Title: Tinnitus in elderly patients and prognosis of mild-to-moderate congestive heart failure: a cross-sectional study with a long-term extension of the clinical follow-up

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Author's response to reviews: see over
Editorial requests:

1) Please include a statement of Ethics/consent: Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html). A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate. A: A statement of Ethics/Consent has been added in the method section.

2) Informed consent must also be documented. A: All participants before the inclusion in the study have signed the informed consent. This has also been added to the Method section.

Reviewer 1: Pietro Di Pasquale

I think that the affirmation of authors of a relation between tinnitus and NYHA class is not supported by performed study.

1) Usually in HF patients the tinnitus is determined by diuretic use with their otohoxic effects mediated by RAAS activation and reduction of effective plasmatic volume. In fact in other study (with high diuretic dose) is reported none tinnitus in patients with effective plasmatic volume maintained by a normal sodium diet.
2) The higher functional class usually is related with a greater dose of diuretic. In their study the author should insert diuretic dose and on this base reivewer the conclusion and modify results and discussion.
3) The otothoxic effect of diuretics has been described for very high doses and mainly for drugs as Bumethanide and Ethacrinic acid. We included in the study only patients in NYHA class ≤ III treated with only Furosemide or Torasemide at doses < 250 mg/day with the exclusion of more severe patients who usually deserve higher doses or a combination of different diuretic compounds. No significant differences has been observed in serum sodium levels between patients with or without tinnitus while any hypothetic difference in circulating volume in response to diuretic treatment would further strengthen the possibility of a negative relationship between heart failure and inner ear circulation. A short statement on this point has been added to the discussion.

3) Could the author to explain the high use of FANS in tinnitus positive? Usually the FANS are forbidden in HF patients, this finding for my opinion is an important bias. A: The use of NSAID's is strongly discouraged but not forbidden by guidelines in patients with CHF since the presence of co-morbidities sometimes requires an antiinflammatory treatment. In the literature, the use of NSAID's has never been definitely associated with the presence of tinnitus and in many of our patients (over 85%) the drugs has not been taken on a regular basis but as single shot treatment to relieve acute symptoms including neck pain or discomfort often considered by the patient as responsible for tinnitus. This also exclude the possibility that NSAID's are responsible for the differences in LV function since they persist unchanged and related to tinnitus even after exclusion of patients undergoing NSAID's treatment. This has now better explained in the method section.

3.1) THE BNP and EF data are related with functional class and appears difficult to relate this result with tinnitus rate. A: We definitely agree with this observation since one of the purposes of the study was to investigate if the presence of tinnitus was associated with multiple evidence of LV dysfunction according to the hypothesis that the systemic hemodynamic failure can promote or enhance the acoustic symptoms.

3.2) It is corrected to claim that hypotension is related with tinnitus, but it has to be explained because this group (higher functional classss) had hypotension. does it depend by treatment? A: As expected an higher functional class can be reasonably associated with lower BP values and can contribute to the higher rate of tinnitus observed in these patients. This can result from the combination of the effects of the baseline hemodynamic derangement and those of drug treatment and we agree with the reviewer.

4) Would be useful to know renal function and laboratory parameters as serum sodium. A: The data about renal function and serum sodium and levels have been added.
5) For my opinion is not corrected the conclusion of authors claiming a relation between tinnitus and functional class, and to suggest the tinnitus as marker of HF worsening. Study claim that the CHF class is related with tinnitus, after having studied in observational study a cohort of patients with HF (I-III class), in addition the authors claim also that patients with tinnitus were more hypotensive. I do not think that this affirmation could be affirmed, because the tinnitus in CHF patients is determined mostly by diuretic treatment responsible of RAAS activation and of Plasma volume effective diuretic dependent. A: If we have correctly understood, the key point is that since tinnitus can be secondary to the hemodynamic and neurohumoral derangement of heart failure, it is hard to support a direct relationship between changes in the characteristics of tinnitus and worsening of heart failure. However this is only an observational study that, for the first time, has provided the evidence that the severity of heart decompensation can be related to an impairment of a neurosensory function that can be perceived by the patients and “might” be shortly related to worsening of heart failure. The assessment of the mechanisms responsible for the onset of tinnitus in our patients with CHF is far from the purposes of the study, while the quantification of the prospective impact of the onset or worsening of tinnitus in patients with HF is currently investigated with an appropriate clinical design. A clarifying statement has been added to discussion.

6) In their study the authors do not report diuretic dose, and in addition an important rate of patients with tinnitus were receiving NSAID, which by prostaglandin inhibition determines a reduction of renal flow, contributing to heart failure worsening. A: We thank you very much for this comment. In fact, actually we have better described the patient selection in the method section. So, we excluded patients with stage 3-5 chronic renal failure, hypoproteinemia, recent increase in diuretic dosage (less than 30 days) or diuretic dosage change during the follow-up, concomitant use of other ototoxic drugs (i.e. aminoglycosides), continuous use of fully dosed non steroidal antiinflammatory drugs (NSAID). NSAID use was considered as acceptable if limited to less than one dose per week and with a limited dosage (i.e.: paracetamol 1000 mg, acetylsalicylate 500 mg). All this to minimize the drug-tinnitus interaction. Moreover, the statistical analysis has been repeated by NSAID use, confirming the results reported for the global population either in NSAID users and non users.

