

ASSESSMENT AND MANAGEMENT

Blood gas tensions in adult asthma: a systematic review and meta-regression analysisTroels Johansen, MSc Eng¹, Peter Johansen, PhD², and Ronald Dahl, MD³¹Department of Respiratory Diseases, Aarhus University Hospital, Aarhus, Denmark, ²Department of Engineering, Aarhus University, Aarhus, Denmark, and ³Allergy Centre, Odense University Hospital, Odense, Denmark**Abstract**

Objective: The last half-century has seen substantial changes in asthma treatment and care. We investigated whether arterial blood gas parameters in acute and non-acute asthma have changed historically. **Methods:** We performed a systematic search of the literature for studies reporting P_{aO_2} , P_{aCO_2} and forced expiratory volume in 1 s, percentage of predicted (FEV1%). For each of the blood gas parameters, meta-regression analyses examined its association with four background variables: the publication year, mean FEV1%, mean age and female fraction in the respective studies. **Results:** After screening, we included 43 articles comprising 61 datasets published between 1967 and 2013. In studies of habitual-state asthma, mean P_{aO_2} was positively associated with the publication year ($p=0.001$) and negatively with mean age ($p<0.01$). Mean P_{aCO_2} showed a positive association with publication year ($p=0.001$) and a negative association with female fraction ($p<0.05$). In acute asthma studies, blood gas levels were unassociated with publication year and mean age, mean P_{aO_2} was positively associated with FEV1% ($p<0.05$) whereas mean P_{aCO_2} showed a negative association with FEV1% ($p<0.05$) for studies with mean FEV1% <40 . In neither acute nor habitual-state studies was mean arterial pH associated with any of the predictor variables. **Conclusions:** In studies of habitual-state asthma, mean reported P_{aO_2} and P_{aCO_2} levels were found to have increased since 1967. In acute asthma studies, mean P_{aO_2} and P_{aCO_2} were associated with mean FEV1% but not with either publication year or patient age.

Keywords

Arterial blood gas, arterial pH, asthma, blood gas tensions, meta-regression, systematic review

HistoryReceived 24 April 2014
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Published online 18 July 2014**Introduction**

Asthma is characterized by episodic and reversible airflow obstruction in combination with airway hyper-responsiveness and airway inflammation. Clinical signs of large airways obstruction are often readily detectable in the form of dyspnoea, wheezing, hyperinflation of the lungs and/or coughing. From the patient's point of view, dyspnea is the most salient and worrying symptom of asthma. From the point of view of the human organism, the danger of asthma lies in the impairment of gas exchange, posing the threat of hypoxia and hypercapnia-induced respiratory acidosis.

Gas exchange defects are generally more difficult to diagnose than large airways obstruction since an arterial blood sample is required for accurate measurement of blood gas tensions, i.e. the partial pressures in arterial blood of oxygen (P_{aO_2}) and carbon dioxide (P_{aCO_2}).

The first large studies of blood gases in asthma were undertaken in the 1960s, prompted by an increase in asthma deaths in the preceding decade [1,2]. Such studies have uniformly shown asthma exacerbations to be associated with

hypoxemia. However, reported P_{aCO_2} levels range between gross hypocapnia, normocapnia or in severe cases hypercapnia [3–6]. Venous admixture due to ventilation/perfusion (V/Q) inequalities have been shown to be the primary factor causing hypoxemia in asthma [7], hypoventilation with resultant hypercapnia only occurring in the most severe exacerbations, as fatigue of the respiratory muscles and/or mucous plugging and airway oedema develop [8].

In the last 50 years, asthma treatment has changed markedly, among other factors by the introduction of inhaled corticosteroids (ICS) [9] and a focus on prevention by anti-inflammatory medication rather than only relying on acute relief by bronchodilators. Concurrently with the last half-century's significant rise in global asthma prevalence [10,11], the severity of the disease and its impact on pulmonary gas exchange may, in general, have been reduced. The historical changes in asthmatics' gas exchange status and blood gas levels have not been systematically investigated however, and we set out to do so, believing that this information would be of value for future epidemiological studies of asthma.

We proposed the hypothesis that the pulmonary gas exchange status of asthmatics has improved over the years, and that this would be reflected in asthmatics having more normal blood gas values now than in the past, both at baseline and during acute exacerbations.

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In the study, the meta-regression statistical method [12,13] was used within the framework of a systematic review, in order to examine the changes in the study means of blood gas values of asthmatics between 1967 and 2013, as well as the blood gas parameters' association with the study means of FEV1%, patient age and female fraction.

The blood gas parameters examined were P_{aO_2} , P_{aCO_2} , alveolar–arterial oxygen partial pressure gradient ($A-aP_{O_2}$) and arterial pH.

From the blood gas values, blood gas contents of oxygen (C_{aO_2}) and carbon dioxide (C_{aCO_2}) were estimated using established algorithms (see Appendix for details).

The presence of an exacerbation is clearly one of the most important confounders in any analysis of blood gases in asthma. Consequently, the studies in the analysis were subdivided into data sets of patients diagnosed with asthma in either (a) their non-acute habitual state (30 datasets in 28 articles) [6,14–40] or (b) during acute exacerbations or in the early stages of remission (31 datasets in 15 articles) [3,5,41–53]. This enabled us to analyze the historical changes of both the baseline and acute state.

