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Clinical Trials Study

Catheter ablation for atrial fibrillation in a subset of patients with concomitant hypertension

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Response to Reviewer # 1

Reviewer: The concept underlying the whole paper, i.e. the patients who have no structural heart disease and a normal left atrium have probably a neurogenic form of hypertension, is not clear to the reader. In other words, it is not clear why the patient population on sinus rhythm at 1 year is subdivided in normal and dilated left atrium. Although this is an hypothesis, which seems to be confirmed by this observation, it should be clearly explained in the introduction.

Response: Thank you for your insightful comment. Accordingly, we have expanded the introduction (sentences underlined) in which we have provided further details on the context in which this study was formulated as well as the rationale for the hypothesis that we put forth at the end of the introduction. The basis for subdividing the patients was the data described in the Results section in which the left atrial dimension measurements manifested as distinguishing biomarkers in patients who responded to reduction of HTN and those that were non-responders.

Reviewer: In the patient screening for catheter ablation of atrial fibrillation the echocardiographic volume or the left atrial area rather than the diameter are taken. Moreover, it is not clear if the authors refer to the antero-posterior or transverse left atrial diameter.

Response: the following sentence has been added to the Methods section, Echocardiographic studies were accomplished transthoracically which provided an anterior-posterior measurement of the left atrial dimension.

Reviewer: The second part of the introduction presents data that are later presented in the methods and therefore is redundant

Response: we have deleted the redundant data from the introduction. That information is now in the first sentence of the Methods Section. Also the first paragraph of the Methods provides a brief description of the ablation procedures. (changes are underlined).

Reviewer: The first paragraph of the results (patient medications) can be summarized in a table

Response: Table 1 now indicates the number of patient taking the various anti-hypertensive drugs before and after the catheter ablation procedure in the 33 patients in sinus rhythm after 1 year. The description of the medications has been abridged in the Results section

Reviewer: The meaning of the asterisks in figure 1 is not explained (statistical significance)

Response: Figures 1 and 2 have been deleted in accordance with the reviewer's suggestion (see below). The statistical significances have been shown in Table 2.

Reviewer: The second part of table 1 reports the same data shown in figure 1 and 2.

Response: Figures 1 and 2 have been deleted since these data are provided in Tables 1 and 2

Reviewer: The last phrase in the abstract should be substituted by the statement of the hypothesis

Response: As suggested by the reviewer, the last sentence of the abstract now reads, "We hypothesize that those with neurogenic HTN (Group1) responded with a reduction in SBP after PVI and GP ablation due to the reduction in autonomic hyperactivity."

Response to Reviewer # 2

Reviewer: Is this a retrospective study? Very low number of patients studied in both groups 12 with normal left atrial dimensions (Group 1), and 21 with enlarged left atria (Group 2)]. Therefore, these findings have to be interpreted with great caution. This has to be reported

Response: This was a retrospective study based on a chart review of 119 patients as mentioned in the abstract and text (Methods). The 119 patients were those who had complete data at all follow-up periods. The 33 patients were those who fit the major inclusion criteria and who responded successfully to catheter ablation, were in sinus rhythm at the end of 1 year of follow-up. The low numbers as a caveat for interpretation of the data has now been added to the Limitation section, "A distinct limitation of this study is the small numbers of patients in groups 1 and 2 which requires that the findings be interpreted with caution." Also at the end of the Conclusion section, "Further studies in patients with hypertension and AF undergoing PVI and GP ablation, using a

prospective protocol and a larger sample size may be required to achieve more definitive results. “

Reviewer: Heterogeneous population with respect to drug medication?

Response: We have added a sentence in the discussion section indicating the heterogeneous distribution of drugs across patients in both groups. This is detailed in the newly added Table 1.

Reviewer: Page 3, Introduction: please modify the last paragraph and focus only on the aim of your study. The same details are provided at the methods.

Response: Accordingly, we have modified the last paragraph of the introduction, “Since 2004 the procedure for catheter ablation in patients with AF in our clinical electrophysiological practice has consisted of PVI plus ablation of hyperactive autonomic nerve clusters called ganglionated plexi (GP) at the PV-atrial junctions. This combined procedure has been shown to increase the success rates for maintaining sinus rhythm compared to PVI alone^(15, 16). It was in this context that we hypothesized that a subset of our patients presenting with HTN and AF would manifest the neurogenic form of HTN based on hyperactivity of the intrinsic cardiac autonomic nervous system. Furthermore, based on the previous report⁽¹⁴⁾ we surmised that the patients with the neurogenic and drug resistant form of HTN would respond with a significant blood pressure reduction due to the decrease of autonomic hyperactivity caused by PVI plus GP ablation. “ (Changes are underlined).

Reviewer: Page 4, Results: The authors report that “Significant interaction was found between follow up periods and the study group ($p=0.004$)”. What do you mean? Which study group

Response: We have deleted this sentence.

Reviewer: Provide details regarding the ablation procedure

Response: The following has been added to the beginning of the Methods section: The procedure for catheter ablation has been previously described in detail⁽¹⁷⁾. Briefly, General anesthesia was administered in all patients. Localization of GP was obtained by application of high-frequency stimulation to each GP (HFS: 20 Hz, 10–150 V and pulse width 1–10 ms; S-88 stimulator, Grass Instruments Division, Astro Med Inc., Warwick, RI, USA). Within 5 seconds of HFS, a marked parasympathetic response is elicited, which is arbitrarily defined as a $\geq 50\%$ increase in mean R-R interval during AF. Each parasympathetic response is verified by both hypotension and high grade AV block. For GP ablation, radiofrequency (RF) current is delivered at 25–35 W for 40–60 seconds during saline irrigation at each site of positive parasympathetic

response to HFS. RF applications are repeated until the parasympathetic response to HFS is eliminated.

After the 4 left atrial GP are ablated, pulmonary vein antrum isolation is performed. The endpoint of PV antrum isolation is elimination of potentials within the isolated antral area. As antrum isolation typically transects the ARGV and SLGP areas, we use the ARGV and SLGP ablation sites as the starting points for right and left antrum isolation, respectively.

Response to reviewer #3

Reviewer: These observations are interesting, and could be helpful in clinic study.

Response: Thank you for your comments. We have added the following to the conclusion section. Last sentence, "Further studies in patients with hypertension and AF undergoing PVI and GP ablation, using a prospective protocol and a larger sample size, may be required to achieve more definitive results."