Non-invasive assessment of pulmonary blood flow using an inert gas rebreathing device in fibrotic lung disease

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Received 5 June 2009
Accepted 30 January 2010

ABSTRACT

Background and aims Pulmonary hypertension (PH) is increasingly recognised in patients with diffuse lung disease, and is associated with increased mortality. Cardiac output (CO) is a prognostic marker in PH. Non-invasive assessment of pulmonary blood flow ($PBF_{INNOCOR}$) with the inert gas rebreathing Innocor device has been validated against CO in PH, but not in PH associated with parenchymal lung disease. $PBF_{INNOCOR}$ may be less accurate in patients with lung disease because of intrapulmonary shunting and/or incomplete gas mixing. Our aim was to determine the variability of $PBF_{INNOCOR}$ in normal subjects, before evaluating $PBF_{INNOCOR}$ in diffuse lung disease against CO measured by the indirect Fick method (CO_{FICK}) at right heart catheterisation (RHC).

Methods and results 23 normal subjects had lung volume measurements by a constant-volume body plethysmograph and three consecutive $PBF_{INNOCOR}$ measurements on the same day. 20 subjects returned for repeat assessment. $PBF_{INNOCOR}$ had good intrasession repeatability (coefficient of variation (CV)=6.57%) and intersession reproducibility (mean CO difference=0.13; single determinant SD=0.49; CV=9.7%). 28 consecutive patients with lung fibrosis referred for RHC had $PBF_{INNOCOR}$ measured within 24 h of RHC. There was good agreement between CO_{FICK} and $PBF_{INNOCOR}$, with no evidence of systematic bias (mean CO_{FICK} 4.3±1.0; $PBF_{INNOCOR}$ 4.0±1.2l/ min; p=0.07). Bland–Altman analysis revealed a mean difference of −0.32 and limits of agreement of −2.10 to +1.45.

Conclusion Non-invasive PBF measured by the inert gas rebreathing Innocor device has good intrasession repeatability and intersession reproducibility. In diffuse lung disease, CO can be accurately and non-invasively measured by the Innocor device.

INTRODUCTION

Pulmonary vascular limitation is increasingly recognised as a major complication of diffuse fibrotic lung disease. In idiopathic pulmonary fibrosis (IPF) the reported prevalence of pulmonary hypertension (PH) ranges from 31% to 85%.[1–6] PH is associated with clinical deterioration and higher mortality in patients with IPF.[3 7 8] Currently, the diagnosis of PH rests on haemodynamic parameters measured on right heart catheterisation (RHC), as non-invasive markers such as echocardiography are less reliable in diffuse lung disease.[9–11] Reproducible, reliable non-invasive prognostic markers are thus highly desirable in this high-risk patient group.

Cardiac output (CO) is an important prognostic marker in pulmonary arterial hypertension (PAH)[12 13] although its role in parenchymal lung disease has not been specifically studied. Traditional assessment of CO is by RHC, using thermodilution or the direct or indirect Fick method. However, RHC is invasive, and not always practicable in the context of diffuse lung disease. The non-invasive assessment of CO by the foreign gas rebreathing method is well established and validated against more invasive CO measurements.[14] The foreign gas rebreathing method involves the inhalation of a gas mixture containing a soluble and an insoluble gas. The pulmonary blood flow (PBF) is proportional to the rate of decline of the soluble compound, and is considered equivalent to CO in the absence of cardiopulmonary shunting. Historically, the respiratory mass spectrometer has been used for such measurements, but these instruments are bulky, difficult to operate and costly to maintain. However, the more recently developed Innocor machine, which uses the inert gas rebreathing technique with continuous photoacoustic gas analysis, is less expensive, portable and easier to use. Non-invasive PBF assessment with the Innocor has been validated against CO measured at RHC in patients with heart failure[15] and PAH,[16] but not in PH associated with parenchymal lung disease. Inert gas rebreathing measures of CO may be less accurate in patients with diffuse lung disease because of intrapulmonary shunting and/or incomplete gas mixing.

In this study, in order to examine its utility in patients with diffuse lung disease, we first determine the intrasession repeatability and intersession reproducibility of the Innocor PBF measurement in normal subjects. Secondly, we examine the Innocor measurement of PBF against invasive CO assessment (by the indirect Fick method) in patients with diffuse fibrotic lung disease.

