Measurement of bronchial blood flow in the sheep by video dilution technique

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ABSTRACT Bronchial blood flow was determined in five adult anaesthetised sheep by the video dilution technique. This is a new fluoroscopic technique for measuring blood flow that requires only arterial catheterisation. Catheters were placed into the broncho-oesophageal artery and ascending aorta from the femoral arteries for contrast injections and subsequent videotape recording. The technique yields bronchial blood flow as a percentage of cardiac output. The average bronchial artery blood flow was 0.6% (SD 0.20%) of cardiac output. In one sheep histamine (90 μ g) injected directly into the bronchial artery increased bronchial blood flow by a factor of 6 and histamine (90 μ g) plus methacholine (4.5 μ g) augmented flow by a factor of 7.5 while leaving cardiac output unchanged. This study confirms the high degree of reactivity of the bronchial circulation and demonstrates the feasibility of using the video dilution technique to investigate the determinants of total bronchial artery blood flow in a stable animal model avoiding thoracotomy.

Recent advances in the techniques of therapeutic embolisation for control of haemoptysis in patients with severely compromised lung function¹ and after lung transplantation^{2,3} have rekindled clinical interest in the bronchial circulation. This interest in the airway blood flow is buttressed by the certainty that the circulation must play a role in airway water and heat exchange⁴ and the likelihood that it plays a part in other airway functions.⁵ Older publications contain many elegant studies of this lesser lung circulation,⁶⁻¹⁰ including the measurement of bronchial artery blood flow (QB) in animals and its physiological and pharmacological reactivity.¹¹⁻¹⁴ Many of these studies used invasive techniques, however, including extensive intrathoracic surgery, and may not have reflected normal conditions. More recent studies using microsphere¹⁵⁻¹⁸ and flowmeter¹⁹ techniques have measured bronchial artery blood flow, but with somewhat discordant results.

Although many different techniques have been used to assess bronchial blood flow in animals none of them is entirely satisfactory.¹⁴ For example,

recently reported techniques for studying QB require either thoracotomy and mediastinal dissection¹⁹ or injections of radioactive microspheres with subsequent need to obtain airway and lung parenchymal tissues.¹⁵⁻¹⁸ An added complexity is that in most large experimental animals, and in man, several small bronchial arteries derived from the aorta or intercostal vessels contain the total QB.^{9,20}

A new video dilution technique has recently been developed as a relatively non-invasive method for measuring regional blood flow.²¹ In the present study the technique was used to determine QB. Sheep were used because most of the airway blood supply in this species is delivered by a single vessel that arises from the proximal, concave part of the descending thoracic aorta.²⁰ The aortic origin of this vessel is the broncho-oesophageal artery. Immediately after leaving the aorta one or more small and variable oesophageal vessels branch off, leaving the larger vessel (the carinal artery) passing to the posterior wall of the trachea near the carina. This vessel supplies blood flow to the lower trachea and to about 90% of the sheep airways¹⁹ and is henceforth referred to as the bronchial artery. Its flow distribution has been fairly well characterised anatomically.^{19,20} This vessel can easily be catheterised under fluoroscopic control.²²

