Can new pulmonary gas exchange parameters contribute to evaluation of pulmonary congestion in left-sided heart failure?

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BACKGROUND: Assessment of pulmonary congestion in left-sided heart failure is necessary for guiding anticongestive therapy. Clinical examination and chest x-ray are semiquantitative methods with poor diagnostic accuracy and reproducibility.

OBJECTIVES: To establish reference values, describe reproducibility, and investigate the diagnostic and monitoring properties in relation to pulmonary congestion of new pulmonary gas exchange parameters describing ventilation/perfusion mismatch (variable fraction of ventilation [fA₂] or the drop in oxygen pressure from the mixed alveolar air of the two ventilated compartments to the nonshunted end-capillary blood [Δ PO₂]) and pulmonary shunt.

METHODS: Sixty healthy volunteers and 69 patients requiring an acute chest x-ray in a cardiac care unit were included. The gas exchange parameters were estimated by analyzing standard bedside respiratory and circulatory measurements obtained during short-term exposure to different levels of inspired oxygen. Nine patients were classified as having pulmonary congestion using a reference diagnosis and were followed during 30 days of anticongestive therapy. Diagnostic and monitoring properties were compared with chest x-ray, N-terminal probrain natriuretic peptide (NT-proBNP), spirometry values, arterial oxygen tension, alveolar-arterial oxygen difference and venous admixture.

RESULTS: The 95% reference intervals for healthy subjects were narrow (ie, fA₂ [0.75 to 0.90], Δ PO₂ [0.0 kPa to 0.5 kPa] and pulmonary shunt [0.0% to 8.2%]). Reproducibility was relatively good with small within-subject coefficients of variation (ie, fA₂ [0.05], Δ PO₂ [0.4 kPa] and pulmonary shunt [2.0%]). fA₂, Δ PO₂ and NT-proBNP had significantly better diagnostic properties, with high sensitivities (100%) but low specificities (30% to 40%). During successful anticongestive therapy, fA₂, Δ PO₂, NT-proBNP and spirometry values showed significant improvements.

CONCLUSIONS: The gas exchange parameter for ventilation/perfusion mismatch but not pulmonary shunt can have a possible role in rejecting the diagnosis of pulmonary congestion and in monitoring anticongestive therapy.

Key Words: Brain natriuretic peptide; Chronic heart failure; Congestive heart failure; Diuretics; Respiratory indexes

Les nouveaux paramètres des échanges gazeux respiratoires peuvent-ils contribuer à l'évaluation de la congestion pulmonaire dans l'insuffisance cardiaque gauche?

HISTORIQUE : Pour orienter le traitement de l'insuffisance cardiaque gauche, il faut évaluer la congestion pulmonaire. Dans ce contexte, l'examen clinique et la radiographie pulmonaire sont des méthodes semi-quantitatives dont la précision diagnostique et la reproductibilité laissent à désirer.

OBJECTIF : Établir les valeurs de référence, décrire la reproductibilité et analyser les propriétés des nouveaux paramètres d'échanges gazeux respiratoires utilisés pour le diagnostic et la surveillance de la congestion pulmonaire, ces paramètres décrivant l'écart ventilation/perfusion (fraction variable de la ventilation [fA₂] ou baisse de la pression d'oxygène de l'air alvéolaire mélangé des deux compartiments ventilés par rapport au sang capillaire non shunté (Δ PO₂)) et au shunt pulmonaire.

MÉTHODE : Soixante volontaires en bonne santé et 69 patients ayant eu besoin d'une radiographie pulmonaire d'urgence dans une unité de soins cardiaques ont été inclus. Les paramètres des échanges gazeux ont été estimés par l'analyse des mesures respiratoires et circulatoires standard au chevet, obtenus durant une exposition brève à différents taux d'oxygène inspiré. À l'aide d'un diagnostic de référence, on a classé neuf patients dans la catégorie 'congestion pulmonaire' et on les a suivis durant un traitement à cet effet d'une durée de 30 jours. L'utilité de ces propriétés pour le diagnostic et la surveillance a été comparée à celle des radiographies pulmonaires, du dosage du fragment N-terminal du peptide natriurétique de type B (NT-proBNP), des valeurs de spirométrie, de la pression d'oxygène artérielle, de la différence de taux d'oxygène alvéolaires-artériels et de l'effet shunt.