Methods

Data sources and searches

A systematic search was conducted in the MEDLINE and EMBASE databases for articles published online before August 1st 2013, the abstract and/or title of which contained at least one keyword from each of the following two groups:

- (1) asthma, asthmatic and asthmatics.
- (2) P_{aO_2} , P_{aCO_2} , ‘‘blood gas’’, ‘‘partial pressure’’, ‘‘oxygen tension’’, ‘‘carbon dioxide tension’’ and ‘‘CO₂ tension’’

Reference lists of all articles chosen for further assessment were manually screened to identify any additional studies. A full flowchart of the study selection procedure can be seen in Figure 1.

Study selection

Inclusion criteria:

- (1) Patients in the dataset were diagnosed with asthma (atopic or non-atopic),
- (2) Values for P_{aO_2} , P_{aCO_2} and FEV1 available and obtained simultaneously, the latter reported as a percentage of the predicted value (FEV1%),
- (3) Five or more patients in the dataset,
- (4) Adults (18+ years) and
- (5) English language articles.

Exclusion criteria:

- (1) Blood gas data obtained while the patients were breathing supplementary oxygen or being mechanically ventilated,
- (2) Data for the group in question obtained after a systematic, prospective intervention with a specific drug or treatment,
- (3) Data obtained after exercise-induced bronchoconstriction,
- (4) Standard deviation of FEV1% in the dataset above 20.0 and
- (5) Patients with concomitant asthma and chronic obstructive pulmonary disease (COPD).

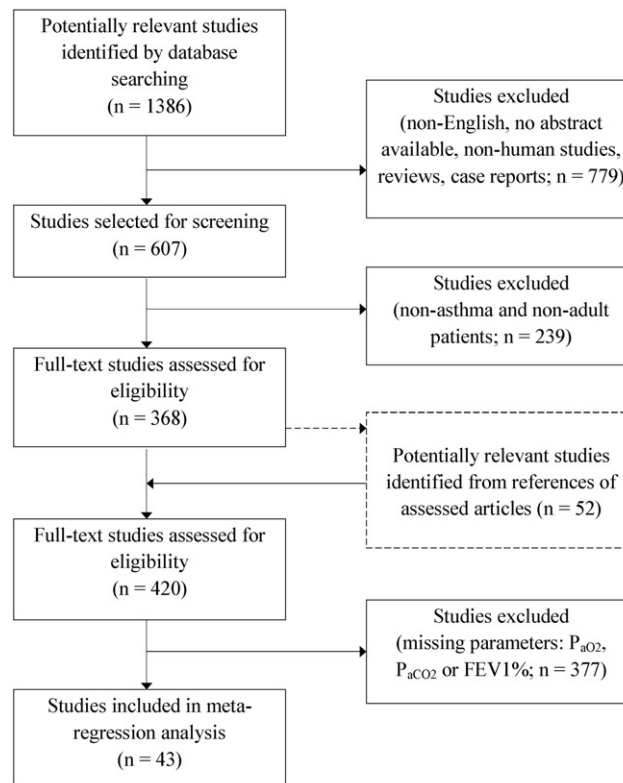


Figure 1. Flow diagram of included/excluded studies. P_{aO_2} arterial partial pressure of oxygen; P_{aCO_2} arterial partial pressure of carbon dioxide; FEV1%: forced expiratory flow in 1 s, % of predicted.

Statistical analysis

Meta-regression analyses were performed using the *metareg* command for STATA version 11.1 (StataCorp LP, College Station, TX), a command which was developed by Sharp [54] and extended by Harbord and Higgins [13]. Using *metareg*, the associations between the data set means of the parameters were analyzed using a random-effects model of the data set heterogeneity. The individual data set weights were calculated as $1/(\sigma^2 + \tau^2)$, σ^2 being the within-data set variance and τ^2 the between-data set variance [13]; in other words, a data set with a small variance will have a larger weight in the analysis than a data set with a large variance.

The meta-regression analyses included the following predictor variables:

- (1) Publication year,
- (2) Mean FEV1% in the dataset,
- (3) Mean age in the dataset and
- (4) Female fraction in the dataset.

There was insufficient data in the reviewed articles to include as predictor variables other spirometric parameters, nationality, race, comorbidities, smoking status/history, BMI or time elapsed between onset of symptoms and blood gas sampling.

Of the 61 studies, 15 included atopic asthma patients only, whereas the remaining 46 studies either provided no info on the type of asthma (atopic/non-atopic) or included both atopic and non-atopic patients. Consequently, there was insufficient data to include atopic/non-atopic type as a predictor variable in the analysis.

Table 1. Data from studies of non-acute asthma.