METHODS

Subjects

Normal subjects

Ethical approval was obtained from the local ethics committee for this study. Twenty-three subjects (eight male; mean age 34±8 years) without underlying lung disease were recruited via in-hospital advertisement, and informed consent was obtained. Lung volumes were measured by a constant-volume body plethysmograph. On the same day, subjects underwent three consecutive PBF measurements with the Innocor device. Twenty-one (91%)

subjects returned on a separate day for repeat CO measurements (1–13 weeks later).

Subjects with fibrotic lung disease

Twenty-eight consecutive patients with fibrotic lung disease (16 males, mean age 63±12 years) undergoing RHC for assessment for PH were recruited, and informed consent was obtained. RHC was performed when there was clinical suspicion of PH based on echocardiographic and pulmonary function parameters, and right heart overload and/or failure on examination. All patients underwent pulmonary function testing prior to RHC.

Non-invasive PBF assessment with the Innocor device was performed within 24 h of RHC by trained personnel, blinded to the RHC results. Three consecutive non-invasive PBF measurements were obtained and the mean value calculated ($PBF_{INNOCOR}$).

Measurements

Non-invasive PBF assessment

Subjects, sitting upright at rest, breathed through a closed-circuit system (Innocor, Innovision, Denmark). This rebreathing system uses an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulfur hexafluoride) and 28% oxygen in N_2 in a 2–4 litre rubber bag. The volume to which the bag was filled was adjusted to 60% of the subjects' vital capacity. Rebreathing was performed over a 30 s period, and subjects followed a graphical tachometer on the computer screen and verbal prompts to ensure a respiratory rate of 20 breaths/min. Subjects were instructed to empty the rebreathing bag completely with each breath, to ensure a constant ventilation volume. Gas was sampled continuously from the mouthpiece, and rapid photoacoustic spectroscopic analysers measured gas concentrations. The PBF was calculated from the rate of uptake of nitrous oxide into the blood. In subjects without pulmonary arterial–venous shunting, $PBF_{INNOCOR}$ is considered equal to CO.

Right heart catheterisation

RHC measurements were performed at rest in the supine position, using standard techniques (Swan-Ganz catheters, Edwards Life Sciences, Irvine, California, USA) and the following pressure measurements were performed: systolic, diastolic and mean pulmonary artery pressure (mPAP); and systolic, diastolic and mean right atrial pressure. Left heart catheterisation was also performed in order to measure systemic arterial pressure, left atrial pressure and left ventricular end-diastolic pressure (LVEDP).

CO was calculated using Fick's principle, with oxygen consumption estimated using standardised reference tables[17] according to the following equation[18 19]:

$$CO_{FICK} = \text{oxygen uptake}/(\text{arterial oxygen concentration} - \text{venous oxygen concentration})$$

CO was adjusted for body surface area to cardiac index.[20]

Pulmonary vascular resistance (PVR) was calculated according to the formula[21]:

$$PVR = (mPAP - mLAP)/CO$$

LVEDP was used to estimate mean left atrial pressure (mLAP). Pulmonary capillary wedge pressure was not detemined due to the potential increased risk of pulmonary arterial rupture and/or haemorrhage in patients with abnormal pulmonary vasculature.[22]

Pulmonary function testing

Predicted pulmonary function values were calculated using a European Community for Coal and Steel publication.[23] The American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines were followed when the lung function tests were performed.[24–26] Lung volumes (constant-volume body plethysmograph), spirometric volumes and single-breath diffusion capacity of the lung for carbon monoxide (DL_{CO}) were measured (Jaeger Masterscreen; Cardinal Health UK 240, Warwick, UK). End capillary (ear-lobe) blood gas analysis was performed on room air (n=21; 348 Blood Gas Analyser; Siemens Healthcare Diagnostics, Sunbury, UK).

Statistical analysis

All analyses were performed using STATA statistical software (version 10.0; StataCorp, College Station, Texas, USA). Data are expressed as the mean and SD or median and range, as appropriate. A p value of <0.05 was considered statistically significant.

Normal subjects

The intrasession repeatability of the $PBF_{INNOCOR}$ measurement was determined by the coefficient of variation (CV) calculated by the following equation: $CV=100\times(SD)/mean$. Intersession reproducibility of the $PBF_{INNOCOR}$ was assessed by Bland–Altman analysis, with single determinant SD, and CV.

Subjects with pulmonary fibrosis

The relationship between invasive (CO_{FICK}) and non-invasive ($PBF_{INNOCOR}$) measures of CO was examined using Bland–Altman analysis. Results are expressed as mean CO difference (bias), limits of agreement (± 2 SD).[27]

RESULTS

Normal subjects

The clinical characteristics of the normal subjects are shown in table 1. Twenty-one subjects were life-long non-smokers, and two were ex-smokers. One had a history of mild asthma, but was taking no regular medication. All subjects had lung volumes within the predicted normal range.

