cyanotic congenital heart disease and diminished pulmonary blood flow. Bing et al. demonstrated that exercise almost invariably causes a fall in arterial saturation in these patients. Although cardiac output increased considerably, the pulmonary blood flow increased proportionally less, which undoubtedly accounted for the fall in saturation. These subjects also demonstrated considerably greater ventilation with exercise, but because of the limited pulmonary blood flow, there was less oxygen extraction from the inspired air.

The relationship of systemic and pulmonary blood flow, the relative resistances in the two circuits, and the effects on arterial saturation must be considered for an adequate

Table 1

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<tr>
<th>Blood Gas and pH Values</th>
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<tr>
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<tr>
<td><strong>Subject</strong></td>
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<tr>
<td>One-year-old tetralogy</td>
</tr>
<tr>
<td>Sleeping</td>
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<tr>
<td>Awake</td>
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<tr>
<td>Normal (our laboratory)</td>
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<tr>
<td>Normal subjects**</td>
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<tr>
<td>96%</td>
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<td>182</td>
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understanding of the role of hyperpnea in patients with cyanotic congenital heart disease and diminished pulmonary blood flow. Figure 3 is a schematic diagram of the circulation in tetralogy of Fallot, including an electrical analog. The two ventricles are connected, in addition to the usual "series" arrangement, by a shunt through a ventricular septal defect, of negligible impedance. The flows in the two circuits, pulmonary and systemic, are determined by the relative resistances in the two circuits. The pulmonic circuit has two resistances in series, a high resistance at the pulmonic valve or right ventricular infundibulum and a much smaller resistance in the pulmonary vascularature. In tetralogy the total resistance through the pulmonary circuit is usually greater than the systemic resistance. The numbers used in the diagram are taken from data on one of our patients with tetralogy of Fallot. This patient had a relatively moderate limitation, with a pulmonary blood flow that was 75 per cent of the systemic blood flow. The pulmonary vascular resistance was one twelfth of the systemic vascular resistance; with the pulmonary vascular resistance considered as one unit of resistance, the systemic resistance is 12, and the pulmonary valve resistance is 15.

If the resistance to flow through the pulmonic valve or infundibulum increased, as suggested by Wood and others, the result would be appreciable. No direct evidence has been presented, however, that "spasm" of the right ventricular infundibulum actually occurs. Of more significance, some of the most severe paroxysms occur in patients with pulmonary atresia, in whom narrowing of the right ventricular infundibulum would be irrelevant.

Hyperventilation has been shown to increase cardiac output an average of 20 per cent, with no appreciable change in arterial pressure, and therefore systemic vascular resistance is reduced by approximately 20 per cent. From figure 3, lowering the systemic resistance by 20 per cent, and leaving the total pulmonary resistance unchanged would reduce the pulmonary flow to 62.5 per
cent of the systemic blood flow. The systemic blood flow is made up of all the pulmonary flow plus the right-to-left shunt. The pulmonary venous return would have an expected saturation of 96 per cent, and the blood shunted from right to left had a saturation of 54 per cent in the patient under discussion. The resulting arterial saturation would be 80 per cent, in contrast to this patient's resting saturation of 86 per cent. The calculated results are in line with the changes in arterial saturation reported by Van Lingen and Whidborne, who observed that the arterial saturation fell from 1 to 6 per cent with voluntary hyperventilation.

Finley, Hill, and Bonica have demonstrated that hyperpnea in animals produces an apparent increase in pulmonary vascular resistance. In their study the resistance approximately doubled with marked hyperpnea. Doubling the pulmonary vascular resistance in figure 3, keeping all other values constant, would produce a relatively slight change in the over-all figures. The total pulmonary resistance would now be 17, and the pulmonary flow would be reduced to 71 per cent of the systemic blood flow, as compared to 75 per cent in the control state. Arterial saturation would be reduced by only 2 per cent. If hyperpnea produced both a 20 per cent decrease in systemic resistance and a doubling of the pulmonary vascular resistance, the pulmonic flow would be reduced to 59 per cent of the systemic, and the arterial saturation would be reduced to 79 per cent.

From this consideration it seems evident that hyperpnea may well be harmful to patients with cyanotic congenital heart disease and decreased pulmonary blood flow. The factors that initiate the hyperpnea in a paroxysmal fashion are more obscure. Any right-to-left shunt necessarily subjects the chemoreceptors and the respiratory center to blood with a lower P02 than is normal for arterial blood. These patients do, in fact, demonstrate hyperpnea, even at rest. The only major enigma in patients with right-to-left shunts and inadequate pulmonary blood flow is not the occurrence of hyperpnea, but the paroxysmal nature of the episodes of marked hyperpnea. The following is a review of the current theories of the cause of these spells, in addition to those mentioned in the above discussion.