Study/year/country	n	f% (%)	Age (SD) (years)	FEV1% (SD) (% of pred.)	P _{aO₂} (SD) (kPa)	P _{aCO₂} (SD) (kPa)	A–aP _{O₂} (SD) (kPa)
Tai & Read [14]/1967/Australia	16		43.0 (NA)	40.8 (17.7)	8.9 (1.4)	5.3 (0.6)	5.2 (1.5)
Lane [15]/1969/UK	20	60	48.4 (NA)	45.2 (11.3)	8.8 (0.9)	5.5 (1.0)	5.3 (0.8)
Brooks et al. [6]/1972/USA	6	67	44.8 (14.0)	69.8 (14.5)	10.6 (1.5)	3.7 (0.4)	5.1 (0.8)
Brooks et al. [6]/1972/USA	6	67	32.2 (9.7)	53.2 (19.8)	9.6 (2.0)	3.9 (0.5)	5.4 (2.1)
Tashkin et al. [16]/1975/USA	20	40	36.7 (20.6)	53.6 (16.5)	11.1 (1.4)	5.1 (0.3)	2.7 (1.4)
Wagner et al. [17]/1978/USA	6	50	31.3 (9.1)	81.2 (17.8)	11.3 (1.9)	4.4 (0.8)	3.2 (1.5)
Ancic et al. [18]/1984/Chile	6	33	24.0 (NA)	101.1 (9.3)	10.3 (0.9)	4.7 (0.3)	2.5 (0.6)
Hida et al. [19]/1985/Japan	6	33	40.8 (NA)	79.8 (15.2)	10.8 (0.9)	5.0 (0.4)	2.8 (1.0)*
Ballester et al. [20]/1990/Spain	9	100	56.0 (10.0)	39.0 (10.0)	10.3 (0.9)	5.2 (0.3)	3.5 (0.9)
Rodriguez-Roisin et al. [21]/1991/Spain	16	50	36.6 (15.2)	92.0 (18.8)	11.7 (1.4)	4.8 (0.4)	3.1 (1.8)
Lagerstrand et al. [22]/1992/Sweden	8	25	26.0 (8.0)	97.0 (8.0)	13.1 (0.9)	5.4 (0.5)	0.5 (0.6)
Forster et al. [23]/1993/USA	10	50	29.3 (9.0)	98.0 (8.5)	13.3 (1.4)	4.8 (0.3)	0.4 (1.5)*
Felez et al. [24]/1994/Spain	6	17	23.0 (5.1)	90.0 (10.3)	12.9 (0.9)	4.7 (0.2)	2.3 (1.2)
Lagerstrand et al. [25]/1995/Sweden	8	25	30.0 (NA)	78.6 (7.1)	13.0 (1.0)	5.4 (0.2)	0.4 (1.0)*
Diaz et al. [26]/1997/Spain	8	63	26.0 (5.7)	93.0 (8.5)	13.5 (1.1)	4.7 (0.4)	1.7 (0.8)
Gómez et al. [29]/1998/Spain	10	40	24.0 (3.2)	94.0 (12.6)	12.6 (0.6)	5.1 (0.4)	1.1 (0.6)
Gómez et al. [30]/1998/Spain	12	33	24.0 (3.5)	93.0 (10.4)	13.1 (1.4)	5.1 (0.5)	0.8 (1.1)
Spanevello et al. [27]/1998/Italy	24	25	58.0 (10.0)	79.1 (16.3)	10.2 (1.1)	5.2 (0.5)	1.8 (1.4)
Takahashi et al. [31]/1998/Japan	6	67	54.6 (8.7)	96.8 (19.9)	12.0 (0.6)	5.3 (0.3)	1.7 (0.9)
Valente et al. [28]/1998/Italy	14	71	38.4 (12.5)	79.0 (14.7)	11.7 (1.0)	4.7 (0.7)	3.1 (1.6)
Echazarreta et al. [33]/1999/Spain	11	64	21.5 (2.7)	95.0 (13.9)	12.9 (0.8)	5.1 (0.4)	1.1 (0.5)
Ferrante et al. [32]/1999/Italy	12	0	19.3 (1.1)	94.0 (10.6)	12.9 (0.5)	5.3 (0.2)	0.5 (0.3)
Echazarreta et al. [34]/2001/Spain	11	73	22.0 (3.3)	90.0 (16.6)	12.7 (0.4)	4.9 (0.4)	1.1 (0.9)
Echazarreta et al. [35]/2001/Spain	13	54	23.0 (3.6)	95.0 (14.4)	12.4 (1.4)	4.9 (0.5)	0.9 (1.0)
Acuna et al. [36]/2002/Spain	12	50	24.0 (3.5)	89.0 (10.4)	12.8 (1.9)	5.3 (0.5)	1.1 (1.4)
Casas et al. [37]/2005/Spain	10	70	26.0 (6.3)	89.0 (15.8)	13.6 (1.3)	5.2 (0.8)	0.3 (0.4)
Haverkamp et al. [38]/2007/USA	9	44	28.7 (5.9)	94.4 (14.6)	12.5 (1.4)	5.0 (0.5)	1.5 (1.2)
Haverkamp et al. [38]/2007/USA	10	40	23.7 (5.3)	82.8 (13.4)	12.5 (0.7)	5.1 (0.3)	1.0 (0.5)
Munoz et al. [39]/2008/Spain	11	73	27.0 (4.0)	86.0 (8.0)	12.7 (0.7)	5.1 (0.4)	1.1 (0.7)
Dahlen et al. [40]/2012/Spain	12	67	28 (6.9)	87.9 (15.6)	13.1 (0.9)	5.2 (0.5)	1.2 (1.0)

Abbreviations: n number of patients in the dataset; f% fraction of females in the dataset (%); FEV1% forced expiratory volume, percent of predicted (%); P_{aO₂} arterial partial pressure of oxygen (kPa); P_{aCO₂} arterial partial pressure of carbon dioxide (kPa); A–aP_{O₂} alveolar–arterial oxygen partial pressure gradient (kPa); pH arterial pH.

*Value not provided in original article but calculated by the Alveolar Gas Equation, assuming a respiratory exchange ratio of 0.8.

Results

The initial database searches retrieved 1386 unique publications, of which 368 were assessed for eligibility (Figure 1). From the references of these 368 articles, 52 additional articles were identified and included in the assessment. Of the total 420 assessed articles, 43 included one or more datasets which met the inclusion criteria.

In total, 61 datasets were included, comprising 31 acute datasets and 30 non-acute datasets. Sample sizes of the studies ranged from 6 to 122 patients (mean 17), with mean age ranging from 19 to 65 years (mean 34.7 years) and including both sexes, the proportion of females ranging between 0 and 100% (mean 51%). Mean values of relevant parameters in the acute studies are tabulated in Tables 1 (non-acute asthma studies) and 2 (acute asthma studies).

