Title: Cardiac Asthma in Elderly Patients: Incidence, Clinical Presentation and Outcome.

Authors:

- Stephane Jorge (stéphanejorge@psl.aphp.fr)
- Marie-Helene Becquemin (marie-hélèneBecquemin@psl.aphp.fr)
- Samuel Delerme (samueldelerme@psl.aphp.fr)
- Richard Isnard (RichardIsnard@psl.aphp.fr)
- Mohamed Bennaceur (MohamedBennaceur@psl.aphp.fr)
- Rony Achkar (RonyAchkar@psl.aphp.fr)
- Jacques Boddaert (JacquesBoddaert@psl.aphp.fr)
- Bruno Riou (BrunoRiou@psl.aphp.fr)
- Patrick Ray (patrick.ray@psl.aphp.fr)

Version: 3 Date: 2 May 2007

Author's response to reviews: see over
Dear Editor,

Could you kindly consider for publication in BMC Cardiovascular Disorders, the third version of this original paper entitled: Cardiac Asthma in Elderly Patients: Incidence, Clinical Presentation and Outcome.

Dr Patrick Ray is the corresponding author. The final manuscript has been seen and approved by all authors. The paper has not been published (in part or in full) elsewhere. There is no conflict of interest for any authors in connection with this submitted paper.

Below, a point-by-point response to the Claudio Tantucci comments is given.

Correspondence should be addressed to: Dr P. Ray, Email: patrick.ray@psl.aphp.fr

Looking forward to hearing you

Sincerely yours

Dr Patrick RAY
Cardiac Asthma in Elderly Patients: Incidence, Clinical Presentation and Outcome

Response to reviewers’ comments

Abstract
Line 14 - ..patients experienced more distal airway obstruction:
It would be better: ...patients had greater peripheral airway obstruction:
We made the correction.

Line 16 – “...of vital capacity of 0.99 vs 0.76 liter (p<0.05).”
It should be written: “...of vital capacity of 0.76 vs 0.99 L/s (p<0.05).”
We apologize for this mistake, and made the correction.

Line 17- “...19%) and one year mortality rates (48% vs 43%) were similar.”
It would be better: “...19%) and one year (48% vs 43%) mortality rates were similar.”
We made the correction.

Line 19 – “...and experienced more distal airway obstruction;”
It would be better: “...and experienced greater peripheral airway obstruction.”
We made the correction.

Page 3
Introduction
Last paragraph, line 2 : “during CPE” should be changed in “during CHF”
We made the correction.

Patients and Methods
First paragraph, line 2 : “ED” must be specified. I suppose Emergency Department.
We made the correction.

Page 4
Selection and Participants
Line 5 : “by the experts”. Please, use “by experts” throughout the whole manuscript.
We made the correction throughout the whole manuscript.

Data collection and processing
Line 9 and 10 : “As recommended for confirmed CHF in elderly patient,” should be changed in “As recommended for confirming CHF in elderly patients,”
We made the correction.

Page 5
Line 4 : “as ejection fraction of left ventricle above 50%.” should be changed in “when the ejection fraction of left ventricle was above 50%”.
We made the correction.

Line 6-7 : “,accordingly to orders by physicians in charge.” should be changed in “,accordingly to the orders of the physicians in charge.”
We made the correction.
Line 9: “The following variables were measured” should be changed in “The following indices were measured”.

We made the correction.

“Confirmation of Congestive Heart Failure and BPCO” should be changed in “Confirmation of Congestive Heart Failure and COPD”

We apologize for this mistake, and made the correction.

Page 6
First paragraph
Line 1: “The diagnosis of COPD was made by the experts according to a report…etc. etc.…” should be changed in: “The diagnosis of COPD was made by experts based on reports from a general practitioner, respirologist or medical chart from previous admission, symptoms (chronic cough and sputum production), clinical findings (including clinical signs of distension) and radiographic (chest X-ray and CT scan) findings of thoracic distension (21,22).

We made the correction.

Please, deleted the sentence: “In the COPD group we also included chronic bronchitis and emphysema without broncho-constriction.” It can be better rewritten as follows: “Patients with history of chronic bronchitis and signs of emphysema but without PFT were also included in the COPD group.”

We made the correction.

Outcome measures
Line 2: “followed-up….” could be more clearly written as follows: “followed-up by a phone call three months and one year after discharge.”

We made the correction.