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Methods

PREPARATION AND PROCEDURES

Five castrated male sheep (36–45 kg) were anaesthetised with thiamylal 10–15 mg/kg, intubated, ventilated with a mixture of 1–2% halothane and oxygen, and paralysed with succinyl choline 15 mg/kg. A Swan-Ganz catheter was placed in the pulmonary artery for frequent determinations of cardiac output by thermal dilution. The right carotid artery was catheterised to monitor heart rate and arterial pressure. A 7 French gauge high flow pigtail catheter (Cook) was introduced under fluoroscopic control into the aortic root via the right femoral artery. A 5 French gauge catheter (Cook) was then introduced via the left femoral artery and manipulated into the broncho-oesophageal artery at the origin of the bronchial artery. Rectal temperature and blood gas tensions were monitored at frequent intervals. After contrast injections (diatrizoate meglumine and diatrizoate sodium) into the bronchial artery and the aortic root a bronchial artery branch was monitored under fluoroscopic control with locked voltage (60 KVP) and amperage (3.5 MA). Oesophageal arterial branches were small and sometimes not even visualised by our angiographic technique. The fluoroscopic image of the bronchial artery was simultaneously recorded on 3/4" video cassette (Sony). A three phase constant potential x ray generator connected to a triple mode caesium iodide image intensifier was used. $\dot{Q}_B$ was determined in all five sheep by the video dilution technique (see below) as a percentage of cardiac output. In one sheep $\dot{Q}_B$ was determined after bronchial arterial injections of adrenaline, histamine, and methacholine in concentrations insufficient to affect peripheral haemodynamics. Single 0.5 ml doses of contrast agent were injected manually into the broncho-oesophageal artery via the selective catheter with a tuberculin syringe. Three or four injections of 20–40 ml were made alternately into the aortic root catheter by angiographic pressure injector (Cordis) at 1000 lb/in² (6900 kPa). Throughout the experiments the animal and fluoroscope were in a fixed position. All injection images were videotaped in the same phase of suspended respiration (end expiration). The videotape was replayed after the experiments and $\dot{Q}_B$ was determined by a digital video densitometer, VDT Mark I (Angiotec).

The position of the catheter in the broncho-oesophageal artery at the origin of the bronchial artery was documented on film by digital subtraction (ADAC) after injection of 4 ml of a 25% solution of contrast agent into this vessel (fig 1). Before the animals were killed methylene blue was injected through the selective catheter. The bronchial

Fig 1 Bronchial arteriography by digital subtraction technique showing catheter position in the broncho-oesophageal artery.

arteries were then dissected post mortem to verify both catheter placement and the extent of the bronchial arterial distribution. Typically, the dye was distributed to the lower trachea and to the airways of all lobes and visceral pleura with the exception of the right upper lobe airways, which received variable perfusion from this vessel.

VIDEO DILUTION TECHNIQUE

The video dilution technique is an indicator dilution technique using angiographic contrast medium as the flow indicator. Density changes in the fluoroscopic image caused by intra-arterially injected contrast medium are recorded by a digital electronic densitometer with a linear output. For densitometric recording of indicator dilution in an arterial cross section of the fluoroscopic image the densitometric window replaces the sampling catheter used with the conventional Stewart-Hamilton technique.²³ There is one important difference in recording characteristics between the Stewart-Hamilton technique and the video dilution technique. In addition to indicator concentration (c) the densitometer measures the cross sectional volume (v) at the sampling site. As concentration and volume represent the mass (m) of contrast ($m = c \times v$), the densitometric recording represents a mass-time curve as opposed to the concentration-time curve obtained by catheter sampling. Thus the integrated area, A , under the mass-time curve will then be $k_1 \int m \times dt$, where the constant k_1 accounts for radiographic and electronic conversion factors. The area reflects the flow at the

injection site and the cross sectional volume at the sampling site. Use of the same recording site for comparison of different proximal flows allows cross sectional volume of the vessel and temporal and density uncertainties of the contrast bolus to be ignored. The small area of interest represented by the densitometric window reduces considerably the requirements for data acquisition and storage and the flow estimates can be read on line. The integrated area, A , is the basis for the calculation of blood flow by the video dilution technique. If the conditions at the recording site are kept constant (radiation intensity, video densitometric window size, position of image intensifier and object), the integrated densitometric area, A , is directly proportional to the amount of injected contrast material, M , and inversely proportional to the flow, $\dot{Q}$, at the injection site. $A = M/\dot{Q} \times k_2$ or $\dot{Q} = M/A \times k_2$, where k_2 , which implicitly depends on vessel diameter, is a calibration constant. The constancy of vessel diameter can be verified on the radiographic image. As k_2 cannot be easily determined, flow, $\dot{Q}$, is expressed in arbitrary units. After two contrast injections, (M_1 , M_2) at two separate sites in a flow system, the integrated areas (A_1 , A_2) recorded at the same distal measuring site will reflect the flows ($\dot{Q}_1$, $\dot{Q}_2$) at the two injection sites. $\dot{Q}_1 = M_1/A_1 \times k_2$ and $\dot{Q}_2 = M_2/A_2 \times k_2$ where $\dot{Q}_1$ and $\dot{Q}_2$ are expressed in arbitrary units. The ratio can then be described $\dot{Q}_1/\dot{Q}_2 = M_1 \times A_2/M_2 \times A_1$. For further details the reader is directed to previous reports.^{21 24-26}