A preliminary analysis divided the studies into four subgroups according to the patient group's prehistory of steroid use: (1) no information available, (2) no history of steroid use, (3) a history of oral steroid use and (4) a history of ICS use without oral steroid use. As is evident from Figure 2, more than half of the articles lacked information about the prior steroid use. Consequently, the presence of steroid premedication was unsuited as a predictor variable in the analysis. Even so, Figure 2 does indicate a (unsurprising) trend of increasing frequency of reported ICS premedication in more recent studies.

Non-acute studies

In the analysis of the *non-acute* datasets, P_{aO₂} showed a positive correlation with the publication year ($p = 0.001$) and a negative correlation with the mean age of the patients ($p < 0.01$) (adjusted R^2 of the model = 0.78). Mean P_{aO₂} fell on average 0.44 kPa for every 10 years of mean age and increased on average by 0.51 kPa for every decade of historical time; whereas the P_{aO₂} means of the four pre-1975 studies were all below 10.7 kPa (80 mmHg), mean P_{aO₂} values in recent (post-2000) studies were all above 12 kPa (93 mmHg) (Table 1; Figure 3a).

There was no statistically significant association between the publication year and mean patient age.

P_{aCO₂} showed a positive correlation with the publication year ($p = 0.001$) (Figure 3a) as well as negative correlations with the proportion of females in the study group ($p < 0.05$) and FEV1% ($p < 0.05$). The overall predictive value of the multiple regression model was lower for P_{aCO₂} than for P_{aO₂} (adjusted $R^2 = 0.39$), and the mean absolute change in P_{aCO₂} over the historical period was less than 0.7 kPa.

The historical increases in P_{aCO₂} and P_{aO₂} in combination produced a very clear negative association between study year and A–aP_{O₂} ($p < 0.001$) (Figure 3b). Whereas in the six pre-1980 studies the mean of the A–aP_{O₂} study means was 4.5 kPa (SD 1.2 kPa), in the eight post-2000 studies the mean of the

Table 2. Data from studies of acute asthma.

Study/year/country	N	f% (%)	Age (SD) (years)	FEV1% (SD) (% of pred.)	P _{aO₂} (SD) (kPa)	P _{aCO₂} (SD) (kPa)	A-aP _{O₂} (SD) (kPa)
McFadden and Lyons [3]/1968/USA	11			58.7 (10.0)	11.0 (1.5)	3.3 (0.5)	4.9 (1.6)*
McFadden and Lyons [3]/1968/USA	36			34.9 (10.0)	9.5 (1.1)	4.3 (0.6)	5.2 (1.3)*
McFadden and Lyons [3]/1968/USA	54			17.6 (10.0)	8.4 (1.2)	5.2 (0.9)	5.3 (1.5)*
Palmer and Diamant [42]/1969/UK	29		40.8 (15.7)	67.0 (16.1)	11.6 (1.2)	5.0 (0.5)	2.3 (1.3)*
Palmer and Diamant [42]/1969/UK	9		37.6 (14.7)	34.2 (9.1)	10.3 (2.0)	5.3 (0.6)	3.2 (2.1)*
Palmer and Diamant [42]/1969/UK	34		39.7 (12.0)	49.3 (12.2)	10.8 (1.3)	5.4 (0.8)	2.6 (1.5)*
Miyamoto et al. [41]/1970/Japan	12			72.3 (6.6)	11.4 (1.4)	5.1 (0.4)	2.2 (1.4)*
Miyamoto et al. [41]/1970/Japan	10			49.6 (6.3)	10.7 (1.3)	5.1 (0.6)	2.9 (1.4)*
Miyamoto et al. [41]/1970/Japan	17			29.9 (5.3)	10.0 (1.2)	5.2 (0.8)	3.4 (1.4)*
Miyamoto et al. [41]/1970/Japan	13			16.6 (3.2)	9.2 (1.3)	5.8 (1.0)	3.5 (1.7)*
Melville and Iravani [43]/1974/Germany	18	44	38.1 (11.9)	75.0 (14.8)	11.3 (2.1)	5.3 (0.7)	2.0 (2.2)*
Melville and Iravani [43]/1974/Germany	18	44	38.1 (11.9)	52.9 (13.3)	8.5 (2.0)	5.7 (0.9)	4.3 (2.2)*
Yu and Lee[44]/1976/Hong Kong	10	40	46.7 (10.4)	37.4 (13.0)	11.4 (1.5)	4.9 (0.6)	2.4 (1.6)*
Hetzel et al. [45]/1977/UK	16			42.4 (12.9)	9.4 (2.1)	4.6 (0.4)	4.8 (2.1)
Fanta et al. [46]/1983/USA	9	67	31.0 (9.0)	32.0 (9.0)	8.5 (0.4)	4.1 (0.4)	6.4 (0.6)*
Fanta et al. [46]/1983/USA	11	82	32.0 (6.6)	25.0 (10.0)	8.3 (1.3)	4.4 (0.9)	6.4 (1.6)*
Freedman et al. [47]/1983/USA	18	56	49.0 (14.0)	43.0 (16.0)	9.5 (1.5)	4.7 (0.7)	4.9 (1.6)*
Jonsson et al. [48]/1988/Iceland	11	55	64.7 (11.0)	50.6 (15.4)	9.2 (1.0)	3.9 (0.5)	6.1 (1.1)*
Jonsson et al. [48]/1988/Iceland	11	64	61.5 (10.1)	41.9 (15.2)	9.3 (1.1)	4.1 (0.3)	5.8 (0.5)*
Ballester et al. [49]/1989/Spain	19	89	42.0 (19.4)	41.0 (13.0)	9.4 (1.7)	4.7 (0.5)	4.7 (0.4)
Ferrer et al. [50]/1993/Spain	9	56	43.2 (12.0)	60.9 (8.7)	12.3 (2.1)	4.5 (0.7)	2.0 (2.2)*
Ferrer et al. [50]/1993/Spain	9	56	34.6 (10.8)	46.0 (17.4)	9.7 (1.1)	4.6 (0.4)	4.4 (1.1)*
Ferrer et al. [50]/1993/Spain	9	56	43.2 (12.0)	31.3 (9.9)	7.2 (1.4)	5.5 (1.4)	5.9 (2.0)*
Kunitoh et al. [51]/1994/Japan	40	33	36.0 (16.7)	27.0 (17.3)	9.4 (1.1)	5.3 (0.6)	4.2 (1.2)
Kunitoh et al. [51]/1994/Japan	18	61	36.1 (14.5)	25.1 (10.1)	7.4 (0.4)	5.4 (0.5)	6.0 (0.7)*
Kunitoh et al. [51]/1994/Japan	21	38	32.7 (12.2)	12.6 (3.9)	7.7 (0.7)	6.7 (0.5)	4.2 (0.8)*
Montserrat et al. [52]/1995/Spain	6	50	36.0 (12.0)	37.0 (7.0)	9.2 (1.3)	4.7 (0.3)	4.9 (1.5)
Rodrigo et al. [53]/2005/Uruguay	18	50	42.9 (2.7)	32.2 (10.9)	10.2 (1.6)	4.8 (0.4)	4.0 (1.6)*
Raimondi et al. [5]/2013/Argentina	25			46.7 (5.4)	9.4 (1.9)	4.3 (1.0)	5.4 (2.1)*
Raimondi et al. [5]/2013/Argentina	122			27.6 (4.8)	8.9 (1.5)	4.4 (0.7)	5.8 (1.7)*
Raimondi et al. [5]/2013/Argentina	73			16.1 (3.3)	8.4 (1.5)	4.9 (0.8)	5.6 (1.7)*

