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Original Article

A modelling study of atrial septostomy for pulmonary arterial hypertension, and its effect on the state of tissue oxygenation and systemic blood flow

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Abstract Atrial septostomy is performed in patients with severe pulmonary arterial hypertension, and has been shown to improve symptoms, quality of life and survival. Despite recognized clinical benefits, the underlying pathophysiologic mechanisms are poorly understood. We aimed to assess the effects of right-to-left shunting on arterial delivery of oxygen, mixed venous content of oxygen, and systemic cardiac output in patients with pulmonary arterial hypertension and a fixed flow of blood to the lungs. We formulated equations defining the mandatory relationship between physiologic variables and delivery of oxygen in patients with right-to-left shunting. Using calculus and computer modelling, we considered the simultaneous effects of right-to-left shunting on physiologies with different pulmonary flows, total metabolic rates, and capacities for carrying oxygen. Our study indicates that, when the flow of blood to the lungs is fixed, increasing right-to-left shunting improves systemic cardiac output, arterial blood pressure, and arterial delivery of oxygen. In contrast, the mixed venous content of oxygen, which mirrors the average state of tissue oxygenation, remains unchanged. Our model suggests that increasing the volume of right-to-left shunting cannot compensate for right ventricular failure. Atrial septostomy in the setting of pulmonary arterial hypertension, therefore, increases the arterial delivery of oxygen, but the mixed systemic saturation of oxygen, arguably the most important index of tissue oxygenation, stays constant. Our data suggest that the clinically observed beneficial effects of atrial septostomy are the result of improved flow of blood rather than augmented tissue oxygenation, provided that right ventricular function is adequate.

Keywords: Shunting; congenital heart disease; analytical modelling

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IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION IS A progressive disease, which still carries a poor prognosis.[1] Balloon atrial septostomy has been proposed as a therapeutic option for highly symptomatic patients refractory to advanced vasodilator therapy.[2–4] The artificially created interatrial communication may function as a "pop-off" valve, allowing decompression of the right ventricle and maintenance of systemic blood flow when metabolic demand is increased,[5] for example during exercise and pulmonary arterial hypertensive crises, albeit at the expense of cyanosis.[6] Clinically, atrial septostomy has been

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shown to improve haemodynamics and quality of life, and prolong survival.[2,7–11]

It is not clear whether the benefits from atrial septostomy arise entirely from the increased flow of blood, that is preservation of an adequate perfusion pressure, or whether a contribution is made by improved transport of oxygen. There is no doubt that systemic flow increases and arterial saturation of oxygen falls after atrial septostomy. It is unclear whether the increase in blood flow is adequate to compensate for the decrease in saturation. It is not known, therefore, whether tissue oxygenation improves, stays the same, or deteriorates. Clinical studies have revealed an increase in calculated arterial delivery of oxygen,[2] and this is currently widely accepted as evidence of improved tissue oxygenation.[2,9,12] Delivery of oxygen, however, is potentially flawed in patients with abnormal circulatory connections.

Because of these uncertainties, we have performed a modelling study into the effect of right-to-left shunting on useful delivery of oxygen, mixed venous content of oxygen, and systemic cardiac output in patients with pulmonary arterial hypertension and a fixed flow of blood to the lungs.

Materials and methods

We used a standard model of the circulation in the presence of a right-to-left shunt at atrial level, as shown in Figure 1 and explained in the legend.

In the presence of a right-to-left shunt, the systemic flow of blood (Q_S) represents the sum of the flow of blood to the lungs (Q_P) and the volume of the right-to-left shunt (Q_{RL}). As a consequence of admixture of the venous blood bypassing the lungs with the pulmonary venous blood, the arterial content of oxygen (C_{aO_2}) is the weighted mean of the mixed venous and the pulmonary venous content of oxygen:

$$C_{aO_2} = \frac{C_{MVO_2} \cdot Q_{RL} + C_{PVO_2} \cdot Q_P}{Q_{RL} + Q_P} \qquad (1)$$

C_{aO_2} = arterial oxygen content; C_{MVO_2} = mixed venous oxygen content; C_{PVO_2} = pulmonary venous oxygen content; Q_P = pulmonary blood flow; Q_{RL} = right to left shunt.