RÉSULTATS : Les intervalles de référence à 95 % chez les sujets en bonne santé étaient étroits (c.-à-d., fA₂ [0,75 à 0,90], Δ PO₂ [0,0 kPa à 0,5 kPa] et shunt pulmonaire [0,0 % à 8,2 %]). La reproductibilité s'est révélée relativement bonne, avec de faibles coefficients de variation chez les sujets (c.-à-d., fA₂ [0,05], Δ PO₂ [0,4 kPa] et shunt pulmonaire [2,0 %]). Les valeurs de fA₂, Δ PO₂ et NT-proBNP présentaient des propriétés diagnostiques significativement meilleures, avec des sensibilités élevées (100 %), mais des spécificités faibles (30 % à 40 %). Durant le traitement approprié contre la congestion, les valeurs de fA₂, de Δ PO₂, de NT-proBNP et de spirométrie se sont améliorées significativement.

CONCLUSION : Contrairement à l'effet shunt, le paramètre mesurant l'écart entre les échanges gazeux ventilation/perfusion permettraient d'écarter le diagnostic de congestion pulmonaire et de surveiller les résultats du traitement, le cas échéant.

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Left-sided heart failure (LHF) is an increasing medical problem of a heterogeneous nature associated with high morbidity, mortality and cost (1). Methods to evaluate and monitor the severity of pulmonary congestion in LHF are required for guiding anticongestive therapy. Clinical examination and chest x-ray are semiquantitative methods with poor diagnostic accuracy and reproducibility (2,3). Diagnosis and monitoring can be strengthened by performing additional paraclinical examinations. Measurement of brain natriuretic peptides is recommended but chronic systolic dysfunction can result in persistently high levels, despite successful anticongestive therapy (4). The traditional description of pulmonary dysfunction can, in some cases, contribute to the evaluation of pulmonary congestion with hypoxemia and various kinds of abnormal values for dynamic spirometry, but measurements can be within normal reference limits in patients with pulmonary congestion (5,6). A more detailed description of pulmonary gas exchange may also contribute to the evaluation of pulmonary congestion. In the past decade, several mathematical physiological models have been published to describe abnormalities in pulmonary gas exchange using simultaneous estimation of parameters for ventilation/perfusion (V/Q) mismatch and pulmonary shunt (7-10). The parameter describing V/Q mismatch has been suggested as a possible useful marker for pulmonary congestion (11).

The aim of the present study was to establish reference values, describe reproducibility and investigate diagnostic and monitoring properties for new pulmonary gas exchange parameters when used to evaluate pulmonary congestion in LHF.

METHODS

The present study conforms to the principles outlined in the Declaration of Helsinki and was approved by the local science ethics committee. The study subjects were older than 18 years of age and informed written consent was obtained in all cases.

Study subjects

Sixty healthy subjects were included to establish reference values for the new gas exchange parameters. They were volunteers recruited among current and former health care workers at Aalborg Hospital (Aalborg, Denmark), and were uniformly distributed in age from 20 to 80 years. They were required to have no symptoms of cardiopulmonary disease (dyspnea, coughing, chest pain, palpitations and peripheral edema), no regular use of medication, normal blood pressure, no murmurs at heart auscultation, no rales or wheezing at lung auscultation, and normal dynamic spirometry.

Sixty-nine patients recruited from a cardiac care unit at Aalborg Hospital were included to investigate both the reproducibility, and the diagnostic and monitoring properties of the new gas exchange parameters. Patients requiring an acute chest x-ray in the daytime during a two-month period were considered eligible to enter the study. Patients with acute coronary syndrome and other critically unstable conditions were excluded due to the nature of the intensive investigation program of the present study.