Page 8
Results
First paragraph, Line 4: “patients with CHF; 135 (64%) who were aged 80 years and above.” should be changed in: “patients with CHF of whom 135 (64%) were aged 80 and above.”

We made the correction.

Line 5-6: “…asthma had a higher frequency…..” should be written as: “…asthma had a higher frequency of tobacco use and diagnosis of COPD. They presented with hypercapnic acidemia…..”

We made the correction.

Last pragraph, Line 3: “The median length of stays was 11 (95% confident…..”). Why not interquartiles here?

We made the correction, and use median with interquartiles range.
First paragraph, Line 4: “Cardiac asthma patients…..” This sentence would be clearer as follows: “Cardiac asthma patients exhibited greater peripheral airflow obstruction as shown by the reduced forced expiratory flow-rates at low lung volumes (Table 2)”.

We made the correction.

Discussion
Page 10
Line 3: “Cardiac asthma patients experienced …..” again: “Cardiac asthma patients exhibited greater airflow obstruction in the peripheral airways”.

We made the correction.

Page 11
Second paragraph, line 5: “found the rate of wheezing to be 10-15% of non-elderly patients…”. It would be better: “found the rate of wheezing to be 10-15% in non-elderly patients…..”

We made the correction.

Third paragraph, line 3 and 4: 20% or 22% (as in the Results section); 43 or 42% (as in the Results section)?

We apologize for this mistake, and made the correction.

Last paragraph, Line 1: “The method used in our study to diagnose the cause of CHF and COPD …” should be: “The method used in our study to diagnose CHF and COPD …”

We made the correction.

Page 12
First paragraph, line 1: Please delete “In retrospect…”

We deleted the sentence.

Limitations of our study
Comment
Usually the functional definition of COPD (according to the GOLD guidelines) is a post-bronchodilator FEV1/FVC % lower than 70. The reduction of FEV1 (as % predicted) is used to define the severity of disease.

We agree and made the correction.

Page 13
First paragraph, line 4: “independent of FEV1/FVC the usual index of obstruction in most groups…” could be more precisely written as follows: “independent of FEV1/FVC % the usual index of overt obstruction in most groups…”

We made the correction.

Line 6: “history ….” should be: “history or decrease in FEV1/FVC %, appeared to be more flow limited during tidal expiration than those..”

We made the correction.

Third paragraph, line 3: “wheezing” instead of “broncho-obstruction”
Fourth paragraph, line 3: “…to have an efficiency in cardiac asthma..” should be: “…to be surely effective in cardiac asthma…”.

*We made the correction.*

Page 14
Line 2 and 3. It would be clearer to write as follows “, patients with cardiac asthma still had peripheral airway obstruction, suggesting a more marked airflow reduction if PFTs had been performed at admission to the emergency room.”

*We made the correction.*

Conclusion
Line 3. Again, I would prefer for more clarity to write as follows; “Cardiac asthma patients were more hypercapnic and had greater peripheral airway obstruction. However, in these patients short and long term outcomes were not dissimilar from those of patients with classical CPE.”

*We made the correction.*

Table 1
Page 23
Instead of “RV signs” please write “Signs of RV failure”.

*We made the correction.*

Table 2. Comparison of lung function parameters according to clinical presentation.
AGAIN (!?) FEV1 is expressed in L/s. Please, FEV1 is a volume!

*We apologize for this mistake, and made the correction.*

“PEF rate” could be more simply written as “PEF”.

*We made the correction.*

Figure 1. Immediate and long-term outcomes in either group.
Y-axis label “% of patients” instead of “Percentage”.

*We made the correction.*

Legend : Cardiac asthma (n=75)
Classical CPE (n=137)

*We made the correction with CHF rather than CPE.*

**Quality of written English:** Needs some language corrections before being published.

*We made the correction (i.e. rephrased the sentences) as recommended by the reviewers,*

and the manuscript was already reviewed by a native English-speaking colleague.
Cardiac Asthma in Elderly Patients: Incidence, Clinical Presentation and Outcome

Response to reviewers’ comments

We add a new author (Samuel Delerme), who helped us for reviewing the all statistical analysis, and for the revision of the manuscript for important intellectual content. The manuscript was carefully reviewed by a native English-speaking colleague.

Response to Alain Rudiger’s report

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract:

1) Please mention the significance level of your analysis (p-values).

We did in the abstract.

2) Two hundred and twelve patients (not two)

We apologize for this mistake, and made the correction.