The mixed venous saturation represents the difference between the arterial content of oxygen and the amount of oxygen removed by the tissues:

$$C_{MVO_2} = C_{aO_2} - \frac{VO_2}{Q_S} \qquad (2a)$$

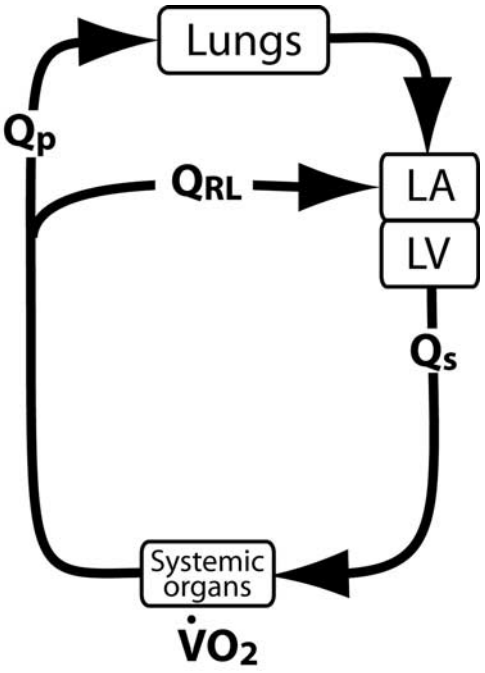

Figure 1.
The cartoon shows a model of the circulation in the presence of a right-to-left shunt at atrial level. LA = left atrium, LV = left ventricle; Q_p = pulmonary blood flow; Q_{RL} = right to left shunt; Q_S = systemic blood flow; VO_2 = total consumption of oxygen by the body.

C_{MVO_2} = mixed venous oxygen content; C_{PVO_2} = pulmonary venous oxygen content; Q_P = pulmonary blood flow; VO_2 = total body oxygen consumption.

By combining Equations 1 and 2a, systemic venous content of oxygen can equally be expressed as:

$$C_{MVO_2} = C_{PVO_2} - \frac{VO_2}{Q_P} \qquad (2b)$$

Arterial content of oxygen can then be calculated by combining Equations 1 and 2b, thus eliminate C_{MVO_2} from the equation, and solving for C_{aO_2} as follows:

$$1.\ C_{aO_2}(Q_{RL} + Q_P) = \left(C_{PVO_2} - \frac{VO_2}{Q_P}\right) \cdot Q_{RL} + C_{PVO_2} \cdot Q_P$$

$$2.\ C_{aO_2}(Q_{RL} + Q_P) = C_{PVO_2} \cdot Q_{RL} - \frac{VO_2}{Q_P} \cdot Q_{RL} + C_{PVO_2} \cdot Q_P$$

$$3.\ C_{aO_2}(Q_{RL} + Q_P) = C_{PVO_2} \cdot (Q_{RL} + Q_P) - \frac{VO_2}{Q_P} \cdot Q_{RL}$$

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after dividing by $(Q_{RL}+Q_P)$:

$$4.\ C_{aO_2} = C_{PVO_2} - \left(\frac{Q_{RL} \cdot VO_2}{Q_P \cdot (Q_{RL} + Q_P)}\right) \qquad (3)$$

C_{aO_2} = arterial oxygen content; C_{PVO_2} = pulmonary venous oxygen content; Q_P = pulmonary blood flow; Q_{RL} = right to left shunt; VO_2 = total body oxygen consumption.

The content of oxygen represents the product between saturation of oxygen, haemoglobin concentration, and the capacity of blood to carry oxygen, which is κ, equal to 1.38×10^{-3} L of O_2 per gram of haemoglobin.[13]

The arterial saturation of oxygen can be calculated by dividing Equation 3 by κ:

$$Sat_{aO_2} = Sat_{PVO_2} - \left(\frac{Q_{RL} \cdot VO_2}{\kappa \cdot Hb \cdot Q_P \cdot (Q_{RL} + Q_P)}\right) \qquad (4)$$

Sat_{aO_2} = arterial oxygen saturation; Sat_{PVO_2} = pulmonary venous oxygen saturation; Q_P = pulmonary blood flow; Q_{RL} = right to left shunt; Hb = haemoglobin concentration; κ = oxygen carrying capacity of blood; VO_2 = total body oxygen consumption.