Reference diagnosis for pulmonary congestion

No simple reference technique to diagnose and monitor pulmonary congestion in LHF is agreed on. Therefore, a combination of tough criteria was used for the reference diagnosis to ensure a correct positive classification of patients with pulmonary congestion. This reference diagnosis was assigned to patients with a low left ventricular ejection fraction of no more than 45% (Vingmed System FiVe; GE Vingmed Ultrasound, Norway) (12), combined with a high clinical decompensation score of at least 2 (13). The clinical decompensation score is based on the Framingham criteria for diagnosing decompensated heart failure and was calculated based on the sum of the following symptoms and signs (weights in brackets): orthopnea (one-half); paroxysmal nocturnal dyspnea (one); reduction in exercise tolerance (one-half); resting sinus tachycardia above 100 (one-half); jugular venous pressure above 4 cm water (one-half); hepatojugular reflex (one); third heart

sound (one); basal crackles (one); hepatomegaly (one-half); and peripheral edema (one-half).

Traditional paraclinical examinations

Chest x-rays were performed in all patients and were evaluated by two experienced radiologists who were blinded to the clinical information. Consensus decisions were obtained for grading of pulmonary congestion according to the following Kostuk criteria: no pulmonary congestion (grade 1), redistribution of pulmonary blood flow to upper lobes (grade 2), interstitial pulmonary edema (grade 3) and alveolar pulmonary edema (grade 4) (14).

N-terminal probrain natriuretic peptide (NT-proBNP) was determined in all patients based on a venous blood sample taken after at least 15 min of rest. All samples were stored in cryotubes to be simultaneously analyzed by a skilled laboratory technician using a sandwich test method (Eleclys systems; Roche Diagnostics, Germany).

The mechanical properties of the lungs were examined in all study subjects using dynamic spirometry (Microlab ML3500; Micro Medical Ltd, United Kingdom) by measuring forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). Results were automatically presented as relative values (percentage of predicted value according to age, height and sex) (15).

Arterial oxygen tension, alveolar-arterial oxygen difference and venous admixture were determined in all study subjects based on a blood sample from the radial artery (16). The blood sample was analyzed within 3 min, giving pH, carbon dioxide tension, oxygen tension, hemoglobin concentration and fractions of dyshemoglobins (ABL 525; Radiometer, Denmark). The alveolar-arterial oxygen difference was then calculated from the arterial oxygen and carbon dioxide tensions, and the ideal alveolar oxygen pressure from the alveolar air equation with an assumed respiratory exchange ratio of 0.86. The venous admixture was calculated using the shunt equation, with an assumed arterial-venous oxygen content difference of 3.5 mL/dL.

New pulmonary gas exchange parameters

The parameters describing abnormalities in pulmonary gas exchange were determined using the Automatic Lung Parameter Estimator (ALPE) system, consisting of a computer (ALPE software version 2.6; ALPE, Denmark), which sampled data from a ventilator (Servo Ventilator 300; Siemens, Sweden), a gas analyzer (Anesthetic Gas Monitor type 1304; Brüel & Kjær, Denmark) and a pulse oximeter (COSMO plus model 8100; Novamatrix Medical Systems, USA) (10). The ventilator was connected to an oxygen outlet in the wall at the hospital and to a gas cylinder with pharmaceutical nitrogen to enable delivery of different levels of inspired oxygen fraction to the study subject. The subjects were resting in supine or semirecumbent positions while breathing spontaneously and were connected to the system via a mouthpiece and a pulse oximeter probe placed on a finger with a good capillary response. The semiautomatic experimental procedure lasted approximately 15 min, during which an examiner blinded from clinical information about heart failure decompensation status chose four to seven levels of inspired oxygen fraction, giving arterial blood saturations from 90% to 100%. Following each change in the level of inspired oxygen fraction, a period of at least 2 min was waited before taking measurements of tidal volume, respiratory rate, inspired and expired oxygen, and carbon dioxide fractions, arterial oxygen saturation and pulse frequency.

