Effectiveness of *Moxonidine* to Reduce Atrial Fibrillation Burden in Hypertensive Patients

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There is substantial evidence that the autonomic system plays an important part in the pathogenesis of atrial fibrillation (AF). It appears that, although some patients have a preponderantly sympathetic or vagal overactivation leading to AF, a combined sympathovagal drive is most commonly responsible for AF triggering. The purpose of this hypothesis-generating study was to test whether moxonidine, a centrally acting sympathoinhibitory agent, on top of optimal antihypertensive treatment, can lead to a decrease in AF burden in hypertensive patients with paroxysmal AF. This was a prospective, double-blind, 1-group, crossover study. Hypertensive patients with paroxysmal AF sequentially received treatment with placebo and moxonidine for two 6-week periods, respectively. The change in AF burden (measured as minutes of AF per day in three 48-hour Holter recordings) between the 2 treatment periods was the primary outcome measure. Fifty-six patients (median age 63.5 years, 35 men) were included. During moxonidine treatment, AF burden was reduced from 28.0 min/day (interquartile range [IQR] 15.0 to 57.8) to 16.5 min/day (IQR 4.0 to 36.3; $p < 0.01$). European Heart Rhythm Association symptom severity class decreased from a median of 2.0 (IQR 1.0 to 2.0) to 1.0 (IQR 1.0 to 2.0; $p = 0.01$). Systolic blood pressure levels were similar in the 2 treatment periods, whereas diastolic blood pressure was lower ($p < 0.01$) during moxonidine treatment. The most frequent complaint was dry mouth (28.6%). No serious adverse events were recorded. In conclusion, treatment with moxonidine, a centrally acting sympathoinhibitory agent, results in reduction of AF burden and alleviation of AF-related symptoms in hypertensive patients with paroxysmal AF. **(Am J Cardiol 2013;112:684−687)**

There is substantial evidence that the autonomic system plays an important part in the pathogenesis of atrial fibrillation (AF).[1] Although some patients have a preponderantly sympathetic or vagal overactivity leading to AF, a combined sympathovagal activation is most commonly responsible for AF triggering.[2−4] Additional evidence that modulation of the autonomic system and its sympathetic limb in particular, can be of therapeutic interest in AF has been provided by experimental[5] and clinical[6] studies, which showed that renal sympathetic denervation (an intervention that results in suppression of central sympathetic tone) leads to a significant reduction in atrial vulnerability to AF induction and postablation AF recurrence, respectively. The present study tests the hypothesis that modulation of central nervous sympathetic activation by administration of moxonidine, a centrally acting sympathoinhibitory agent, can lead to a decrease in AF burden in hypertensive patients with paroxysmal AF.

Methods

This was a prospective, double-blinded, single-group, crossover study. The study population included hypertensive patients with symptomatic paroxysmal AF. At least 5 minutes of AF per 24 hours in the baseline Holter recording were required for a patient to be considered eligible. Hypertension was defined, for the purposes of the present study, as known treated hypertension or as newly diagnosed hypertension (arterial pressure >140/90 mm Hg in >2 measurements on 2 different days). Exclusion criteria were age <25 or >80 years, left atrial volume >80 ml, known hypersensitivity to moxonidine, sick sinus syndrome or sinoatrial block or conduction abnormalities, bradycardia (<50 beats/min at rest), estimated glomerular filtration rate <30 ml/min/1.73 m^2, history of angioneurotic edema, impaired left ventricular function (ejection fraction <0.40), stable or unstable angina pectoris, intermittent claudication or known peripheral artery disease, Parkinson's disease, epileptic disorders, glaucoma, history of depression, pregnancy or lactation, and inability or unwillingness to adhere to standard treatment or to provide consent. The protocol