To illustrate the effect of changes in distribution of flow of blood to the lungs, total consumption of oxygen by the body, and left ventricular output on the arterial and systemic mixed venous contents of oxygen, we developed a computer model using commercial mathematical modeling software (Matlab 6.5, Mathworks, USA and R version 2.6.1, R Foundation for Statistical Computing, Vienna, Austria). If not otherwise stated, the capacity of the blood for carrying oxygen was taken as 0.207 l O_2/l blood, based on conventional values of 1.38×10^{-3} L O_2 per gram haemoglobin, and a haemoglobin concentration of 150 g/l.[13]

Results

Effect of changes in right-to-left shunting and pulmonary blood flow on arterial oxygen saturation

We examined the impact of different combinations of flow of blood to the lungs and right-to-left shunting on arterial saturations of oxygen. For any given combination of pulmonary flow and uptake of oxygen, arterial saturation of oxygen decreases with increasing degree of right-to-left shunting, as illustrated in Figure 2. In Figure 2b, we demonstrate that, for low values of pulmonary flow, even small increases in the volume of the shunt drastically reduce the arterial saturation, whereas at higher levels of flow, saturations are relatively independent of changes in the volume of the shunt.

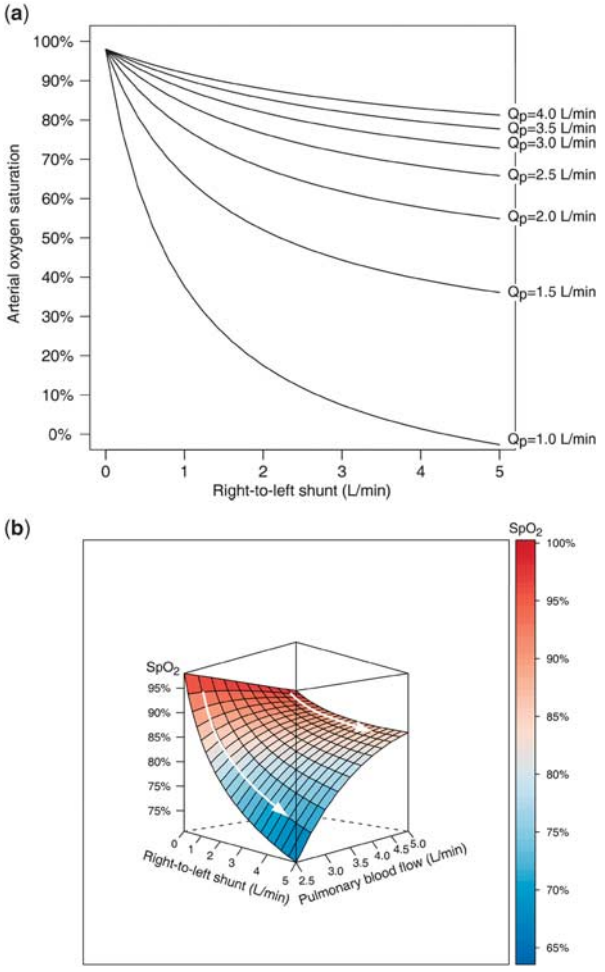

Figure 2.
In Fig. 2a, arterial oxygen saturation (%) is shown as a function of right-to-left shunting (Q_{RL}) for a given total consumption of oxygen by the body, taken as 300 ml/min for this example, and different values of flow of blood to the lungs (Q_P). In Fig. 2b, arterial oxygen saturation is shown for different combinations of pulmonary flow and right-to-left shunting. The arrows demonstrate that the same increase in right-to-left shunting causes a bigger decrement in oxygen saturations when flow of blood to the lungs is lower.

Impact of changes in right-to-left shunt volume on haemodyanamic parameters and arterial delivery of oxygen

We studied the effect of varying right-to-left shunt fractions on systemic cardiac output, arterial blood pressure, arterial oxygen saturation and delivery of oxygen in the presence of a fixed flow of blood to the lungs. As systemic blood flow represents the sum of pulmonary flow and the volume of right-to-left shunting, any increase in shunting will lead to a

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linear increase in systemic cardiac output. If total systemic vascular resistance remains constant, arterial blood pressure, representing the product between systemic blood flow and systemic vascular resistance, will increase in proportion to increased systemic flow.