The collected data were automatically analyzed using a two-parameter model of the pulmonary gas exchange. The mathematical details of the model have previously been published (9). Figure 1 illustrates the concept of the model. It consists of one pulmonary shunt compartment with no ventilation but a variable perfusion, one compartment with a variable fraction of ventilation ($fA2$) receiving 90% of the nonshunted blood, and one compartment receiving the remaining fraction of ventilation ($1-fA2$) and 10% of the nonshunted blood. An $fA2$ equal to 0.90 indicates a perfect match between ventilation and perfusion, whereas lower values of $fA2$ indicate increasing severity

of V/Q mismatch. The effects of V/Q mismatch (fA2) can also be expressed as ΔPO_2 (ie, the drop in oxygen pressure from the mixed alveolar air of the two ventilated compartments to the nonshunted end-capillary blood). Model simulations show that pulmonary shunt results in a vertical depression of a plot of end-expiratory oxygen fraction against arterial blood saturation, whereas V/Q mismatch results in a horizontal shift to the right. Hence, the parameters can be estimated simultaneously by fitting the model to data describing the relationship between end-expiratory oxygen fraction and arterial blood saturation. In doing so, the model was calibrated for each study subject using values of hemoglobin, pH and arterial carbon dioxide tension provided by an arterial blood sample. To simplify data collection, other values required to perform model fitting were assumed to be constant. These were a diphosphoglycerate concentration of 5 mM, a dead space of 2 mL/kg and a cardiac index of 3.3 L/min/m².

Eleven patients were examined two times at baseline to describe reproducibility of the new gas exchange parameters. Furthermore, nine patients, classified by the reference diagnosis as having pulmonary congestion, were followed during anticongestive therapy. Measurements were taken on five and 30 days after inclusion and were used to describe changes in the gas exchange parameters in relation to clinical therapeutic response.

Statistics

Statistical analysis was performed using Stata 9.1 (StataCorp LP, USA), with a significance level (alpha) of 0.05.

Differences at baseline between patients with and without pulmonary congestion were tested using unpaired *t* tests for continuous variables or the Mann-Whitney U test in case of non-normal distributions. Fisher's exact test was used for dichotomous variables. Reference values for the gas exchange parameters were calculated as the 95th percentile limits of the healthy subjects. Differences for sex and smoking were tested using the unpaired *t* test or the Mann-Whitney U test in case of non-normal distributions. Associations with age, height and weight were tested using Spearman's rho correlation. The reproducibility of the gas exchange parameters was analyzed using Bland-Altman plots and quantified by within-subject SDs. The diagnostic properties for the gas exchange parameters to separate patients with and without pulmonary congestion were analyzed using receiver operating characteristic analysis, providing sensitivities, specificities and the areas under receiver operating characteristic curves (AUCs). Pairwise comparisons of AUCs were performed to compare the diagnostic abilities with traditional paraclinical examinations. For almost all paraclinical examinations, cut-offs for determination of sensitivity and specificity were chosen to be the 95th percentile limits of the healthy subjects. Exceptions to this were x-ray (Kostuk grade 2 or higher) (14) and NT-proBNP (less than 300 ng/L) (17). The ability of the new gas exchange parameters to monitor anticongestive therapy was analyzed using line plots and repeated measures ANOVA.

RESULTS

Statistical analysis was performed on data from all study subjects, but three patients were excluded from the parts of the analysis requiring arterial oxygen tension measurements because they received supplementary oxygen therapy during baseline arterial blood sampling. Two patients dropped out during follow-up due to severe disease deterioration.

Table 1 illustrates the baseline characteristics of the study subjects. In the healthy subjects, no signs of cardiopulmonary disease were observed. More than three-quarters of patients had functional dyspnea and the remaining patients had other clinical signs of cardiopulmonary disease. Patients with and without pulmonary congestion were comparable according to age, sex, body mass index and smoking. Patients with pulmonary congestion had significantly more frequent symptoms and signs of decompensation, lower left ventricular ejection fraction, lower values for dynamic spirometry, higher NT-proBNP, lower fA2 and higher ΔPO_2 .