A practical example of determination of $\dot{Q}_B$ as a percentage of cardiac output should clarify the details of the technique. After insertion of the aortic root catheter and the bronchial artery catheter during fluoroscopic control, the image intensifier was focused over an area of the bronchial artery which was free from crossing vessels such as the intercostal arteries. Then 0.5 ml of contrast agent was injected into the bronchial artery and a recording was made on videotape with respiration suspended at end expiration. After two minutes a 20 ml pressure injection was performed in the aortic root and the passage of contrast recorded on videotape with the image intensifier focused over the identical area of the bronchial artery. The videotape was then replayed and a densitometric window placed over a cross section of the bronchial artery. A second densitometric window was placed in a neutral area. This second window served to record possible variation in radiation intensity or cardiac motion to be subtracted from the readings of the window covering the bronchial artery (fig 2). Recordings from the bronchial artery and the aortic root injections were displayed (fig 3). $\dot{Q}_B$ was calculated by the densitometer, the amount of injected contrast

and the integrated area under the curve being taken into account (for example, $\dot{Q}_B = 23$). Flow in the aortic root was calculated in a similar way after integration of the dilution curve (for example $\dot{Q}_A = 4021$). Thus the relative flow in the bronchial artery compared to the cardiac output in the example is $23/4021 \times 100 = 0.6\%$. If the cardiac output in absolute units determined by thermal dilution technique immediately before the two contrast injections was 4800 ml/min, then $\dot{Q}_B$ would be 28.8 ml/min.

Results

The bronchial blood flow ($\dot{Q}_B$) was less than 1% of the cardiac output in each of the five sheep (table).

Fig 2 Above: Diagram showing selective catheter in bronchial artery and pigtail catheter in ascending aorta. Window A is covering a cross section of the broncho-oesophageal artery recording the mass-time curves after the aortic and selective injections. Window B is positioned in a neutral area and records possible variations of x ray intensity, breathing, and cyclic heart motions of the animal. Such variations of the baseline are electronically subtracted from the parallel (synchronous) recordings in window A. Below: Diagram to illustrate the importance of ensuring that other arteries from the aorta—that is, intercostal arteries—are not found to be crossing over any of the windows after aortic injections.

Fig 3 Video dilution technique recordings over cross section of bronchial artery after selective aortic root (above) and broncho-oesophageal artery (below) injections of contrast medium (20 and 0.5 ml respectively).

The mean flow in 27 determinations was 0.62% (SD 0.20%) of cardiac output, or 28.5 (7.0) ml min⁻¹ when matched with the corresponding cardiac output determination. The cardiac output was stable throughout each experiment, which lasted several hours (fig 4).

In sheep 2 we assessed the applicability of the video dilution technique as a means of measuring changes in $\dot{Q}_B$. We injected intra-arterially adrenaline (4.5 μ g), histamine (4.5 and 90 μ g) and histamine (90 μ g) with methacholine (4.5 μ g). A decrease in $\dot{Q}_B$ was observed 30 seconds after an injection of adrenaline. The low dose of histamine almost doubled $\dot{Q}_B$. A high dose of histamine (90 μ g) increased $\dot{Q}_B$ to 3–4% of cardiac output and in combination with methacholine $\dot{Q}_B$ increased further to about 4–5%, also within 30 seconds. $\dot{Q}_B$ returned to normal values within five minutes.

The effect of the presence of the catheter itself was investigated in five additional sheep. No 5 French catheters were passed into the broncho-oesophageal artery and the descending aorta. Simultaneously measured mean aortic and broncho-oesophageal artery blood pressures were 89–89, 67–62, 77–80, 68–69, and 103–104 mm Hg respectively, suggesting that placement of the angiographic catheter at the origin of the bronchial artery had no systematic effect on blood flow in this vessel under baseline conditions.

Fig 4 Example of bronchial blood flow ($\dot{Q}_B$) and cardiac output (CO) measurements obtained from sheep 2 throughout the experiment. The figure shows the general stability of this preparation through the experimental period of about 2.5 hours.