Exploring the relationship between the volume of shunting and arterial delivery of oxygen reveals that delivery (D_{aO_2}) increases in a linear fashion with increasing degree of right-to-left shunting (Equation 5):

$$D_{aO_2} = \left(C_{PVO_2} - \frac{VO_2}{Q_P} \right) \cdot Q_{RL} + Q_P \cdot C_{PVO_2};$$

$$\text{as } \left(C_{PVO_2} - \frac{VO_2}{Q_P} \right) = C_{MVO_2} \text{ this is identical to}$$

$$D_{aO_2} = (C_{MVO_2} \cdot Q_{RL}) + (Q_P \cdot C_{PVO_2})$$

D_{aO_2} = arterial oxygen delivery; C_{PVO_2} = pulmonary venous oxygen content; Q_P = pulmonary blood flow; Q_{RL} = right to left shunt; VO_2 = total body oxygen consumption; ≡ identical to.

The relationship between the volume of right-to-left shunting and arterial content of oxygen is illustrated in Figure 3.

Impact of changes in right-to-left volume of shunting on mixed venous content of oxygen

Our modelling study indicates that, in contrast to arterial delivery of oxygen, the mixed venous content of oxygen, which mirrors the tension of oxygen in the tissues, is independent of the degree of right-to-left shunting, and therefore is unaffected by an increased shunt fraction, as is demonstrated by Equation 2 and illustrated in Figure 3.

Impact of right ventricular dysfunction on oxygenation

Adequate right ventricular function is critical in maintaining the flow of blood to the lungs. If the right ventricle is unable to increase its output to match pulmonary flow, then this in itself can become the limiting factor to oxygenation. As shown in Figure 3, any reduction in right ventricular output impairs arterial delivery of oxygen, and mixed venous oxygen saturation.

Lower limit of pulmonary flow for any given consumption of oxygen and oxygen carrying capacity

To maintain adequate tissue oxygenation, a minimal flow of blood to the lungs is required for any given combination of oxygen consumption, oxygen carrying capacity, and the ability of peripheral organs to extract oxygen. As illustrated in Equation 6, the minimal required flow to the lungs ($Q_{P\ Limit}$) is

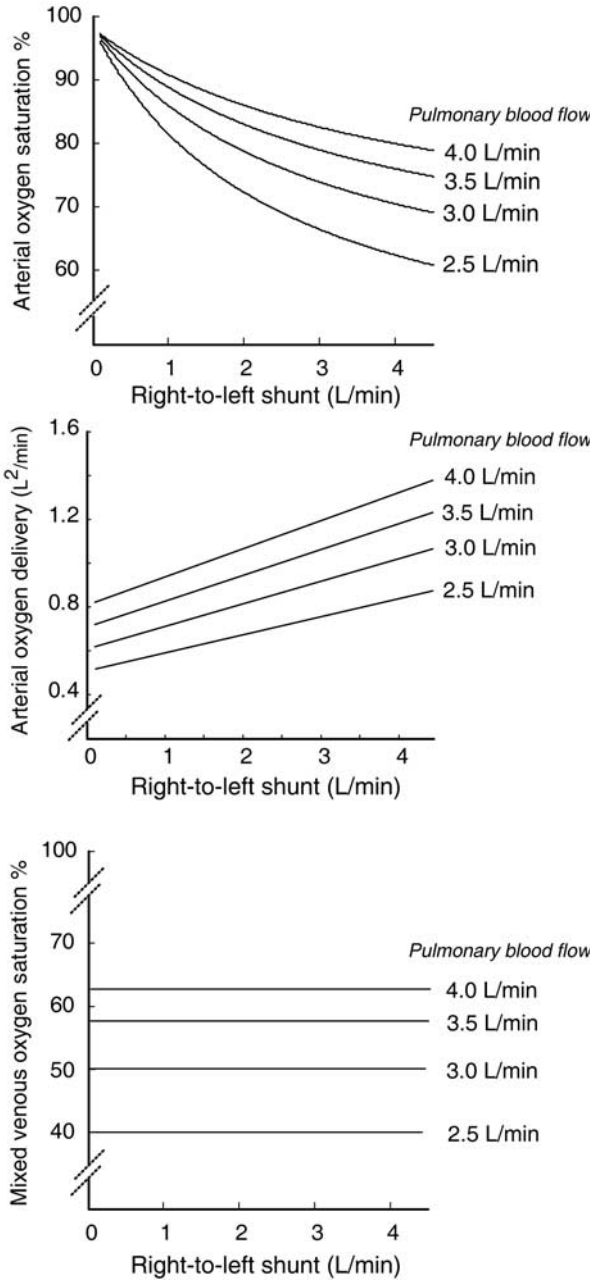

Figure 3.
Arterial oxygen saturation (black), arterial oxygen delivery (red) and mixed systemic venous oxygen saturation (blue) as a function of right-to-left shunting for a given total consumption of oxygen by the body, taken as 300 ml/min in this example, and different values for flow of blood to the lungs. Note that, despite a drop in arterial oxygen saturation, arterial delivery is augmented and mixed venous content is unaffected as right-to-left shunting increases. RV = right ventricle.