Figure 1 The conceptual structure of the model describing pulmonary gas exchange. $C_a O_2$ Oxygen concentration in arterial blood; $C_c O_2$ Oxygen concentration in nonshunted end-capillary blood; $C_v O_2$ Oxygen concentration in mixed venous blood; fA2 and ΔPO_2 Ventilation/perfusion mismatch; $P_a O_2$ Arterial oxygen tension; $P_A O_2$ Oxygen pressure in the alveolar air; $P_c O_2$ Oxygen tension in the alveolar capillary blood; $P_v O_2$ Oxygen tension in mixed venous blood; Q Cardiac output; V_A Alveolar ventilation

Table 2 illustrates values of gas exchange parameters for healthy subjects and their reproducibility. The majority of healthy subjects had gas exchange parameters indicating no pulmonary abnormalities. Values of gas exchange parameters were significantly correlated with age, with no significant correlation to height and weight. Sex and smoking were not significantly correlated to the gas exchange parameters (not illustrated in table). Within-subject coefficients of variation indicate relatively good reproducibility.

Table 3 illustrates the diagnostic properties of the gas exchange parameters and traditional paraclinical methods. NT-proBNP, FEV₁, FVC, fA2 and ΔPO_2 had positive diagnostic abilities, with AUCs significantly higher than 0.50. fA2 and ΔPO_2 had better diagnostic abilities than all other investigated methods, except NT-proBNP, which was associated with significantly higher AUCs. NT-proBNP, fA2 and ΔPO_2 all had perfect sensitivities of 100%, whereas their specificities were 30% to 40%. The majority of the false-positive patients had known pulmonary comorbidities (pneumonia, pulmonary embolism or chronic obstructive pulmonary disease), Kostuk grade 2 or 3 at chest x-ray, or minor symptoms or signs of decompensated LHF not satisfying the tough criteria applied for the reference diagnosis. The scatter plots in Figure 2 demonstrate that alternative optimal cut-off levels could be selected, which would substantially improve the specificities without impairing the sensitivities of the diagnostic tests. In addition, Figure 2 illustrates that the effect of age on the gas exchange parameters in healthy subjects is minor compared with the abnormalities observed in pulmonary congestion.

Figure 3 illustrates the time course of changes during anticongestive therapy in the nine patients classified with pulmonary congestion

TABLE 1
Baseline characteristics of study subjects

	Healthy subjects	Patients		P
		No pulmonary congestion	Pulmonary congestion	
n	60	60	9	—
Age, years	50±16	65±12	72±9	0.17
Male, %	52	65	56	0.71
BMI, kg/m ²	24±4	27±4	26±4	0.51
Smoker, %	20	43	44	1.0
Ischemic heart disease, %	0	47	78	0.15
Pneumonia, %	0	5	0	1.0
Pulmonary embolism, %	0	3	0	1.0
COPD, %	0	12	33	0.11
Clinical signs of decompensation and cardiopulmonary status				
NYHA class	—	2.2±0.8	3.3±0.5	<0.001
Dyspnea walking level, %	0	37	100	<0.001
Dyspnea walking uphill, %	0	75	100	0.19
Orthopnea, %	0	5	89	<0.001
Paroxysmal nocturnal dyspnea, %	0	12	89	<0.001
Reduction in exercise tolerance, %	0	80	100	0.34
Resting sinus tachycardia >100, %	0	3	11	0.35
Neck venous pressure >4 cm H ₂ O, %	0	3	33	0.01
Hepatjugular reflex, %	0	2	0	1.0
Third heart sound, %	0	0	0	1.0
Basal crackles, %	0	13	56	0.01
Hepatomegaly, %	0	0	0	1.0
Peripheral edema, %	0	23	67	0.01
Decompensation score	0	0.8±0.8	2.9±0.8	<0.001
LVEF, %	—	50±13	25±11	<0.001
Traditional paraclinical examinations				
x-ray, grade	—	1.2±0.5	1.4±0.5	0.13
NT-proBNP, ng/L	—	1889±2285	11083±8085	<0.001
FEV ₁ (% of predicted)	104±10	80±22	59±25	0.03
FVC (% of predicted)	104±14	88±22	69±23	0.03
FEV ₁ /FVC (% of predicted)	106±11	96±9	89±14	0.05
P _a O ₂ , kPa	12.1±1.2	9.9±1.4	10.3±2.2	0.48
A-a difference, kPa	2.1±1.2	4.5±1.5	4.8±1.6	0.68
Venous admixture, %	7.1±4.8	16.8±7.6	15.0±8.9	0.58
New gas exchange parameters				
fA2	0.88±0.06	0.70±0.16	0.48±0.05	<0.001
ΔPO ₂ , kPa	0.1±0.2	1.3±1.6	3.3±0.8	<0.001
Pulmonary shunt, %	1.6±3.6	6.5±5.6	7.3±6.0	0.66