3) Make sure that the order of results is correct, e.g. FEV1: 1.33l vs 1.09l or 1.09 vs 1.33l?

Again, we made the correction in the new version and apologize for this mistake.

Methods:

4) The authors mention Doppler echocardiography measurements (septal E/Ea ratio) in order to assess elevated filling pressures, but I cannot find the corresponding results. Is there a possibility to show echo results in a table?
Unfortunately, these results were not prospectively collected, thus not available. Only the results of the ejection fraction, thus the presence or not of diastolic/systolic function were available.

5) The authors used the median and its 95% confidence interval. This is surprising, as the variability of non-parametric data is usually reported with the range (minimum, maximum) or the interquartile range, whereas the 95% CI is traditionally used for hazard and odds ratios.

We agree. In the second version we reported the non-parametric data as median interquartile range (for BNP and NT-proBNP levels, creatinine clearance and results in table 2), see also response to Claudio Tantucci’s comments.

6) Please clarify the way you performed your multivariable analysis, e.g.: A multivariable analysis was performed in order to assess predictors of cardiac asthma. Only variables with a p value <0.1 in the univariate analysis were included in this test.

We made the correction (see Primary data analysis section).

Abstract:

7) Conclusion: Patients with cardiac asthma (no comma) represent (no s)

8) Please re-phrase the last sentence.

Methods/results:
9) 12 lead (not led) electrocardiogram

10) flow volume loop (s) were performed in several (how many?) patients

11) Skip “as suspected” in the result section

Table 1

12) What do you mean with arteritis? Arteriosclerosis or inflammation of the arteries as a result of infection or autoimmune disease?

We change to peripheral arterial disease (in abstract and table 1).

13) Replace “RV signs” by “Signs of RV failure”

14) Creatinine clearance (and not clairance).

The manuscript was carefully reviewed by a native English-speaking colleague.
Response to Claudio Tantucci's report

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The study is interesting looking at a neglect aspect of acute ventricular failure in a quite large cohort of elderly patients (n=212) where 75% had Doppler-echocardiography and 50% had NT-proBNP levels measured. The above mentioned aims are fulfilled even though they should be more precisely stated in the Introduction section.

We agree, and rephrased the last sentence of the Introduction: “Therefore, the objectives of this study were to 1) define the incidence of wheezing, though to reflect the occurrence of bronco-obstruction (“cardiac asthma”), during CPE, and 2) compare the characteristics (clinical and functional), and prognosis of patients with cardiac asthma to that of classical CPE (non wheezing CPE) in patients aged 65 years and over. “

What does it mean past history of COPD? COPD is a functional syndrome and its diagnosis is made by spirometry showing chronic airflow obstruction not or scarcely reversible. Do they have the previous PFT of the patients to make diagnosis or they report just symptoms suggestive of chronic bronchitis and/or emphysema. This point must be carefully addressed by the Authors.

To define past medical history of COPD, we used the conclusion (report/letter) of the family doctor, the respirologist, and the medical chart (spirometry) from the previous hospitalization if available, the clinical and radiographic findings. Unfortunately, (when done) these previous spirometry are not available for report in the manuscript. We are aware that the diagnosis is usually confirmed by spirometry: i.e. presence of a postbronchodilator $\text{FEV}_1 < 80\%$ of the predicted value in combination with an $\text{FEV}_1/\text{FVC} < 70\%$. We agree that the definition used in the study is frail, because
sometimes the definition were based only upon clinical and radiographic signs [Reference 29 added, Pauwels RA, Buist AS, Calverley PMA, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1256–1276]. Thus, we agree that it is possible that the diagnosis of COPD with broncho-constriction was sometimes overestimated in our study (chronic bronchitis/emphysema or mild moderate rather than moderate or severe COPD). However, we think that if the diagnosis of COPD was overestimated, it should have been affected both groups (cardiac asthma and classical CPE), thus this should have not change the results of the pulmonary function’s differences observed between two groups. However, it could explain why the FEV1/FVC % was almost normal in the cardiac asthma group (see below). We clarified this in the Limitations section.

Which were the criteria to perform or not perform PFT? Chance? Decision of the physician who took care of the patient? Symptoms? Previous history? The Authors should comment this point and convince the reader that there is no bias because of it.

Fortunately, the percentages of patients who had PFT are quite similar in those with (35%) and without (30%) broncho-obstruction at the admission and this helps.