Baseline parameters as assessed by the Innocor device are displayed in table 1 including a mean $PBF_{INNOCOR}$ of 5.27±1.14 l/min, and a mean SD of 0.32±0.20 l/min. There was good intrasession repeatability, with a CV of 6.34%. The intersession reproducibility was high, with a mean PBF difference of 0.12 and a single determinant SD of 0.49. The intersession CV was 9.29%.

Subjects with pulmonary fibrosis

Baseline parameters

The baseline characteristics of the 28 patients are summarised in table 2. Patients had fibrotic lung disease, including IPF (n=15), non-specific interstitial pneumonia (n=10) and chronic hypersensitivity pneumonia (n=2). Sixteen (52%) were life-long non-smokers, with 12 (43%) ex-smokers (mean 18 pack-years). One patient had a history of atrial fibrillation, and eight had systemic hypertension, with the remaining 18 patients having no significant cardiac history. Most patients were functionally impaired, in WHO functional class III (n=13) or IV (n=12). Eight (26%) were in right heart failure.

Table 1 Baseline characteristics of normal subjects (n=23)

Characteristics*	
Age (years)	34±8
Gender	8 male; 15 female
Height	170±9 cm
Weight	73±21 kg
Pulmonary function tests:	
Total lung capacity (%)	101±14%
Functional residual capacity (%)	105±17%
Vital capacity (%)	102±15%
Baseline Innocor parameters:	
Heart rate	77±9 bpm
Residual volume (V_L)	2.96±0.40 litres
Pulse oximetry	98±2%
Pulmonary blood flow (cardiac output)	5.27±1.14 l/min
Cardiac index	2.90±0.53 l/min/m^2
Stroke volume	69.68±19.13 ml

*Mean±SD.

Baseline mean gas transfer was 23.4±7.4%, forced vital capacity 61.5±29.6%, and Pa_{O_2} 7.98±1.9 kPa. Twenty of 28 (71%) had PH on RHC: mPAP 28.5 ± 9.4 mm Hg; LVEDP 9.1±4.0 mm Hg, PVR 4.7±3.0 Wood's units and CO_{FICK} 4.3±1.0 l/min. With the Innocor device, mean $PBF_{INNOCOR}$ was 4.0±1.2 l/min.

Relationship between invasive and non-invasive CO measurements

There was good agreement between CO_{FICK} and $PBF_{INNOCOR}$ (figure 1), with no evidence of systematic bias, as judged by

Table 2 Baseline characteristics of subjects with pulmonary fibrosis (n=28)

Characteristics*	
Age (years)	63±12
Height	168±9 cm
Weight	78±16 kg
Pulmonary function tests	
Total lung capacity (%)	61.4±21.0%
DL_{CO} (%)	23.4±7.4%
K_{CO} (%)	49.3±14.1%
FEV_1 (%)	60.7±18.2%
FVC (%)	61.5±19.6%
Pa_{O_2} (n=21)	8.0±1.9 kPa
Right heart catheter	
mPAP	28.5±9.4 mm Hg
mRAP	5.1±3.0 mm Hg
LVEDP	9.1±4.0 mm Hg
Cardiac output	4.3±1.0 l/min
Cardiac index	2.3±0.5 l/min/m^2
Pulmonary vascular resistance	4.7±3.0 WU
Baseline Innocor parameters:	
Heart rate	84±14 bpm
Residual volume	2.0±0.5 litres
Pulse oximetry	91.3±4.8%
Pulmonary blood flow (cardiac output)	4.0±1.2 l/min
Cardiac index	2.1±0.6 l/min/m^2
Stroke volume	47.8±17.1 ml

*Mean±SD.
DL_{CO}, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; K_{CO}, diffusion capacity corrected for alveolar volume; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; Pa_{O_2}, arterial partial pressure for oxygen; WU, Wood's units.