Data presented as mean ± SD unless otherwise indicated. A-a Alveolar-arterial oxygen; BMI Body mass index; COPD Chronic obstructive pulmonary disease; Decompensation score Additive score based on signs and symptoms of decompensation; fA2 and ΔPO₂ Ventilation/perfusion mismatch; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; LVEF Left ventricular ejection fraction; NT-proBNP N-terminal probrain natriuretic peptide; NYHA New York Heart Association; P_aO₂ Arterial oxygen tension; x-ray Pulmonary congestion at chest roentgenogram according to Kostuk

at baseline. Twelve subplots illustrate the changes in decompensation score, traditional paraclinical examinations and the gas exchange parameters. Two patients had severe disease deterioration and dropped

TABLE 2
Gas exchange parameters in healthy subjects and reproducibility

Gas exchange parameter	fA2	ΔPO ₂ , kPa	Pulmonary shunt, %
Mean	0.88	0.1	1.6
Minimum	0.61	0.0	0.0
Maximum	0.90	1.3	19.0
95th percentile limit	0.75	0.5	8.2
Age, p	−0.33*	0.29*	0.40**
Height, p	0.08	0.04	−0.05
Weight, p	−0.04	0.07	0.18
CV	0.05 (0.03–0.08)	0.4 (0.3–0.6)	2.0 (1.4–3.6)

*P<0.05; **P<0.01. CV Within-subject SD (95% CI); fA2 and ΔPO₂ Ventilation/perfusion mismatch; p Spearman's rho

out of the study. The remaining seven patients had a good clinical response to anticongestive therapy with a significant reduction in decompensation score. Similar significant improvements were seen for NT-proBNP, FEV₁, FVC, fA2 and ΔPO₂. Complete normalization of the measurements was not seen in all patients and NT-proBNP remained very high in some patients.

DISCUSSION

We investigated reference values, reproducibility, and diagnostic and monitoring properties for new pulmonary gas exchange parameters when used for evaluation of pulmonary congestion in LHF. The performance of these parameters was compared with chest x-ray, NT-proBNP, FEV₁, FVC, arterial oxygen tension, alveolar-arterial oxygen difference and venous admixture. The major findings were that the gas exchange parameters had narrow reference intervals for healthy subjects and relatively good reproducibility, and the parameter for V/Q mismatch (fA2 or ΔPO₂) had comparable superior diagnostic and monitoring abilities to NT-proBNP, with high sensitivities but low specificities.