Abbreviations: *n* number of patients in the dataset; *f*% fraction of females in the dataset (%); *FEV1*% forced expiratory volume, percent of predicted (%); *P_{aO₂}* arterial partial pressure of oxygen (mmHg); *P_{aCO₂}* arterial partial pressure of carbon dioxide; *A-aP_{O₂}* alveolar-arterial oxygen partial pressure gradient (mmHg); *pH* arterial pH.

*Value not provided in original article but calculated by the Alveolar Gas Equation, assuming a respiratory exchange ratio of 0.8.

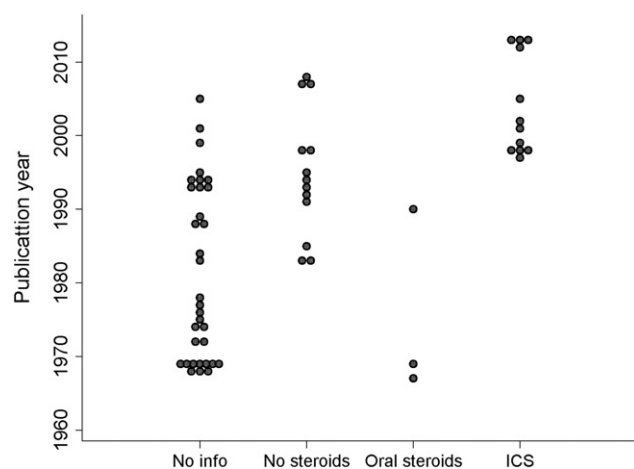


Figure 2. Scatter plot showing the publication years of the 61 datasets sorted according to the history of steroid use in the dataset (*ICS* inhaled corticosteroids).

A-aP_{O₂} means was 1.0 kPa (SD 0.3 kPa). Mean arterial pH values were uncorrelated with all predictor variables.

Acute studies

In the *acute* datasets, none of the blood gas parameters showed an association with the publication year or mean age

of the patient group. The best predictor of mean *P_{aO₂}* among the background variables was mean *FEV1*% ($p < 0.001$) (Figure 4a), showing a mean increase of 0.52 kPa for every increase of 10% points in mean *FEV1*% in the multiple regression model. This trend was also reflected in a negative association between *A-aP_{O₂}* and *FEV1*% ($p < 0.05$) (Figure 4b).

Looking at the entire data range, mean *P_{aCO₂}* showed no association with mean *FEV1*%, but when restricted to the more severe attacks (*FEV1*% lower than 40%), a negative association was apparent ($p < 0.05$) – signifying a tendency for *P_{aCO₂}* to rise as obstruction becomes more severe (Figure 4a). Just as for the non-acute studies, *P_{aCO₂}* showed a negative association with the fraction of females in the study ($p < 0.05$). Mean pH was not associated with any of the background variables.

Blood gas contents

Figure 5 shows blood gas data for all 61 datasets, plotted as blood gas tensions (Figure 5a) and calculated blood gas contents (Figure 5b), respectively¹.