independent of the degree of right-to-left shunting. It is determined by the ratio between consumption of oxygen, the product of haemoglobin concentration, κ, and the difference between pulmonary venous saturation and the minimal achievable mixed venous saturation (Sat_{MVO_2}min). Reducing

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the consumption of oxygen, augmenting the ability of tissue to utilize oxygen by reducing $Sat_{MVO_2}min$, and increasing the haemoglobin concentration will reduce the minimal required flow of blood to the lungs.

$$Q_{PLimit} \geq \frac{VO_2}{Hb \cdot \kappa \cdot (Sat_{PVO_2} - Sat_{MVO_2min})} \quad (6)$$

$Sat_{MVO_2}min$ = minimal mixed venous saturation; Sat_{PVO_2} = pulmonary venous oxygen saturation; Q_P = pulmonary blood flow; Hb = haemoglobin concentration; κ = oxygen carrying capacity of blood; VO_2 = total body oxygen consumption.

Impact of haemoglobin concentration on arterial delivery of oxygen and tissue oxygenation

Exploring the relationship between haemoglobin concentration and arterial delivery of oxygen revealed that the latter (D_{aO_2}) increases in a linear fashion with increasing haemoglobin concentration (Hb). Re-arranging Equation 5, and replacing C_{PVO_2} by $Sat_{PVO_2} \cdot \kappa \cdot Hb$ yields:

$$D_{aO_2} = [(Sat_{PVO_2} \cdot \kappa \cdot (Q_{RL} + Q_P)] \cdot Hb - \frac{Q_{RL} \cdot VO_2}{Q_P} \quad (7)$$

D_{aO_2} = arterial oxygen delivery; Sat_{PVO_2} = pulmonary venous oxygen saturation; Q_P = pulmonary blood flow; Q_{RL} = right to left shunt; VO_2 = total body oxygen consumption; Hb = haemoglobin concentration; κ = oxygen carrying capacity of blood.

For any given combination of pulmonary venous saturation of oxygen (Sat_{PVO_2}), oxygen carrying capacity (κ), and systemic blood flow (Q_P+Q_{RL}), the arterial content of oxygen increases in proportion to the concentration of haemoglobin with a slope of $[(Sat_{PVO_2} \cdot \kappa \cdot (Q_{RL} + Q_P)]$. In addition, mixed venous concentration of oxygen increases with increasing haemoglobin concentration:

$$Sat_{MVO_2} = Sat_{PVO_2} - \frac{VO_2}{\kappa \cdot Hb \cdot Q_P} \quad (8)$$

Sat_{MVO_2} = mixed venous saturation; Sat_{PVO_2} = pulmonary venous oxygen saturation; Q_P = pulmonary blood flow; Hb = haemoglobin concentration; κ = oxygen carrying capacity of blood; VO_2 = total body oxygen consumption.

As a consequence, decreases in the flow of blood to the lungs can be offset by a proportional increase in haemoglobin concentration (Equation 8), as shown in Figure 4.

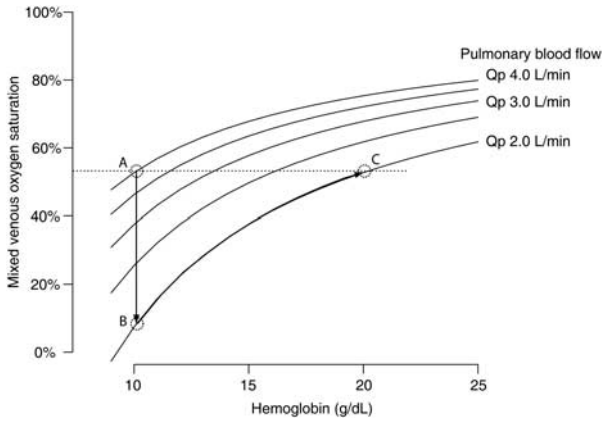

Figure 4.
Effect of haemoglobin concentration on mixed venous oxygen saturation. A reduction (from 4 L/min to 2 L/min in this example [segment AB]) in pulmonary flow is offset by a proportional increase in haemoglobin concentration (from 10 g/dL to 20 g/dL in this example [segment BC]).