Pulmonary gas exchange in healthy subjects

Pulmonary gas exchange is nearly perfect in healthy subjects, but mild degrees of V/Q mismatch can develop with age due to changes in the elastic properties of the lungs with airway closure during tidal breathing (18,19). This is in accordance with the narrow reference intervals for the new gas exchange parameters of healthy subjects in the present study, with only mild deterioration with age (Table 2 and Figure 2). However, the pulmonary shunt was surprisingly high in a few healthy subjects, probably due to high sensitivity of this parameter to pulse oximeter inaccuracy (20). As illustrated in Table 2, the diagnostic potential for the parameter describing V/Q mismatch (fA2 or ΔPO₂) is better than for pulmonary shunt. The observation that smoking did not affect the gas exchange parameters in healthy subjects was slightly surprising, as normal changes with age can be accelerated by smoking. This is probably explained by the fact that the participating healthy smokers were indeed healthy (Table 1). Similar findings have been reported in a study with inert gas analysis of pulmonary gas exchange in healthy subjects (18).

Reproducibility of the new pulmonary gas exchange parameters

It is necessary to validate the reproducibility of new clinical methods to ensure that clinical decisions are based on repeatable measurements. The results of the present study illustrate relatively good reproducibility of the gas exchange parameters, especially for the V/Q mismatch parameter (fA2 or ΔPO₂), with small within-subject SDs compared with overall differences between healthy subjects and patients with pulmonary congestion (Table 2 and Figure 2).

Diagnosis of pulmonary congestion in LHF

The backward failure in LHF with pulmonary congestion can affect pulmonary gas exchange, with increased V/Q mismatch and pulmonary

TABLE 3
Diagnostic rates for separating patients with and without pulmonary congestion

Test variables	Cut-off	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC (95% CI)
Traditional paraclinical examinations				
x-ray (grade)	≥2	44 (14–79)	80 (68–89)	0.61 (0.48–0.72)
NT-proBNP, ng/L	<300	100 (66–100)	30 (19–43)	0.88 (0.78–0.95)
FEV ₁ (% of predicted)	<88	100 (66–100)	38 (26–52)	0.73 (0.60–0.83)
FVC (% of predicted)	<84	67 (30–93)	57 (43–69)	0.73 (0.60–0.83)
FEV ₁ /FVC (% of predicted)	<89	33 (7–70)	80 (68–89)	0.63 (0.50–0.74)
P _a O ₂ , kPa	<10.1	50 (12–88)	50 (37–63)	0.47 (0.35–0.60)
A-a difference, kPa	>4.3	50 (12–88)	53 (40–66)	0.54 (0.42–0.67)
Venous admixture, %	>16.3	50 (12–88)	48 (35–62)	0.43 (0.30–0.55)
New gas exchange parameters				
fA2	<0.75	100 (66–100)	38 (26–52)	0.90 (0.80–0.96)
ΔPO ₂ , kPa	>0.5	100 (66–100)	37 (25–50)	0.88 (0.78–0.95)
Pulmonary shunt, %	>8.2	44 (14–79)	65 (52–77)	0.55 (0.43–0.67)

A-a Alveolar-arterial oxygen; AUC Area under the receiver operating characteristic curve; fA2 and ΔPO₂ Ventilation/perfusion mismatch; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; NT-proBNP N-terminal probrain natriuretic peptide; P_aO₂ Arterial oxygen tension; x-ray Pulmonary congestion at chest x-ray according to Kostuk

shunt, by blunting the hypoxic pulmonary vasoconstriction and by the development of increased distal airway resistance due to edema formation (6,21). This can produce clinically evident hypoxemia, but the true picture can be veiled, in cases of mild disease, because compensatory mechanisms or temporary changes in alveolar ventilation or perfusion can balance the actual suboptimal gas exchange (5,6). These effects provide an explanation for the poor diagnostic ability of arterial oxygen tension seen in the present study (Table 3). The diagnostic accuracy may be improved by taking the compensatory hyperventilation into account by estimation of alveolar-arterial oxygen difference or venous admixture (16), but these considerations failed to improve the diagnostic accuracy in the current study. Similar diagnostic failure was observed for evaluation of pulmonary congestion using chest x-ray in accordance with the well-known poor diagnostic accuracy and reproducibility of this method (2,3). The use of dynamic spirometry in the evaluation of pulmonary congestion is complex, as both obstructive and restrictive patterns have been observed previously (6) and in the present study (Table 1). Despite this, both FEV₁ and FVC had significant diagnostic abilities (Table 3), emphasizing the value of this very simple and fast bedside examination.