¹The content values were with few exceptions not reported by the original authors but were computed by the authors of this article by using established algorithms (see Appendix for details)

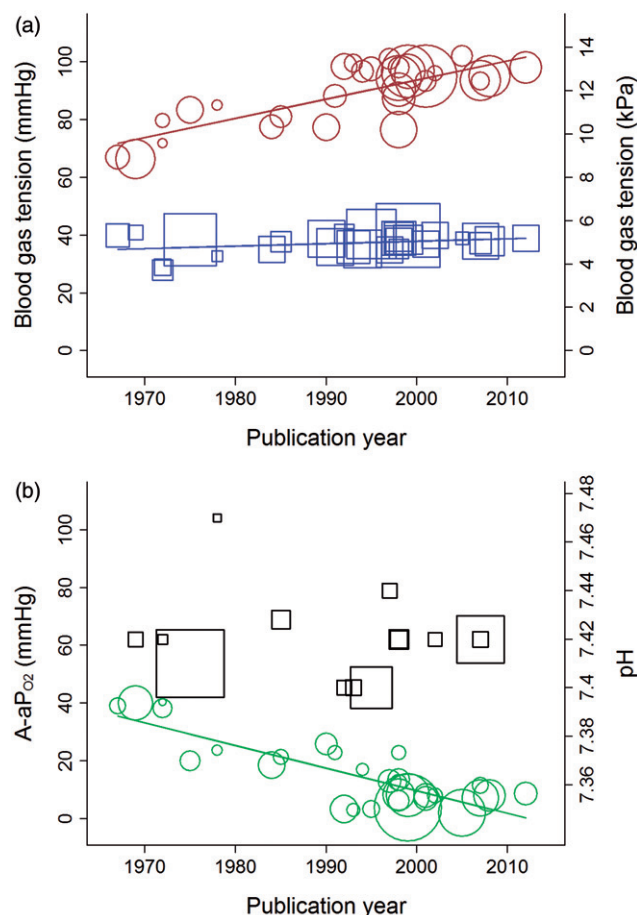


Figure 3. Trends over time of mean study values of (a) P_{aO_2} (○) and P_{aCO_2} (□) and (b) $A-aP_{O_2}$ (○) and arterial pH (□), in studies of patients diagnosed with asthma in their non-acute habitual state. Weighted lines of regression are shown for statistically significant correlations ($p < 0.05$). The sizes of the symbols are inversely related to the variances in the specific studies.

These data indicate that the absolute oxygen contents are relatively well preserved over this spectrum of asthma severities and even more stable than the carbon dioxide contents. The lowest calculated value of C_{aO_2} was 18.1 mL/dL (at a P_{aO_2} of 7.2 kPa) [50], which should be compared with the normal value of approximately 20 mL/dL.

Discussion

This study analyzed arterial blood gas data from 61 datasets in 43 asthma studies published between 1967 and 2013, aiming to quantify the changes in P_{aCO_2} , P_{aO_2} , $A-aP_{O_2}$ and pH over a period in time which has seen great developments in asthma treatment and care.

In the studies of non-acute asthma, a clinically and statistically significant increase since 1967 was seen in both P_{aO_2} as well as an even more clear decrease in $A-aP_{O_2}$, indicating an improvement in pulmonary gas exchange status. The well-documented decrease of P_{aO_2} with age was also evident in the analysis.

For P_{aCO_2} , a minor but statistically significant increase over historical time was seen. There was some evidence of an association of non-acute asthma with habitual hyperventilation in earlier though not in more recent studies: in three

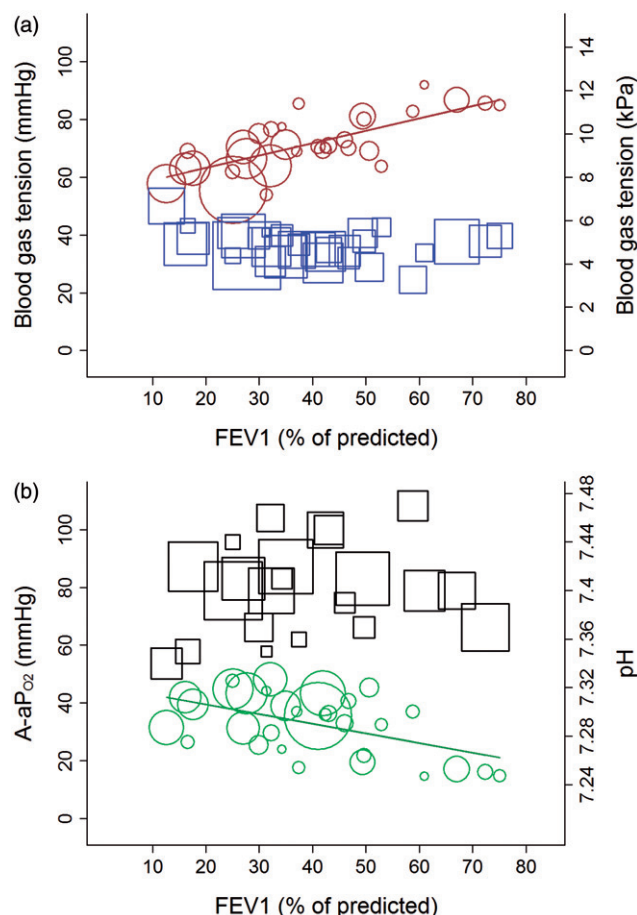


Figure 4. Mean study values of (a) P_{aO_2} (○) and P_{aCO_2} (□) and (b) $A-aP_{O_2}$ (○) and arterial pH (□) at the corresponding mean FEV1%, in studies of patients diagnosed with asthma during acute attacks or in the early stage of remission. Weighted lines of regression are shown for statistically significant correlations ($p < 0.05$). The sizes of the symbols are inversely related to the variances in the specific studies.

out of six pre-1980 studies, the mean P_{aCO_2} was below 4.7 kPa (35 mmHg), but none of the eight post-2000 studies had a mean P_{aCO_2} below 4.7 kPa. The historical increases in P_{aO_2} and P_{aCO_2} and decrease in $A-aP_{O_2}$ seem to have primarily taken place from 1970 to 1990 (Figure 3a).

