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## Collateral ventilation

# Collateral ventilation

E J Cetti, A J Moore, D M Geddes

Understanding collateral ventilation is probably central to planning new bronchoscopic techniques for treating emphysema

The phenomenon of collateral ventilation in the human lung is defined as “the ventilation of alveolar structures through passages or channels that bypass the normal airways”. This phenomenon seems to be prominent in emphysema and is emerging as a key issue for those working in the new and exciting field of bronchoscopic techniques for treating emphysema.

The existence of channels within the lungs through which such collateral flow could occur was realised a century ago,<sup>1</sup> but it was not until the 1930s that the possible significance of this flow was recognised.<sup>2</sup> This significance was largely ignored by physiologists and physicians alike,<sup>3</sup> apart from a select band of investigators in the 1960s and 1970s.<sup>4–7</sup> However, with the emergence of new bronchoscopic techniques for treating emphysema, the phenomenon of collateral ventilation has gained a renewed importance and the paper by Higuchi *et al*<sup>8</sup> in this issue of *Thorax* casts some welcome light on the issue of collateral ventilation in the emphysematous lung.

## ANATOMICAL, PHYSIOLOGICAL AND CLINICAL EVIDENCE FOR THE EXISTENCE OF COLLATERAL VENTILATION

In order for collateral flow of air to occur within the lungs, there must exist collateral channels with a pressure gradient across them. Candidate pathways for collateral ventilation include interalveolar pores,<sup>9</sup> accessory bronchiole-alveolar communications,<sup>10</sup> and accessory respiratory bronchioles

connecting bronchiole to bronchiole.<sup>4</sup> As Higuchi *et al*<sup>8</sup> point out in this issue of *Thorax*, interlobar collateral flow across fissures has been demonstrated, and while this may be via some of the above pathways, in the context of lung destruction by emphysema new channels may develop. The resistance to collateral flow in human lungs has been measured and found to be 50 times greater than the resistance to flow through the normal airways.<sup>5–11</sup> It therefore seems that collateral ventilation cannot exist to any significant degree in normal airways. However, the resistance to collateral flow is markedly reduced in emphysema to such an extent that the resistance to flow in segmental airways (increased by expiratory collapse and mucus plugging) can actually be greater than the resistance to flow through the collateral pathways.<sup>5–12</sup> Significant airflow obstruction is a hallmark of emphysema and this leads to areas of uneven ventilation resulting in the creation of pressure gradients within the lung. Low resistance collateral channels can therefore exist in emphysema with pressure gradients across them—a situation likely to lead to significant collateral ventilation.

The fact that collateral ventilation does occur can be inferred by some simple observations. In 1947 Baarsma noticed that total lower lobe bronchus occlusion following foreign body aspiration by a patient did not lead to any atelectasis. He hypothesised that air must have been ventilating the occluded segments via collateral channels and

went on to demonstrate segmental collateral flow experimentally.<sup>13</sup> A similar recognised phenomenon is the lack of lobar collapse in emphysema when total lobar occlusion occurs due to tumour, and the technique described by Higuchi *et al*<sup>8</sup> is an extension of a well documented anaesthetic/surgical phenomenon. When an emphysematous lung is ventilated it is often observed that selective lobar intubation does not lead to collapse of the other lobes—that is, air must be passing into these other lobes via collateral channels.

## THE IMPORTANCE OF COLLATERAL VENTILATION IN DISEASE

Collateral ventilation does not seem to exist in infancy but develops later in life and to a much greater degree in emphysema.<sup>14</sup> As emphysema is “an increase beyond the normal in the size of the air spaces distal to the terminal bronchiole, accompanied by destruction of their walls”,<sup>15</sup> it is possible to hypothesise how the disease process might lead to the formation of collateral channels. Perhaps the destruction of the alveolar walls together with changes in mechanical strain<sup>5–6</sup> opens up new channels for flow or simply causes enlargement of existing channels, thereby reducing their resistance.