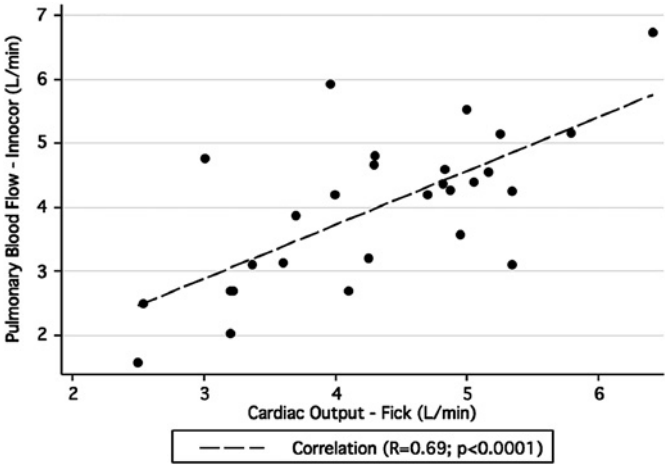

Figure 1 Correlation of cardiac output measured by right heart catheter and pulmonary blood flow measured by the inert gas rebreathing technique (Pearson correlation).

Student paired t test: mean CO_{FICK} 4.3±1.0, mean $PBF_{INNOCOR}$ 4.0±1.2 l/min (p=0.07). Bland–Altman analysis revealed a mean difference of −0.32 (95% CI −0.67 to 0.02) with limits of agreement of −2.10 to +1.45 l/min (figure 2).

DISCUSSION

In this study we demonstrate that PBF as measured on the Innocor device is both repeatable and reproducible in normal control subjects. The intrasession CV of 6.3% and intersession CV of 9.3% are similar to those for other pulmonary physiological parameters, and within acceptable limits. Secondly, we assess the accuracy of the non-invasive $PBF_{INNOCOR}$ against the invasive CO_{FICK} measurement in patients with interstitial lung disease. We demonstrate good agreement between these measurements.

Pulmonary vascular limitation and PH are important complications of diffuse lung disease. PH is associated with increased mortality in diffuse lung disease. In the search for reliable prognostic markers, a number of pulmonary vascular parameters have been studied. On RHC, elevated mPAP is

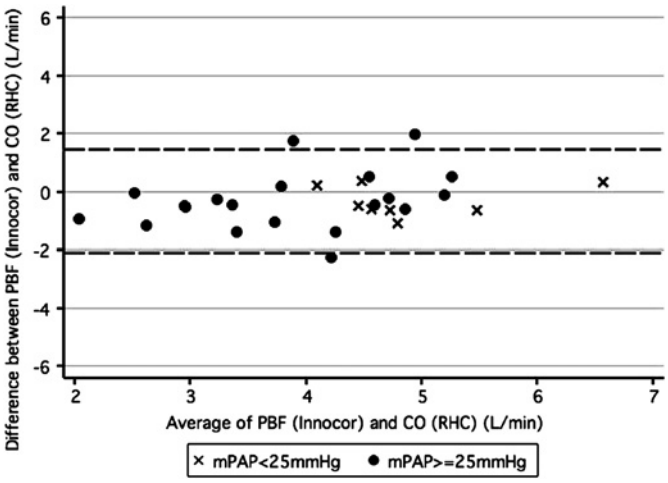

Figure 2 Bland–Altman plot for cardiac output (CO) measured by right heart catheter (RHC) and pulmonary blood flow (PBF) measured by the inert gas rebreathing technique (Innocor). mPAP, mean pulmonary artery pressure.

associated with increased mortality in IPF,[3 8] and elevated PVR is related to higher mortality in advanced lung disease.[28] Reduced CO has been established as an important poor prognostic marker in PAH,[12 13] but this has not been specifically studied in diffuse lung disease. While it is current practice to perform an RHC in the assessment of PH in patients with lung fibrosis, RHC is not always practicable in these patients. Furthermore, repeat RHC for monitoring disease progression and response to treatment is clearly undesirable in this patient population. For this reason, a reliable, reproducible, non-invasive prognostic marker is desirable for this patient group.

Foreign gas rebreathing methods non-invasively estimate PBF. PBF is calculated using a rebreathing manoeuvre whereby the patient breathes a mixture containing a soluble and an insoluble gas. By continuous sampling of the gas concentrations, the rate of reduction of the soluble gas can be calculated. This rate is proportional to the PBF, and CO in the absence of a significant shunt. Respiratory mass spectrometers use the foreign gas rebreathing method, and are safe and reliable in the estimation of PBF and CO.[14] There is good correlation between CO measured on mass spectrometry and the direct Fick method in healthy subjects, PAH and severe heart failure.[29 30] Limited data for the clinical utility of mass spectrometers are available outside the intensive care setting. Gatzoulis *et al* demonstrated an increase in PBF in Eisenmenger patients following bosentan treatment, and suggested that it may be a useful clinical tool in monitoring of PAH.[31 32] In practice, however, respiratory mass spectrometers are bulky, costly and require regular calibration and maintenance, making their widespread clinical use difficult.