It seems likely that these increases at least in part reflect the changes in asthma treatment over this period, especially the introduction of ICS as a first line anti-inflammatory preventive treatment. The use of ICS was absent or rare in earlier studies and frequent in more recent studies (Figure 2).

In the acute studies, an association between FEV1% and blood gas levels was evident, P_{aO_2} unsurprisingly being lower in more obstructed patients, and P_{aCO_2} showing a tendency to rise as FEV1% falls below 40%. The present study thus confirmed the finding of previous studies that P_{aCO_2} is only above baseline in cases of very severe airway obstruction [3,41,51].

A high proportion of women in a study was associated with a low-study mean P_{aCO_2} , a result which is in accordance with earlier studies showing lower P_{aCO_2} values in women compared with men [55].

Serious asthma exacerbations are a more rare occurrence today than during the peak in the 1960s, and the incidence of asthma deaths seems still to be declining [2,56].

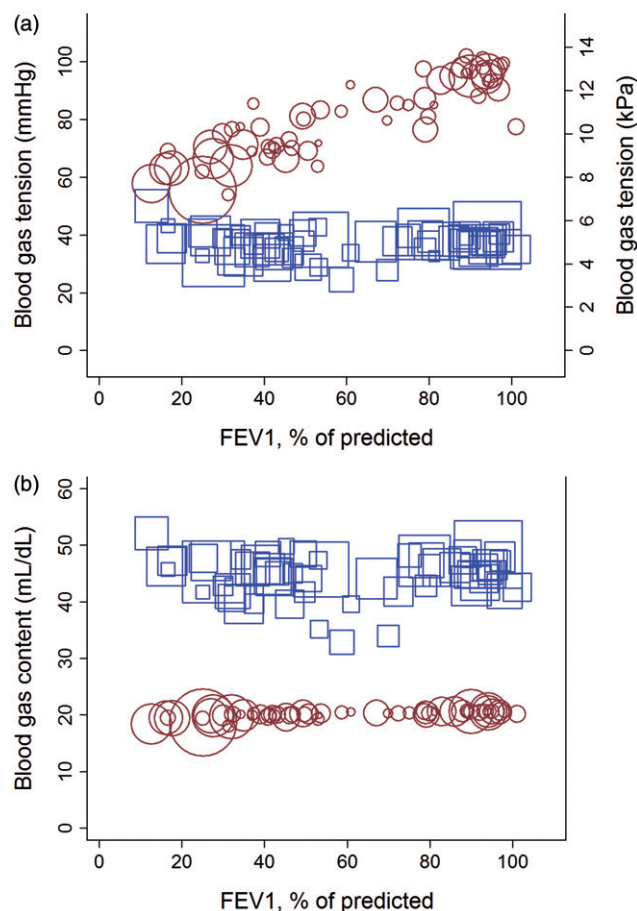


Figure 5. Mean study values of (a) P_{aO_2} (○) and P_{aCO_2} (□) and (b) calculated values of C_{aO_2} (○) and C_{aCO_2} (□) shown at the corresponding mean study values of forced expiratory volume in 1 s, % of predicted (FEV1%). The sizes of the symbols are inversely related to the variances in the specific studies.

However, the meta-regression analysis of the studies of acute asthma found no correlation between blood gas tensions and mean patient age or publication year. This would indicate that when asthma exacerbations *do* occur, the impact on the gas exchange status can be as severe today as in the past. It should, however, be noted that the present study only included studies that had *measured* FEV1% and where blood gases were obtained while breathing air. By their very nature, these limitations excluded studies of the most severe asthma cases in which patients are very often unable to perform a spirometry and/or are receiving supplementary oxygen. A recent study found P_{aCO_2} to be very high among patients who were unable to perform a spirometry [5], indicating that this inability should alert the clinician to the risk of a serious blood gas derangement.

Several limitations and potential sources of error must be pointed out when interpreting the results of the present study.

First of all, a selection bias may account for part of the observed rise in $A-aP_{O_2}$ and P_{aO_2} with publication year in the non-acute studies, due to the possible inclusion in earlier asthma studies of “chronic asthma” or “asthmatic bronchitis” patients that according to today’s criteria would be diagnosed as having both asthma and COPD.

However, despite the fact that the criteria for an asthma diagnosis have become more rigorous over the years, the

criteria used in the oldest of the included non-acute studies are in fact very familiar: intermittent flow limitation and dyspnea with at least partial reversibility with bronchodilators, as well as an explicit aim to exclude from the studies’ patients with either emphysema or chronic bronchitis [6,14,15]. Furthermore, the mean ages in the seven pre-1980 non-acute studies all lie between 31 and 49 years, making it unlikely that COPD patients would have made up more than a small minority of the study groups.