So, if emphysema leads to increased collateral ventilation, what are the consequences? In an area of lung that is completely obstructed, without collateral ventilation, alveolar gas tensions within the obstructed area rapidly equilibrate with mixed venous blood, no further gas exchange occurs, alveolar gas is absorbed, and atelectasis develops.<sup>7</sup> It is easy to see that collateral ventilation can prevent atelectasis in the setting of airflow obstruction, but does this have any significant functional benefits? The fact that collateral ventilation is of functional importance is supported by the observation that horses do not have collateral ventilation and tolerate obstructive lung diseases very poorly while dogs have a substantial degree of collateral ventilation and

tolerate airflow obstruction much better.<sup>6</sup> This functional benefit was confirmed experimentally by Lindsog and Bradshaw.<sup>16</sup> They measured gas partial pressures in an obstructed area of lung ventilated purely by collateral ventilation. As expected, the arterial oxygen tension (Pao<sub>2</sub>) was lower and the Paco<sub>2</sub> higher than in air expired from unobstructed lung (it has undergone more gas exchange). However, interestingly, they found that the Pao<sub>2</sub> was higher and the Paco<sub>2</sub> lower than concurrent arterial blood gases. In other words, areas of lung that are only collaterally ventilated can still carry out useful gas exchange—that is, collateral channels allow obstructed areas to maintain a useful degree of function. Gas exchange in emphysema can be remarkably well preserved despite severe airflow obstruction, and it is possible that this relies to an extent on the phenomenon of collateral ventilation.

### RELEVANCE TO BRONCHOSCOPIC TECHNIQUES FOR TREATING EMPHYSEMA

The last decade has seen renewed enthusiasm for lung volume reduction surgery (LVRS) as a treatment option in severe emphysema. However, the careful patient selection required and the fact that 90 day postoperative mortality is still around 5%<sup>17</sup> has led to the development of alternative less invasive techniques.

The development of one way endobronchial valves has been an attempt to create a bronchoscopically placed device for treating emphysema. These valves allow airflow in only one direction, can be inserted through the working channel of a flexible bronchoscope under conscious sedation, and are designed to occlude target segmental bronchi. In a patient with a heterogeneous pattern of emphysema and upper lobe predominant disease, an alternative to LVRS could be valve insertion. Following insertion, expiration of air from the upper lobes continues as normal through the valves. However, inspiratory flow to the upper lobes is blocked by the valves so, in theory, the upper lobes will gradually lose volume and collapse, thereby having a similar beneficial effect to surgically resecting them.

The early pilot data from studies of endobronchial valves have shown the reality to be somewhat more complicated. The beneficial effects following valve insertion seen in the various non-randomised trials to date have varied a lot but include improved forced expiratory volume in 1 second,<sup>18 19</sup> improved gas transfer,<sup>18 20</sup> improved exercise tolerance,<sup>19 21 22</sup> improved quality of life,<sup>21</sup>

and a reduction in dynamic hyperinflation.<sup>22</sup> However, although the valves were designed to cause obstruction of segmental bronchi, in the human trials to date the proportion of patients who developed atelectasis has varied between 0 and 50%.<sup>18–22</sup> Intuitively, atelectasis following valve insertion would be necessary for physiological improvement to occur, and it is true that the patients who develop atelectasis tend to have significantly greater benefits in terms of exercise tolerance and lung function.<sup>22</sup> Nevertheless, some patients do benefit (albeit to a lesser degree) without radiologically detectable atelectasis. The mechanism here may be a reduction in dynamic hyperinflation as the endobronchial valves shunt ventilation away from the upper lobes during exercise. In fact, end expiratory lung volume as a measure of dynamic hyperinflation was significantly reduced following valve insertion both in patients with atelectasis and in those without.<sup>22</sup>

If atelectasis is crucial to achieving maximum benefit from endobronchial valve insertion, then the pilot data raise an important question: Why should only a proportion of patients develop atelectasis after valve insertion? One possibility is simply that the valves have a tendency to leak, but this is not borne out by extensive testing. The other possibility is that collateral ventilation is the deciding factor. This concept is supported by the fact that, at repeat bronchoscopy after valve insertion, in patients with no atelectasis the valves can be seen venting continually on expiration.<sup>18</sup> This would be explained by the continued presence of significant collateral flow distal to the valve. The important hypothesis thus generated is that the heterogeneity of response to endobronchial valve insertion is due to variability in the amount of collateral ventilation. If this hypothesis is correct, then a patient with no collateral flow between the upper lobes and elsewhere would develop atelectasis after total upper lobe occlusion and its consequent physiological benefits, while a patient with much collateral flow will not as the upper lobes will continue to be ventilated via collateral channels. In order to test this hypothesis we need to be able to quantify collateral ventilation.