The gas exchange parameter for V/Q mismatch (fA2 or ΔPO₂) shows even more promising results with diagnostic abilities comparable with NT-proBNP (Table 3 and Figure 2). However, the specificities for fA2, ΔPO₂ and NT-proBNP were rather poor. This is probably explained by pulmonary comorbidity and several cases of less severe pulmonary congestion that did not satisfy the applied tough criteria for the reference diagnosis. The high sensitivities and low specificities suggest that these methods can only be used for excluding the diagnosis of pulmonary congestion, whereas none of the methods can stand alone for a positive diagnosis.

Monitoring of pulmonary congestion in LHF

In the present study, LHF patients with pulmonary congestion had a good clinical response to anticongestive therapy, with a significant

Figure 2 Scatter plots of age versus the baseline values for all study subjects for the three measures with the best diagnostic performance in the receiver operating characteristic analysis (ventilation/perfusion mismatch [fA2 and ΔPO₂] and N-terminal probrain natriuretic peptide [NT-proBNP])

reduction in symptoms and signs of decompensation, and comparable significant improvements in NT-proBNP, FEV₁, FVC, fA2 and ΔPO₂ (Figure 3). The lack of complete normalization despite successful anticongestive therapy is well-known for NT-proBNP due to persistent systolic dysfunction (4). The lack of complete normalization of spirometry values, fA2 and ΔPO₂ may, on the other hand, be explained by pulmonary comorbidity (22). These data indicate that

Figure 3) Line plots illustrating the individual changes during anticongestive therapy in the nine patients with pulmonary congestion. P values indicate results from repeated measures ANOVA between baseline, five days and 30 days. Two patients dropped out during follow-up. Only a few lines are seen in the plot for x-ray because most patients had the same values. A-a Alveolar-arterial oxygen; Decompensation score Additive score based on signs and symptoms of decompensation; fa2 and ΔP_{O_2} Ventilation/perfusion mismatch; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; NT-proBNP N-terminal pro-brain natriuretic peptide; P_aO₂ Arterial oxygen tension; x-ray Pulmonary congestion at chest roentgenogram according to Kostuk

in patients with pulmonary comorbidity, NT-proBNP is the best method for evaluating pulmonary congestion, whereas, in patients with chronic LHF, the parameter for V/Q mismatch (fa2 or ΔP_{O_2}) or even spirometry values may outperform NT-proBNP. Further studies are required to investigate the appropriate clinical and scientific use of these parameters.

Limitations

The results of the present study were limited by the relatively small number of patients with pulmonary congestion. Future studies including larger groups of patients with pulmonary congestion should be performed before widespread clinical use of the gas exchange parameters occurs. The

estimation of the gas exchange parameters required several assumed values including cardiac index. However, it has previously been shown that parameter values are relatively insensitive to errors in these assumed values (8). The present study is a necessary first step in the evaluation of the potential clinical role of the new gas exchange parameters. We used very tough criteria for the reference diagnosis of pulmonary congestion and a few patients with isolated diastolic dysfunction could have been classified incorrectly for the diagnostic analysis, resulting in small errors in the diagnostic rates. We did not investigate diastolic dysfunction at echocardiography or right heart catheterization. Therefore, it could be interesting to address the relationship between the gas exchange parameters and diastolic dysfunction in future studies, which should also focus on the diagnostic and monitoring performance in patients with less clear signs and symptoms of pulmonary congestion. This is a patient group in which the use of the new gas exchange parameters could be especially interesting.

CONCLUSIONS

The new gas exchange parameters have narrow reference intervals for healthy subjects and relatively good reproducibility, and the present

study suggests that the parameter for V/Q mismatch, but not pulmonary shunt, has a possible role in rejecting the diagnosis of pulmonary congestion and in monitoring anticongestive therapy.

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