Discussion

The purposes of the present report were, firstly, to develop a system providing for simultaneous study of anatomy and physiology of the bronchial circulation using the relatively non-invasive radiological technique of video dilution; secondly, to assess this method as a possible means of studying the determinants of airway blood flow by perturbing bronchial artery blood flow with bolus injections of histamine, cholinergic, and adrenergic stimuli; and, thirdly, to speculate on the possible importance of this blood flow in airway pathophysiology.

Anatomically, the bronchial circulation is complex in that it has a variable origin from the aorta and is distributed not only to airways but also to other intrathoracic structures such as the mediastinum and pleura.⁹ In the sheep the origin is less complex in that the major portion of the bronchial circulation is supplied from a single large broncho-oesophageal vessel that arises from the aorta and is distributed to airways, anterior oesophagus, pleura, and mediastinum.^{9 19 20} Dye injections performed as a part of the present study confirmed that this vessel supplied all of the major airways except for variable distribution to the right upper lobe. In agreement

Cardiac output (CO) and total bronchial blood flow ($\dot{Q}_B$) in five anaesthetised sheep determined by video dilution technique

Sheep	Weight kg	Mean (SD) CO (l min ⁻¹)	Mean (SD) total ($\dot{Q}_B$)		
			% of CO	ml min ⁻¹	ml min ⁻¹ kg ⁻¹
1	36.3	4.36 (0.86)	0.55 (0.08)	24.1 (3.4)	0.66 (0.09)
2	44.5	5.62 (0.70)	0.49 (0.12)	27.7 (7.0)	0.62 (0.16)
3	45.3	7.22 (1.09)	0.59 (0.02)	42.8 (1.13)	0.95 (0.02)
4	36.4	3.25 (0.38)	0.85 (0.16)	27.4 (5.1)	0.75 (0.14)
5	36.3	5.44 (0.59)	0.54 (0.14)	29.4 (7.4)	0.81 (0.20)
Mean (SD)	39.8 (4.2)	5.18 (1.33)	0.62 (0.20)	28.5 (7.0)	0.71 (0.17)
n	5	110	27	27	27

with another recent study,¹⁹ the broncho-oesophageal artery does not appear to contribute a large fraction of its flow either to the anterior oesophageal or to pleural and mediastinal structures. Thus this vessel appears to be a reliable approach for selective quantitative angiographic assessments of the sheep airway circulation.

The influence of our model and technique on the results has to be discussed. We used intubated, anaesthetised, and paralysed animals with positive pressure ventilation to keep blood gases in the normal range. Previous studies have shown that anaesthesia diminishes pulmonary reflexes, including bronchoconstrictor²⁷ and pulmonary vascular²⁸ responses to histamine. Other workers have shown that tracheal intubation increases $\dot{Q}_B$ ²⁹ and that positive pressure ventilation reduces it.^{30, 31} We have no data that would contribute directly to these confounding variables. We considered the possibility that the presence of the broncho-oesophageal catheter could alter $\dot{Q}_B$. Simultaneous measurements of flow by a different technique would have provided confirmation, by allowing comparison of video dilution technique determinations of blood flow with flowmeter measurements of flow in the same way that we have studied other regional circulations.^{21, 25} We believe, however, that obstruction artefacts on the resting bronchial artery flow determinations are largely excluded by the fact that (1) no systematic differences were noted between simultaneously measured aorta and the broncho-oesophageal artery pressure; (2) no changes in bronchial blood flow occurred with time (fig 4) as might be expected if catheter induced "vasospasm" had occurred; and (3) our measurements of bronchial artery flow are reasonably consistent with flow determinations made by other investigators using a variety of other techniques.

Radiographic contrast media have been shown to induce haemodynamic effects, possibly via localised histamine release.³² We found that our contrast agent induced bronchial artery vasodilation 15 seconds after an injection, but there was a return to baseline flow after about 60 seconds. This effect occurs *after* the flow data have been obtained and does not interfere with the measurement from a single injection. A two minute interval between injections is required to assure return to baseline flow concentrations.²¹ In unreported studies using one of the newer non-ionic contrast agents (iohexol) no or little vasodilatory effect on $\dot{Q}_B$ was noted (Lantz BMT, unpublished observations). The densitometric window measures the contrast agent in the entire cross section of the vessel, avoiding the sampling errors caused by inadequate mixing that may occur with conventional indicator dilution

techniques.