More recently, the foreign gas rebreathing method has been incorporated with photoacoustic spectroscopy analysis in the Innocor device. Photoacoustic spectroscopy uses pulsatile exposure of the measured gases to filtered light, creating pressure oscillations. Measurement of these oscillations by a microphone provides an indirect measurement of gas concentrations. This device is simple to use, mobile and less costly than the traditional respiratory mass spectrometer. $PBF_{INNOCOR}$ correlates with CO_{FICK} better than CO as measured by thermodilution.[33] $PBF_{INNOCOR}$ has been validated against CO_{FICK} in heart failure at rest and on exercise,[15 33–35] and PAH (published in abstract form).[16]

However, no studies have specifically focused on patients with diffuse lung disease. There are potential limitations for this device in the context of parenchymal lung disease.[36 37] First, parenchymal lung disease may inhibit complete alveolar gas mixing (which is an essential assumption for the calculation of CO by this method). Secondly, intrapulmonary shunting of blood through areas of poor gas exchange will not be measured by this method, therefore potentially underestimating the total PBF in these patients. However, these potential problems are not supported by the results of the current study in which a good agreement between $PBF_{INNOCOR}$ and CO_{FICK} is demonstrated.

The results of this study are limited by the fact that the $PBF_{INNOCOR}$ and CO_{FICK} measurements were not performed simultaneously. CO is a relatively labile measurement, varying with body position and time of day. Despite the potential variability in CO, we showed good agreement between the two measurements when performed within 24 h of each other. However, the lability of CO may partly explain the imperfect agreement between the two measurements.

The results of the current study are necessarily limited by selection bias, by recruiting patients referred for RHC. To minimise selection bias, a simple, inclusive, prospective approach was undertaken in which consecutive patients with interstitial lung disease referred for RHC were recruited. As a result, the present study includes patients with a variety of histological diagnoses, including two patients with hypersensitivity pneumonitis. It is possible that patients with hypersensitivity pneumonitis may have increased intrapulmonary shunting related to local areas of consolidation. However, this is unlikely, as our results remained significant with the exclusion of these two patients (results not shown). We also have a high proportion of patients with PH (71%), and patients on supplemental oxygen (81%) in our cohort. It is possible that results may differ for patients with milder disease. However, patient numbers in this study are relatively small, and do not allow analysis of subgroups according to the presence of PH, or oxygen requirements. The results of this study cannot be generalised to the interstitial population at large.

In this study, the oxygen consumption necessary for calculating CO by the Fick principle was estimated from normograms rather than directly measured. While measurement of oxygen consumption is desirable, it can be cumbersome and prone to technical errors in non-intubated patients relating to inadequate timing or collection of samples, continuous oxygen administration and abnormal breathing patterns due to anxiety, sedation or pulmonary disease. Still, estimation of CO by the Fick principle is more reliable than thermodilution methods, especially in patients with low CO. As most adult catheterisation laboratories nowadays use assumed VO_2 values, our study was designed to compare the Innocor with standard catheter laboratory practice. Further studies are needed comparing Innocor measurement and Fick calculation with assumed VO_2 values with the gold standard of Fick with direct VO_2 measurement.

On the basis of the current study, PBF measurement with the Innocor is a repeatable, reproducible, easily performed technique. Although we demonstrate good agreement between $PBF_{INNOCOR}$ and CO_{FICK}, $PBF_{INNOCOR}$ is unlikely to replace CO_{FICK} as other important markers such as pulmonary arterial pressures are also measured at RHC. However, $PBF_{INNOCOR}$ is a potential prognostic marker for patients with diffuse lung disease, and may be useful in follow-up in monitoring for disease progression and response to advanced treatment. Clearly, the widespread clinical application of this technique in the evaluation of patients with diffuse lung disease and possible PH remains to be determined. A larger study inclusive of patients with varied disease severity, and with clinical follow-up is warranted to establish its prognostic value.

CONCLUSION

Non-invasive PBF as measured by the inert gas rebreathing Innocor device has good intrasession repeatability and intersession reproducibility. In patients with diffuse fibrotic lung disease, CO may be accurately and non-invasively measured by the Innocor inert gas rebreathing device. Further longer term studies are required to determine the potential clinical and prognostic role of this non-invasive CO measurement.

Funding Actelion Pharmaceuticals-Educational Grant.

Competing interests None.

Ethics approval This study was conducted with the approval of the Brompton, Harefield and NHLI Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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