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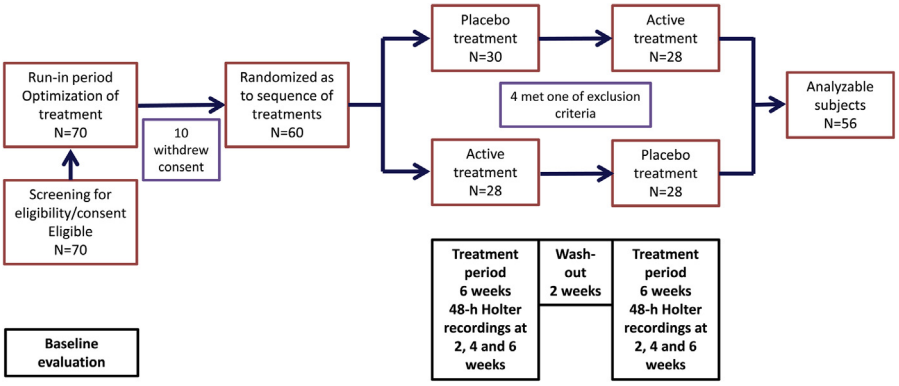

Figure 1. Study flow chart.

Table 1
Patient baseline characteristics (n = 56)

Feature	Value
Age (yrs)	63.5 (61.0–68.8)
Men	35 (63)
Body mass index (kg/m^2)	26.0 (24.3–30.0)
Smokers	22 (39)
Hypertension (by history)	40 (71)
Newly diagnosed hypertension	16 (29)
Diabetes mellitus	17 (30)
AF duration (yrs)	3.8 (1.6–7)
Left ventricular ejection fraction (%)	55.0 (49.3–60.0)
Left atrial volume (ml)	62 (57–68)
Systolic blood pressure (mm Hg)	143 (136–148)
Diastolic blood pressure (mm Hg)	83 (76–88)
European Heart Rhythm Association class	2.0 (1.0–2.0)
AF burden (min/day)	28.0 (12.5–51.8)
AF episodes (no/day)	3 (2–3)
17-item Hamilton depression rating scale score	6.0 (4.0–7.8)
Treatment	
β Blocker	24 (43)
Angiotensin-converting enzyme inhibitor/ Angiotensin receptor blocker	44 (79)
Calcium channel blocker	36 (64)
Antiarrhythmic treatment	28 (50)
Amiodarone	8 (14)
Propafenone	10 (18)
Sotalol	10 (18)

Continuous variables are represented as median (interquartile range). Categorical ones are summarized as count (percentage).

was approved by the Institutional Review Board. All patients provided informed consent. Eligible patients who provided consent were entered in a run-in period of 2 months during which previous treatment was stabilized and antihypertensive treatment was optimized. After the run-in phase, all patients received the study treatment for two 6-week periods: 1 period of active treatment with moxonidine and 1 period of placebo treatment. The patients were randomized as to the sequence of treatments (Figure 1). Moxonidine was started at a dosage of 0.2 mg/day and was increased to 0.4 mg/day after 3 weeks, if well tolerated. If hypotension ensued, it was managed by reducing the doses of other antihypertensives.

Patient clinical details, symptom severity, and laboratory and echocardiographic parameters were recorded at baseline and on each subsequent visit (visits were scheduled at the end of the second, fourth, and sixth week of each treatment period). Forty-eight-hour Holter recordings were obtained at these time points. The 17-item Hamilton depression rating scale was administered in the last visit of each treatment period.

Patients who failed to present for >1 Holter recordings during each treatment period or who had their antiarrhythmic treatment changed during the study treatment periods were excluded from the analysis. Patient adherence to treatment was checked with pill counts of the drug containers returned by the patients on each study visit. All patients received anticoagulation treatment according to the current guidelines.

The primary outcome measure was AF burden, defined as the minutes of AF per day in the three 48-hour Holter recordings in each treatment phase. Secondary outcome measures were the number of AF episodes per day (AF runs had to be separated by >1 minute of sinus rhythm to be considered as separate episodes of AF), European Heart Rhythm Association symptom severity class, and the 17-item Hamilton depression rating scale score. Monitoring of adverse events focused on xerostomia, gastrointestinal manifestations, headaches, depressive symptoms, and sleep disorders. Procedure implementation and data entry were carried out by researchers who were blinded as to the current patient treatment assignment.