7) In conclusion, it is not corrected to affirm that NYHA class is correlated with tinnitus, and that tinnitus could be inserted as a marker of HF worsening. Further, it is clear that patients with worst HF needed more diuretic dose. A: see answer to point 5.

Reviewer 2: Berthold Langguth

In this study the authors investigated the relationship between tinnitus and congestive heart failure (CHF). They found that among patients with CHF the presence of tinnitus was associated with reduced blood pressure, reduced left ventricular function, increased BNP, and increased use of diuretics, angiotensin receptor blockers and NSAIDs. Most important, combined one-year mortality and hospitalization was significantly higher in patients with tinnitus. These data are new, may contribute to a better understanding of the pathophysiology of both diseases and they are clinically relevant.

Major compulsory revisions:

1. The main critic from my side is that the authors interpreted their results in the sense that the data support the assumption that tinnitus is an indicator of insufficient inner ear blood perfusion. This assumption is not pathophysiologically supported, at least not for the majority of tinnitus cases. Also from the reported associations no causal relationship can be deducted. Also the interpretation that onset of tinnitus can be considered as an indicator of decline in cardiac performance is not sufficiently supported by the data. The main observation (more severe CHF and poorer outcome in tinnitus patients) is in my opinion much more likely to be mediated by tinnitus related distress. The possibility that the autonomic nervous system is involved in mediating the relationship, is only shortly mentioned in the last paragraph of the discussion. Indicators for chronically increased stress levels (Hebert 2004, 2007, 2010) and reduced heart rate variability (Datcov E et al. 1999) have been reported among tinnitus patients. Also tinnitus is frequently associated with depression which is known to be a negative predictor for CHF (Jiang et al. Circulation 2004). Since stress is also known as a risk factor for the development of tinnitus, the higher tinnitus prevalence among CHF patients in advanced NYHA classes could be explained by higher stress levels in these patient groups.
Chronic stress and depression as a possible link between tinnitus and CHF should be proposed as a possible and also probable explanation for the presented data. Unfortunately no information about tinnitus distress or tinnitus severity is given. This information would be extremely helpful for investigating the role of tinnitus related stress on CHF. A: First of all we thank very much the Reviewer for is careful review of the manuscript and for giving some very interesting suggestions that significantly contribute to the understanding of such a complex and brand new clinical issue. The first point is that since tinnitus can be secondary to the hemodynamic and neurohumoral derangement of heart failure, it is hard to support a direct relationship between changes in the characteristics of tinnitus and worsening of heart failure. However this is only an observational study that, for the first time, has provided the evidence that the severity of heart decompensation can be related to an impairment of a neurosensorial function that can be perceived by the patients and “might” be shortly related to worsening of heart failure. The assessment of the mechanisms responsible for the onset of tinnitus in our patients with CHF is far from the purposes of the study, while the quantification of the prospective impact of the onset or worsening of tinnitus in patients with HF is currently investigated with an appropriate clinical design (a related statement has been added to the manuscript). The second point is the role of distress, which is more important in patients where tinnitus is the major problem and can led to a variable degree of distress. In patients with CHF the negative impact of heart failure over quality of life is definitely the most important (the worst among chronic diseases, Stewart F et al, JAMA 1999) and it is difficult to hypothesize that the onset of audiologic symptoms can be associated with a condition of distress leading to an negative impact on clinical outcome. I agree with the Reviewer that the activation of the sympathetic nervous system can be involved and some of the paper quoted have been taken into consideration but again we would like to emphasize that the main finding of our paper is the observation that tinnitus might be one of the indirect signs of heart failure syndrome and can be easily perceived by the patients and increase the level of warning against the other evidence of heart decompensation. As far as the definition of the prospective role of these findings see few lines above. The third point is the role of depression, which is a typical feature of most of the patients with CHF (Heart Fail Clin. 2011;7(1):1-10.). We assess the psychic conditions in any of our patient as a mandatory procedure of our protocol of comprehensive clinical assessment and we were unable to demonstrate significant differences in the rate of depressive symptoms between patients with and without tinnitus (47% vs. 44%, p=NS) A clarifying statement has been added to the discussion.