As stated in our Patients and Method section (“Pulmonary function tests (PFTs) including measurement of lung volumes, and flow-volume loop were performed in patients, accordingly to physicians in charge”), the routine care of the patient was not modified. Thus, PFTs were done only after the physician who took care of the patient decided to order them, and sometimes because the patients were too sick and for logistic issues, the PFTs could not be performed or incompletely. Furthermore, in most of the patients, we could not performed pletysmography/lung volumes measurement or it was
not ordered by the physician. We agree that TLC (that needs Residual Volume measurement) is lacking to confirm restrictive deficit and that our conclusions are based only upon normal FEV/VC ratio. We made some changes in the Method section the text in the Limitations Section to clarify this point.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The instruments used to obtain echocardiographic measurements and to perform pulmonary function tests and blood gas analysis should be declared.

We added these informations in the text (Method section).

What does it mean thoracic distension? Presence of radiographic signs of pulmonary hyperinflation, enlargement of costal spaces, horizontalization of the ribs, flat diaphragm?

We detailed in the text (Patients and Method section/ Confirmation of Congestive Heart Failure) the definition that we used for radiological signs of pulmonary distension and for COPD (page 6, second paragraph).

Table 1
The measure of smoking weight is wrong (pack/years is the right one!). The number of patients with “cardiac asthma” who used inhaled bronchodilators is lacking.

We apologize for these mistakes.

Table 2 –
It almost unforgivable express FEV1 in L/s?? (also in the text!) FEV1/FVC ratio in L?? and FEF25-75% in L??
We also apologize for these unforgivable mistakes, and express the values with median interquartile 25-75% rather than median [95%CI].

The numbers of PEF rate (L/min) seem wrong. We added a new line with absolute values of PEF. It should be easier for the reader to have also the maximal expiratory flow-rates expressed as mean ± SD and not only as median and IC95%.

We changed the report of theses results, as also recommended by the reviewer.

What are the predicted used for these parameters?

We added a reference [17].

Based on the functional parameters reported in Table 2 it is not possible to conclude that a restrictive defect is present without measuring TLC. This can be only suggested by the normal FEV1/FVC % predicted with decrease in the FVC and FEV1 % predicted. This has been correctly underlined in the text (last paragraph in the Results section) by the Authors who, however, cited VC (?) that is not given in Table 2.

Moreover, it is really surprising that in a subgroup of patients (cardiac asthma) with a 45% of “past-history of COPD” the PFT performed in more than one third of them showed no obstructive ventilatory defect (i.e: FEV1/FVC% predicted less than lower 5th percentile of normal value).

In order to better understand the functional characteristics of these two subgroups of patients it would have been really useful to measure the Residual Volume (increased in the cardiac asthma patients? And reduced in the others?).

Have the Authors some clues on lung volumes in the patients who underwent PFT?
See above. Unfortunately, because the routine care of the patient was not modified by the study, physicians’ in charge did not specifically ordered lung volumes measurement; thus we did not have enough values to report. This explains why we can not report residual volume ands TLC. As stated above, we added a new sentence to clarify this, and discuss this point in the Limitations of the study Section.

DISCUSSION

(Second page)

Line 3 - The sentence starting with “There is also a large….” and the following starting with “Furthermore, past or current….”must be omitted because irrelevant.

We deleted these 2 phrases.

Line 13 – The right sentence should be: “Our study suggests that emergency physicians should focus on past diagnosis of COPD in patients with CHF and cardiac asthma, especially in those with hypercapnia”.

We made the change, as recommended.

(third page)

Line 3 – The PFT performed show a greater peripheral airway obstruction in “cardiac asthma” patients and therefore do not support, on average, a prevalent “history” of COPD, as claimed by the Authors.

We agree, and deleted this sentence.

LIMITATIONS OF OUR STUDY

(Second page)
We made the change.

English needs to be carefully revised.

The manuscript was carefully reviewed by a native English-speaking colleague.

The possible merit of this observational study is to represent a rationale to plan a prospective study aiming to compare the C-PAP vs BI-PAP effectiveness in the treatment of these two subgroups of patients with (severe) cardiogenic pulmonary edema with the hypothesis (to reject or not) that BI-PAP can have better short-term outcomes in those with “cardiac asthma”.

We agree, and we also briefly suggest that usefulness of B2-agonists should also be evaluated in cardiac asthma, based on these and previous findings.