Because of the relatively small sample size, exclusively nonparametric methods were used for analysis. Continuous variables were expressed as median (interquartile range) and compared using nonparametric tests (Wilcoxon's and Mann-Whitney U test for pairwise and unpaired comparisons, respectively). Categorical variables were expressed as percentages and counts and compared using Fisher's exact test. Spearman's correlation index was used to test for correlations between continuous variables. SPSS 17 software package was used (SPSS Inc., Chicago, Illinois). p Values <0.05 (2 sided) were considered as indicative of statistical significance.

Results

Patient characteristics are listed in Table 1. Most patients had known treated hypertension (71%), whereas the rest were found to be hypertensive as part of the screening

Table 2
Differences in outcome parameters between treatment periods (active vs placebo). The p values correspond to the paired comparisons between treatments (Wilcoxon's signed rank test)

Outcome Parameter	Placebo Treatment Period (n = 56)	Moxonidine Treatment Period (n = 56)	p
AF burden (min/day)	28.0 (15.0−57.8)	16.5 (4.0−36.3)	<0.01
AF episodes (n/day)	3 (2−3)	1 (1−3)	<0.01
European Heart Rhythm Association class	2.0 (1.0−2.0)	1.0 (1.0−2.0)	0.01
Systolic blood pressure (mm Hg)	142 (139−148)	142 (137−149)	0.61
Diastolic blood pressure (mm Hg)	82 (74−87)	78 (71−82)	<0.01
17-item Hamilton depression rating scale score	6.0 (4.0−7.0)	5.5 (4.0−7.0)	0.41

All variables are represented as median (interquartile range).

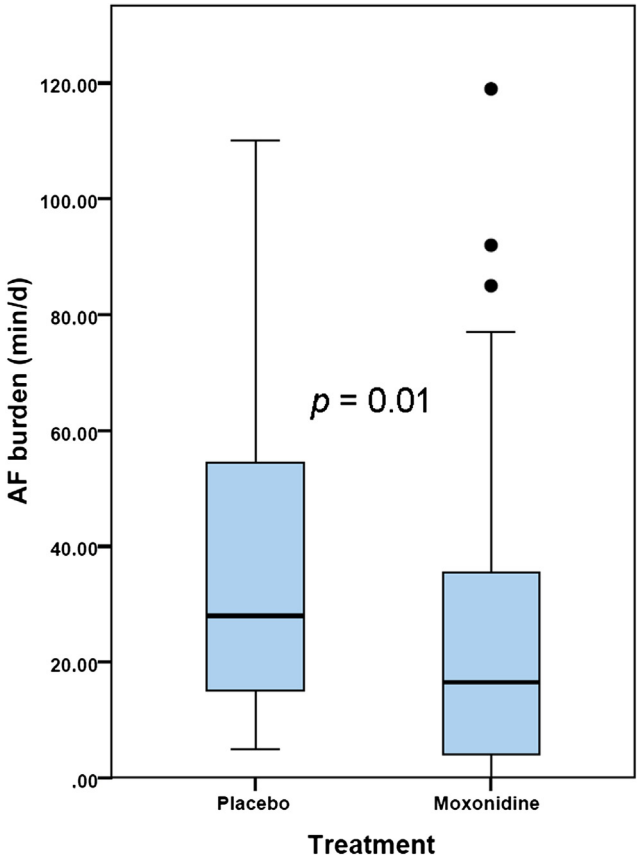

Figure 2. Boxplot graph illustrating the unpaired comparison of AF burden between placebo and active treatment. The *thick horizontal lines* correspond to the median, the *box* to the interquartile range and the *whiskers* to the range of values. *Black dots* represent outliers.

procedures. From 70 initially eligible patients, 60 entered the treatment phases of the study, 4 of whom failed to present for >1 Holter recordings per treatment period and were excluded from the analysis (Figure 1).