Discussion

In this modelling study, we have found that therapeutic atrial septostomy increases systemic arterial delivery of oxygen for any given value of flow of blood to the lungs. This is revealed, however, to be an artefact of the way arterial delivery of oxygen is defined, which may not be appropriate for patients with shunting lesions. In fact, mixed systemic saturation of oxygen, arguably the most important index of tissue oxygenation, is not improved by atrial septostomy. Our findings eliminate the possibility that globally improved oxygenation is a significant benefit of atrial septostomy. Rather, our study suggests that the clinical improvement reported in patients undergoing atrial septostomy must have another explanation, for example the greater leeway for redistribution of flow available because of the increased systemic flow.

Arterial delivery of oxygen is a simple summary measure, which is useful in situations where an increase in cardiac output does not necessarily mean a decrease in arterial saturations of oxygen. It is widely used in quantifying the state of oxygenation, for example in the intensive care unit.[14] In situations where increases in systemic flow are achieved at the expense of decreases in systemic saturation, nonetheless, this simple approach of multiplying flow and arterial saturation can easily be misleading for reasons discussed in previous analytical studies.[15,16] In principle, venous parameters of oxygenation may be better suited to characterize tissue oxygenation in this setting. Venous blood has returned from tissues with which it has recently been in equilibrium. Its saturation of oxygen offers useful information about tissue oxygenation not available from arterial

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parameters.[17] The greater ease of non-invasive measurement of arterial parameters explains their widespread use in clinical practice, but in studies such as this one, venous oxygenation is equally calculable, and is better representative of tissue oxygenation.

Clinical studies have shown that atrial septostomy is safe and effective in patients with idiopathic pulmonary hypertension.[2,3,10] It has been reported that, in many patients, syncope is abolished, functional class improves, and right heart failure ameliorates. Furthermore, by transferring blood from right to left in patients with severe pulmonary hypertension, it has the potential to attenuate right ventricular volume overload and improve left ventricular filling, leading to improved biventricular function.[3,9] But beyond the immediate haemodynamic effect, whether oxygenation is improved is a difficult question to answer by qualitative reasoning alone. It is said that "oxygen transport to the tissues improves due to an increase in cardiac output, despite a modest reduction in systemic arterial oxygen saturation." as a result of atrial septrostomy.[3] Our study endorses the fact that atrial septostomy augments arterial delivery of oxygen. The effect of simultaneously increasing systemic flow and reducing arterial oxygen saturation on arterial delivery of oxygen, however, is not intuitively obvious, and depends on the balance between these two factors. Our study shows that increased delivery of oxygen does not coincide with improved tissue oxygenation in this setting. In fact, average tissue oxygenation, as quantified by venous oxygenation, is found to be entirely unaffected by the addition of the intracardiac shunt, and is determined only by the ratio between total consumption of oxygen and pulmonary blood flow.

Thus, the creation of a shunt increases systemic blood flow, and superficially increases the conventional definition of delivery of oxygen, but without improving mean tissue oxygenation. If, therefore, systemic arterial flow is increased by creating a shunt, which inserts some extra mixed venous blood into the arterial circulation, it should be remembered that that extra blood will travel round the circulation and arrive back at the mixed venous point with the same content of oxygen, and will not have been able to transfer oxygen into the tissues. This extra blood will have travelled to the tissues and travelled back unchanged, but since "delivery of oxygen" is explicitly defined as simply how much oxygen travels to the tissues, it is increased. As far as tissue oxygenation is concerned, there is no improvement. We believe it is unwise to apply the concept of "delivery of oxygen" in this population. By focussing on mixed venous saturation of oxygen, we can see that the net effect of creation of a shunt on mean tissue oxygenation is neutral.