### MEASURING COLLATERAL VENTILATION

Previous investigators have found no correlation between collateral ventilation and age after 30 years, gas transfer, spirometry, lung volume, CT scoring of mean lung density, or even attempts at a histopathological grading.<sup>5 23</sup> The method described by Higuchi *et al*<sup>8</sup> in

this issue of *Thorax* is therefore a welcome attempt to develop a radiological scoring system which will accurately predict the presence or absence of collateral ventilation. Their study gains strength from its very careful quantitative CT scoring method. However, it is worth bearing in mind that this study was performed on explanted lungs at the time of transplantation. The cohort of patients with emphysema who reach the transplant theatre obviously represent a small subset of the sum of emphysematous patients, and it is not known what effect the act of actually removing a lung from the chest will have on the anatomy or physiology of collateral flow. Their gold standard measure of collateral flow between lobes was a subjective measure of how easy it was to ventilate a non-intubated lobe after explantation, so their radiological scoring system developed into a binary one. It was used to predict the presence or absence of collateral interlobar ventilation rather than to quantify the amount of collateral flow. This is inevitably an oversimplification as the amount of collateral ventilation is likely to be a continuous variable, but it may nonetheless help to predict a response to the insertion of endobronchial valves.

The finding of Higuchi *et al* that a homogeneous pattern of emphysema predicted the presence of collateral ventilation while a heterogeneous pattern predicted its absence is interesting. To date, the various groups testing endobronchial valves have concentrated on patients with heterogeneous (mainly upper lobe predominant) disease simply because of the data from the LVRS trials and because of how it was assumed the valves would work. These new data would suggest that the right group may have been chosen, although for reasons that were not appreciated at the time as, according to Higuchi *et al*, patients with heterogeneous disease should have no collateral ventilation and therefore should respond well to endobronchial valve insertion.

Of course this cannot be the whole story and is an oversimplification. If we are already selecting patients for the valve trials based on heterogeneity of emphysema, how can we explain the heterogeneity of the response? The CT scoring system used by Higuchi *et al* has the following characteristics for detecting collateral ventilation as defined by them: sensitivity 69%, specificity 86%, positive predictive value 90%, negative predictive value 60%, and accuracy 75%. Nuclear perfusion scanning in addition to CT scanning only improves the negative predictive value. So if their system defines the pattern of emphysema as homogeneous, then the patient

is very likely to have significant collateral ventilation—an important finding. However, if their system classifies the disease as heterogeneous, then 40% of these patients will still have significant collateral ventilation. This figure is also important as it may well explain the response rates in the valve trials.

Other methods have been used to quantify collateral ventilation such as the one used by Morrell.<sup>10–23</sup> This involves occluding a lobe or segment with a balloon catheter inserted through the working channel of a bronchoscope. The lumen of the catheter opens distal to the balloon and the gas composition of air distal to the occlusion can be sampled and analysed by a mass spectrometer. If the patient breathes 21% oxygen/79% helium following balloon inflation and there is minimal leakage around the balloon, then the rate of rise of the helium concentration distal to the balloon must be a quantitative measure of collateral ventilation to the obstructed lobe/segment. Morrell performed these measurements in 12 normal controls and six patients with emphysema and found much more collateral ventilation in those with emphysema. However, among the emphysematous lung segments studied there was a wide range in the amount of collateral ventilation detected with some segments having normal (undetectable) levels, some having very high levels, and a continuum in between. It would therefore seem that the amount of collateral ventilation in emphysema is a continuous variable with a significant amount present when the disease is homogeneous, but an unpredictable amount—from zero to a lot—when it is heterogeneous.

## CONCLUSION

Understanding collateral ventilation is probably central to planning new bronchoscopic techniques for treating emphysema. One technique that is designed to take advantage of the phenomenon is the airway bypass technique being developed by Broncus Technologies Inc (Mountain View, CA, USA).<sup>24–25</sup> This involves creating artificial communications between pulmonary parenchyma and the segmental airways and keeping these open with stents. It is

hoped that these new low resistance pathways, together with the pre-existing collateral ventilation, would allow improved escape of air on expiration, bypassing the collapsed small airways and thereby reducing both resting and dynamic hyperinflation. The data presented by Higuchi *et al*<sup>8</sup> in this issue of *Thorax* would support the use of this technology in patients with the most collateral ventilation—namely, those with a homogeneous pattern of disease.

More work is needed on endobronchial valves. They are likely to work better in heterogeneous emphysema but they will not benefit all patients. The range of collateral ventilation that exists needs to be clarified with quantitative methods and needs to be measured prospectively in patients before valve insertion. This may use new radiological techniques such as MRI scanning as they are developed or bronchoscopic techniques as already outlined.<sup>26</sup> It will then become clear whether collateral ventilation can accurately predict the response to this treatment.

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