A change in calibre of the bronchial artery segment covered by the electronic window during two consecutive recordings would introduce an error necessitating correction.²⁴ The actual vessel diameter within the window can easily be measured from the video signal by oscilloscope. Ninety-one such measurements of bronchial artery diameter after aortic and selective bronchial artery contrast injections in these five sheep did not show any significant changes. In addition, we did not encounter any demonstrable episodes of catheter induced "vasospasm" during the experiments. Likewise, no significant changes in diameter could be measured after histamine, adrenaline, or methacholine injections. Since the constancy of the vessel diameter is so critical to the validity of the flow calculation, it is important to appreciate to major sources of error in these measurements—that is, the video acuity of the system and human measurement error. Using the worst possible case, we estimate variability in reading of the vessel diameter to be about $\pm 5\%$, yielding a calculated flow error of less than 10%.

Although many different methods have been used to assess $\dot{Q}_B$, none of them is entirely satisfactory.^{9, 16} The older methods, many of which made use of aortic pouches or double heart-lung bypass preparations,^{9, 13, 16} are technically cumbersome. More recently reported techniques require either thoracotomy and mediastinal dissection¹⁹ or injections of radioactive microspheres, with the subsequent need to obtain airway and lung parenchymal tissues.^{15–18} An added complexity is that in most large experimental animals and in man several small bronchial arteries constitute the total $\dot{Q}_B$.^{9, 20}

The present values measured in our relatively non-invasive preparation can be compared with values given in recent publications. For example, in a recent study using an electromagnetic flowmeter around the bronchial artery in sheep with an open thorax, $\dot{Q}_B$ values of 0.4% of cardiac output were reported.¹⁹ This compares reasonably well with the current values of 0.6% of cardiac output. The small discrepancy could possibly be explained by the fact that cardiac outputs were nearly 50% lower in the open thorax flowmeter group, by technical and preparative model differences, or by differences in the regional distributions of the measured blood flows. For example, in our sheep variable small oesophageal branches and right upper lobe-distributions of flow were measured, whereas the flowmeter study measured flow in vessels that were not distributed to the right upper lobe.¹⁹ Studies using microspheres in the anaesthetised dog have reported $\dot{Q}_B$ values representing 1.6%¹⁵ and 1.0%¹⁶ of car-

diac output. One recent microsphere study using unanaesthetised sheep has reported QB values representing 2.5% of cardiac output.¹⁸ Explanations of higher flows recorded after microsphere injections include scoring of non-bronchial artery collateral vessel flows to the airways and technical problems related to corrections for recirculation effects and for shunt flows.

Data were obtained after intra-arterial bolus injections of histamine, methacholine, and adrenaline in qualities insufficient to affect systemic haemodynamics with the object of assessing the feasibility of using the video dilution technique to measure changes in QB. As has been reported by others using different experimental preparations,⁹⁻¹³ histamine and methacholine gave rise to impressive increases in flow, whereas adrenaline reduced flow. So far no attempts to study the dose-response patterns, time course, or mechanisms of responses to these agents have been made.

Large changes in QB may have important pathophysiological implications. For example, it is generally accepted that many agents known to affect blood vessels (for example, histamine, cholinergics, adrenergics, arachidonic acid metabolites) may play an important part in the pathogenesis of allergic bronchial asthma.⁵ While mediator, neural, and humoral mechanisms underlying the heightened bronchoconstrictor and hypersecretory states of this condition have been extensively studied, few studies have specifically addressed the airway vasculature. A report that cold air induces significant increases in dog bronchial blood flow is interesting in this regard.³³

In recent years interest in the physiology and pathology of the gastrointestinal tract circulation has increased considerably.^{34,35} Such studies have emphasised the interdependence of blood flow, smooth muscle motor activity, secretory functions, and absorptive capabilities.³⁴ We may speculate that further understandings of the bronchial circulation and its regional distribution and modulation in health and disease could be an important consideration in future studies of airway function.

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