By their very nature, the studies were conducted at different historical times, with different equipment and using different reference values for calculating FEV1%. In this regard, an important source of error in measuring blood gas tensions is the time elapsed between sampling and measurement, the temperature at which the sample is stored until measurement and the presence of air bubbles in the sample [57]. When samples are stored for too long at a very high temperature, the result will be a decrease in P_{aO_2} and a smaller increase in P_{aCO_2} as a result of the respiration of blood cells. Conversely, when the sample is exposed to the atmosphere or an air bubble, P_{aO_2} will rise and P_{aCO_2} fall as the blood gas tensions approach the atmospheric tensions [57]. These sources of error in blood gas analysis were known long before the start of the period covered by the study [58] but it is very possible that the scarcity of blood gas devices in the past may have given rise to longer delays from sampling to measurement. Only 6 of 41 articles in the study give any information about the measurement delay, so it is not possible to analyze the extent of this error in the data. However, it can be inferred that the effect of longer measurement delays in older studies would be to underestimate P_{aO_2} , causing the meta-regression analysis to overestimate the association between P_{aO_2} and publication year. However, P_{aCO_2} is not generally higher in the older studies (to some extent, the contrary association was found), suggesting that this source of error may be acceptably small. Because P_{aO_2} rises and P_{aCO_2} falls with delayed measurement, the $A-aP_{O_2}$ value will be more resistant to this type of error than either of the blood gas tensions (this has been verified by the authors by calculating $A-aP_{O_2}$ for the P_{aO_2} and P_{aCO_2} data reported by Biswas et al. [57]), strengthening the validity of the result that $A-aP_{O_2}$ fell with publication year.

In spite of the methodological challenges of across-studies and across-era comparisons, we maintain that the results of the meta-regression analysis indicate a general improvement in the baseline gas exchange status of asthmatics over the last half-century. The existence of such a trend is also supported by the decreasing prevalence over the years of V/Q “bimodality” patterns in asthma studies using the Multiple Inert Gas Elimination Technique (MIGET) [17,35,59].

In the analysis of gas exchange status in an individual patient, it is very important to take into account factors both intrapulmonary (e.g. V/Q mismatch and diffusion impairment) and extrapulmonary (minute ventilation, cardiac output, oxygen delivery, oxygen consumption and CO_2 production) [17]. Looking only at the P_{aO_2} value, it is not evident how large a ventilatory effort is made by the patient in order to sustain this value; a patient with a very severe V/Q mismatch may partially mitigate the fall in P_{aO_2} by a vigorous hyperpnea (and/or an increase in cardiac output), but such a patient will

be in danger of acute hypoxemia and hypercapnia when fatigue sets in. To recognize such patients, the $A-aP_{O_2}$ is a considerably better parameter than P_{aO_2} , seeing that it indirectly corrects for a raised minute ventilation.

In most clinical cases of very severe asthma, patients will be breathing an oxygen-enriched gas mixture. In this case, absolute P_{aO_2} is obviously an even poorer indicator of the underlying gas exchange impairment, necessitating the use of parameters such as the P_{aO_2}/F_{iO_2} ratio or the F_{iO_2} -adjusted $A-aP_{O_2}$ value to evaluate the extent of the V/Q derangement – though the absolute P_{aO_2} value will of course still be important in ascertaining the adequacy of the oxygen therapy and/or mechanical ventilation.

The interpretation of P_{aO_2} is further complicated by the non-linear shape of the oxygen dissociation curve; a drop of 3 kPa in P_{aO_2} may in terms of oxygen content represent a very small or a catastrophically large decrease, depending on the absolute level of P_{aO_2} .

As indicated in Figure 5, arterial oxygen contents are relatively well preserved for patients able to perform spirometry. However, asthma patients with a P_{aO_2} in the 7.5 kPa range are tethering on the brink of the steep part of the oxygen dissociation curve, further decreases in P_{aO_2} threatening very severe drops in arterial oxygen content.

In clinical practice, pulse oximetry is often used as a measure of oxygenation and has in some hospitals almost supplanted arterial blood sampling. However, the sometimes poor accuracy of pulse oximeters [60] means that arterial blood gases and their derivative parameters – properly analyzed – should still be regarded as the primary tool for diagnosing gas exchange defects in patients with acute asthma, as this represent a potentially life threatening condition.

Conclusions

In studies of patients diagnosed with asthma in their habitual state, mean reported P_{aO_2} and P_{aCO_2} levels were found to have increased and $A-aP_{O_2}$ values decreased since 1967, indicating an improvement over history in the gas exchange status and blood gas levels. In acute asthma studies, mean P_{aO_2} and P_{aCO_2} were associated with mean FEV1% but not with either publication year or patient age. Arterial oxygen contents were relatively well preserved in both the acute and non-acute studies.

Declaration of interest

No external funding sources.

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Appendix

For the computation of C_{aO_2} , the pH-corrected value of P_{aO_2} [61,62] was used as input to Severinghaus' algorithm for calculating oxygen saturation [63], from which C_{aO_2} could be calculated by the well-known equation: $C_{aO_2} = 1.39 \cdot [Hb] \cdot S_{aO_2} + 0.023 \cdot P_{aO_2}$ [64], assuming a hemoglobin concentration of 15 g/dL and P_{aO_2} measured in kPa.

In the cases where pH was not reported by the articles, the pH value was assumed to be 7.42 for the non-acute datasets (the average value for the non-acute datasets that reported pH) and for the acute datasets calculated according to the Henderson–Hasselbalch equation, using the

measured P_{aCO_2} value and assuming an arterial bicarbonate concentration of 24 mEq/L.

For the computation of C_{aCO_2} , the algorithm developed by Douglas et al. [65] was used.

The calculation of these C_{aO_2} and C_{aCO_2} values obviously rests on multiple assumptions that render the values less valid than the blood gas tensions directly measured and reported in the included articles; the contents presented here are mainly to highlight the impact and importance of the non-linearity between blood gas tensions and contents.