We propose that the source of the clear clinical benefits of atrial septostomy must therefore lie elsewhere. Despite not improving tissue oxygenation, atrial septostomy augments systemic blood flow, potentially benefiting organs that lack the ability to autoregulate blood flow at low blood pressures. It has been reported that a mean arterial pressure of at least 60 mmHg is required to enable cerebral autoregulation.[18] Interestingly, atrial septostomy has been demonstrated to be especially effective in abolishing syncope. Atrial septostomy could protect against syncope by maintaining systemic cardiac output, particularly when the pulmonary arterial pressure rises acutely.[3] In the situation of desperately poor systemic blood flow, autoregulation may not be able successfully to maintain flow to some vital territories. An increase in total flow could permit autoregulatory processes to restore perfusion to vital organs, even if the overall average tissue oxygenation is no better.

The concept of delivery of oxygen is useful in patients without congenitally malformed hearts as a simple means of combining cardiac output, oxygen carrying capacity, and oxygen saturation into a single parameter.[19] In patients with shunting lesions, however, there can be a trade-off between blood flow and arterial oxygen saturation, and the concept of arterial delivery of oxygen should be avoided.[15,16]

Atrial septostomy does not improve average tissue oxygenation as defined by venous oxygenation. Rather, our study suggests that tissue oxygenation can be improved by increasing the flow of blood to the lungs, using advanced medical therapies, limiting maximal consumption of oxygen, for example by discouraging extreme exertion, and improving the capacity of the blood to carry oxygen by maintaining adequate concentrations of haemoglobin, and avoiding iron-deficient anaemia in cyanotic patients.[20,21] Interestingly, our model indicates that a proportional increase in the concentration of haemoglobin can offset a decrease in the flow of blood to the lungs.

Our model also suggests that there exists a critical flow to the lungs below which an adequate tissue oxygenation cannot be achieved. The exact value of this metabolically critical flow depends on consumption of oxygen, the capacity of the blood to carry oxygen, and the abilities of the tissue to extract oxygen, again emphasizing the need of adequate concentrations of haemoglobin in these patients. Metabolically, the critical level of pulmonary flow is found to be independent of the volume of right-to-left shunting.

Right ventricular function is vital in maintaining adequate flow of blood to the lungs. It has been reported that atrial septostomy attenuates any right ventricular volume overload, and has the potential to improve right ventricular function.[9] If, despite atrial septostomy, right ventricular function continues to deteriorate, pulmonary flow also decreases,

and tissue oxygenation worsens. As illustrated in Figure 3, mixed venous content of oxygen is independent of the volume of shunting. Increased right-to-left shunting, therefore, cannot compensate for right ventricular failure in this setting. Hence, our modelling study emphasizes the importance of adequate right ventricular function in patients with pulmonary arterial hypertension considered for atrial septostomy.

Our study has its limitations. It cannot evaluate the relationship between the size of the interatrial communication and the volume of right-to-left shunting. This association is complex, and confounded by numerous dynamic physiologic processes, such as atrial mural distensibility, relative resistance to filling of the right and left ventricles, heart rate, and systemic venous return.[22,23] Our modelling suggests, nonetheless, that the empirically determined size of the interatrial communication is more critical in patients with low pulmonary flow. In these patients, a small increase in the volume of right-to-left shunting will cause a greater decrement in arterial saturation of oxygen compared to patients with higher values of pulmonary flow (Fig. 2b). In addition, our study was not designed to study the effect of increased pulmonary vascular resistance on the degree of shunting, but rather the effect of the volume of shunting on oxygen physiology. The impact of pulmonary pressure on the volume of shunting at atrial level is through a complex interaction with right ventricular function, right ventricular hypertrophy, increased right ventricular enddiastolic pressures, and ultimately reduced right atrial compliance. Further studies are required to investigate the association between elevated pulmonary arterial pressure and the volume of shunting. Unfortunately, right ventricular adaptation to increased afterload is variable, and the complex anatomy and physiology of the right ventricle make it too speculative to generate mathematical models including all these variables. Biological models may be the way to obtain that phase of information.

In summary, while of course atrial septostomy reduces the arterial saturation of oxygen, it increases the arterial delivery, and yet tissue oxygenation stays constant. This is because delivery of oxygen is markedly non-equivalent to tissue oxygenation in the situation when circulatory connections are abnormal. The clinical improvement reported in patients undergoing atrial septostomy, therefore, must have another explanation, such as the greater margin for redistribution of flow made available by the improved systemic flow. Our study also emphasizes the importance of the flow of blood to the lungs, and the capacity of the blood to carry oxygen, in maintaining an adequate supply of oxygen to the tissues.

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