Hamilton et al. regarded the obstruction to pulmonary blood flow as a relatively fixed resistance, and, accordingly, any change in the systemic resistance would determine the magnitude of right-to-left shunting. He concluded that paroxysmal hyperpnea or "cyanotic episodes" were due to decreased systemic resistance. As shown in our calculations (fig. 3), decreasing the systemic resistance lowers the arterial oxygen saturation, but proof is lacking that the cyanotic resistance is initiated by a decrease in systemic resistance.

Recently, two groups independently reported the occurrence of metabolicacidosis in patients with extremely limited pulmonary blood flow. Furthermore, Heins in 1961 and Rudolph in 1963 reported the successful interruption of prolonged "anoxic episodes" with intravenous sodium bicarbonate. The metabolic acidosis apparently resulted from anaerobic metabolism secondary to hypoxia, since the arterial P02 was considerably below the level that will consistently cause accumulation of excess lactate. Although lowered pH is one of the three humoral factors increasing ventilation, this does not explain the paroxysmal nature of the hyperpneic episodes. Further, anaerobic metabolism is unlikely to be the cause of paroxysmal hyperpnea in the tetralogy patient with less severe hypoxemia. Several of our patients with paroxysmal hyperpnea had resting arterial saturations of over 85 per cent, well above the oxygen levels that result in anaerobic metabolism at rest.

Proposed Etiology of Paroxysmal Hyperpnea

In a previous report, we reviewed the pertinent clinical background of paroxysmal hyperpnea. The spells occur in approximately 40 per cent of young children and infants with cyanotic congenital heart disease with decreased pulmonary blood flow. The paroxysms may occur at any time, but most
frequently occur in the early morning after several hours' sleep, and may be precipitated by bowel movements, feeding, or crying. The average rate of occurrence was one to two spells a week.

During sleep, oxygen consumption is reduced considerably over that of even quiet wakefulness\(^{11,26}\) (table 1). It is probable that these children awake in a state of reasonable metabolic balance, with no oxygen debt, and normal arterial pH and pCO\(_2\). Paradoxically, this appears to be the time when they are most susceptible to spells of hyperpnea. In most of these patients, on most days, there is either an adjustment in sensitivity in the respiratory drive mechanism or an adjustment in bicarbonate, which prevents the occurrence of the spells. If, prior to the adjustment, a relatively sudden increase in activity or a Valsalva-like maneuver occurs (such as crying or bowel movement), the resulting increase in right-to-left shunting will immediately decrease arterial pO\(_2\) and pH and increase arterial pCO\(_2\), which may trigger marked hyperpnea. The hyperpnea will increase cardiac output\(^2\) and decrease pulmonary blood flow,\(^4\) resulting in further right-to-left shunting and greater arterial hypoxemia. A vicious cycle may thus be established (fig. 4), interrupted usually by unconsciousness or morphine.\(^{27}\)

**Summary**

Four children with tetralogy of Fallot were studied with an isothermal thermistor flowmeter. Respiratory pumping effect on vena caval flow was demonstrated. Corresponding fluctuations in arterial saturation were recorded in the patients with more severe cyanosis.

Evidence from other work confirms the disadvantage of hyperpnea in tetralogy: increased oxygen consumption, increased cardiac output, and lowered arterial saturation, due to the relatively fixed or decreased pulmonary blood flow. Because of the right-to-left shunt, arterial blood in these patients usually will have low pO\(_2\) and pH and relative hypercapnia, creating a chronic stimulus for hyperpnea. The puzzle is the paroxysmal nature of marked hyperpnea (cyanotic or “anoxic” spells) which these patients demonstrate at times. Earlier theories attempting to explain the onset and mechanism of these paroxysms are reviewed. The following sequence is postulated.

During prolonged sleep, oxygen requirements are reduced, and can be met by the relatively fixed, inadequate pulmonary blood flow. Arterial pO\(_2\), pCO\(_2\), and pH become nearly normal. During the first hour, the respiratory control mechanism is thereby relatively vulnerable, and a sudden increase in cardiac output or decrease in pulmonary blood flow may initiate a vicious cycle of increased arterial pCO\(_2\), decreased arterial pO\(_2\) or pH; hyperpnea; increased systemic venous return with fixed or decreased pulmonary flow; increased R-L shunting leading to increased arterial pCO\(_2\), decreased arterial pO\(_2\) or pH etc. Exercise, bowel movements, or crying could produce sudden alterations in arterial composition to initiate these spells and we found in a previous clinical study that these events frequently initiated paroxysmal hyperpnea.

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References


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