Author's response to reviews

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

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Author's response to reviews: see over
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Editor In Chief

BMC Cardiovascular Disorders

Dear Editor,

Could you kindly consider for publication in BMC Cardiovascular Disorders, the second 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 comments is given.

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Looking forward to hearing you

Sincerely yours

Dr Patrick RAY
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).

Discretionary Revisions (which the author can choose to ignore)

We corrected all these minor mistakes pointed by the reviewer, in the second version.

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 FEV₁ < 80% of the predicted value in combination with an FEV₁/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 over-
estimated 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 plethysmography/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 these 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)
The sentence should be: Although bronchodilators were given in only one third…

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.