2. Also other possible explanations for reported associations are not mentioned. So the relationship between NSAIDs and tinnitus could be explained by the well known induction of tinnitus by salicylate. Diuretics are also known to interfere with inner ear function and such a relationship cannot be excluded for angiotensin receptor blockers. A: The survival analysis was repeated by ARBs and NSAIDs use and the results was similar in users and non users. Anyway, we better explained in the method section that the large use of NSAIDs at high dose was an exclusion criteria from the study. In addition the dose of ASA was, as expected, between 100 and 325 mg/day (the risk of tinnitus has been demonstrated for dosages of ASA > 1 gr/day) and superimposable in both populations of patients, patients treated with very high doses of diuretics have been excluded according to severity of CHF (we included only NYHA I-III) and none of them have been treated with the most dangerous diuretics as bumetanide or ethacrinic acid. As far as ARB’s we have published a paper on their effects in hypertension where they did not affect or reduced the rate of tinnitus (19).

3. in Table 2 there seem to be wrong data (Warfarin treatment in the “tinnitus no” group, Beta blocker treatment in the “tinnitus yes” and “tinnitus no” group. Also the column “No” should be removed since it gives no additional information. A: The figures in table 2 have been corrected and the “No” column has been removed.

Minor essential revisions:
1. Background: the prevalence rates should be referenced, also the statement about reduced blood flow in the ear as trigger for tinnitus should either be removed or referenced. A: Both statements have been referenced in the background session, even whether the information about the reduced blood flow and tinnitus is still under evaluation. No reference has been indicated under the “Background” section of the abstract that simply summarizes the main issues of the background hypothesis.
2. Statistical analysis: 4th line: remove (AU: as meant?) A: Comment removed

3. Results and discussion: 10th line: As expected… sentence should be corrected. A: Sentence corrected

Reviewer 3: Dirk De Ridder
Major Compulsory Revisions
1. the authors analyse a lot of parameters but do not correct for multiple comparisons A: We thank the Reviewer for his comments that are more than useful for an improvement of the manuscript. We have discussed the statistical issue with our statisticians and our shared point of view is as follows. Basically the analysis does not include many formally different variables since most of them are strictly correlated and we have decided to include many of them in the analysis just to confirm the relationship between the presence of tinnitus and the many parameters related to heart failure. The only prognostic information has been provided after adjustment for the most important variables known to influence prognosis and according to the results of the logistic regression analysis as described in the manuscript. The reason why we decided to exclude the correction for multiple comparisons was that for the main outcome we have always based the analysis only on the two main populations of patients while we have considered that any further analysis involving the different determinants of the presence/absence of tinnitus would have “a priori” demonstrate some degree of interaction because of the interrelated nature of the classifying variables taken into consideration. Every variable taken into consideration represents a different approach to the diagnosis of CHF (clinical, echo and bio-humoral) and we would like to achieve information about the possibility that each of them, separately, were correlated to the presence of tinnitus. The primary aim of the study was to provide a reasonable evidence that we can observe some degree of relationship between the severity of heart failure and the presence or worsening of a symptom that can be easily perceived by the patient. The meaning of such observation in term of prospective clinical implications is currently under investigation.

2. in the same sense, the authors correlate tinnitus to hemodynamic changes in circulation of the inner ear caused by CHF. However, as the study was performed in an elderly population, the tinnitus could also be the result of sensorineural hearing loss due to presbyacusis. How can the authors differentiate between CHF related and presbyacusis related hearing loss? This has to be controlled for. Since the authors have audiometric data, it is possible to do so. A: The concern raised by the Reviewer is very important and the issue has been extensively discussed during the preparation of the protocol. Actually, all patients underwent a clinical otological and audiological examination to rule out identifiable causes of tinnitus and no relationship has been found in the distribution of subjects with detectable hearing impairment. In particular no differences have been found in the percentage of patients where tinnitus and hearing loss were combined and the great majority of patients complained tinnitus without hearing loss. This has been added to the Results section

3. one of the claims is that "the patients with tinnitus showed a greater use of angiotensin receptor blockers and diuretics, which probably reflect the larger proportion of patients with more severe NYHA functional class and might explain the lower BP values. Interestingly, tinnitus was also associated with greater use of NSAID, which could partially explain the differences ...". All these medications can have tinnitus as a side effect. How can the authors ascertain that the tinnitus is due to congestive heart failure and not to side effects of these drugs? A: We thank you very much for this comment. In fact, actually we have better described the patient selection in the method section. So, we excluded patients with stage 3-5 chronic renal failure, hypoproteinemia, recent increase in diuretic dosage (less than 30 days) or diuretic dosage change during the follow-up, concomitant use of other ototoxic drugs (i.e. aminoglycosidics), continuous use of fully dosed non steroidal antiinflammatory drugs (NSAID). NSAID use was considered as acceptable if limited to less than one dose per week and with a limited dosage (i.e.: paracetamol 1000 mg, acetilsalicylate 500 mg). All this to minimize the drug-tinnitus interaction. Moreover, the statistical analysis has been repeated by NSAID use, confirming the results reported for the global population either in NSAID users and non users.

Minor Essential Revisions
On page 8 I imagine that "heart rate of 0.61" should be "hazard ratio of 0.61" A: Of course! The mistake has actually been corrected.