AF burden was 41% less during the moxonidine treatment phase, compared with the placebo treatment period (Table 2). The difference in the AF burden between the 2 treatment periods was significant even if an independent (unpaired) comparison was performed (Figure 2). AF burden reduction was not related to gender ($p = 0.52$); age and duration of AF history were also not related to the AF burden difference between placebo and moxonidine treatment ($p = 0.29$ and 0.93, respectively). Although diastolic blood pressure levels were significantly lower in the moxonidine treatment period, the reduction in diastolic blood pressure was not associated to the reduction in AF burden ($p = 0.72$).

A significant 66% reduction in the number of AF episodes per day was also observed. The decrease in AF burden and number of AF episodes was accompanied by alleviation of clinical symptoms, as indicated by the observed decrease in European Heart Rhythm Association class. Systolic arterial pressure levels were similar between the 2 treatment periods, whereas diastolic arterial pressure measurements were, as already mentioned, lower during moxonidine treatment (Table 2).

The most frequently reported side effect during moxonidine treatment was xerostomia (28.6%). Headaches and/or sleep disorders were reported by 4 patients (7.1%). Most importantly, moxonidine had a neutral effect on depressive symptoms, as quantified by the 17-HDRS (Table 2). No significant hypotensive symptoms were reported.

Patient compliance was high, with >95% of study drug doses taken by the patients, as indicated by the pill counts. Study drug discontinuation was recorded in 4 patients, who terminated their participation altogether. Since 2 of these discontinuations occurred during the placebo treatment period, it is doubtful that they were related to moxonidine treatment per se.

Discussion

The principal finding of this small pilot study is that moxonidine, administered in hypertensive patients with paroxysmal AF, is effective in reducing AF burden and the number of AF episodes. This reduction in AF burden was accompanied by a reduction in the severity of AF-related symptoms. The treatment with moxonidine was not associated with serious adverse effects in this population of hypertensive patients without heart failure.

The implication of the autonomic system in the pathophysiology of AF has received considerable research attention in the past. Although it has been postulated that "idiopathic" paroxysmal AF is associated with vagal overstimulation (vagal AF),[7] whereas adrenergic activation is more important for AF induction in patients with heart disease (adrenergic AF),[8] more recent studies suggest that a combined overactivation of both the sympathetic and parasympathetic limbs of the autonomic system may be responsible for eliciting AF episodes. In particular, it has been shown that a primary increase in adrenergic tone followed by a marked modulation toward vagal predominance preceded episodes of paroxysmal AF,[9–11] and no difference was observed, as far as this sympathovagal sequential activation was concerned, between patients with lone paroxysmal AF and patients with structural heart disease.[10]

In the above-outlined pathophysiologic context, suppression of central adrenergic stimulation would be expected to result in suppression of atrial arrhythmogenesis, and it is a plausible explanation for the findings of the present study: moxonidine is a centrally acting sympathoinhibitory agent, acting mainly through stimulation of the I1-imidazoline receptor. As a consequence, moxonidine reduces the levels of central sympathetic tone, resulting in significant hemodynamic and metabolic effects. In addition, it does this with minimal effect on α-2 adrenergic receptors, resulting in marked reduction in undesired effects, compared with older centrally acting antihypertensives, including clonidine (whose side effects are mainly mediated by α-2 adrenoreceptors).[12] A recent study showing that renal sympathetic denervation (which results in reduction of central sympathetic outflow toward the peripheral organs, including the heart), when performed in conjunction with pulmonary vein isolation, leads to less AF recurrences[6] may also be construed as providing ex juvantibus evidence that sympathetic tone plays an integral part in AF pathogenesis. One would expect β blockers to be effective in this context; however their efficacy in preventing AF relapses after cardioversion has been shown to be at most modest (approximately 18% reduction in relapses in 1 study[13]) and are, thus, not recommended for rhythm control in patients with paroxysmal AF.[14]

One cannot exclude, however, the possibility that the reduction in diastolic blood pressure levels, observed during moxonidine treatment in the present study, may be responsible, at least in part, for the decrease in AF burden. Still, were it the case, one would expect the reduction in diastolic blood pressure to be correlated to the reduction of AF burden or the number of AF episodes, which was not true. On the whole, arterial pressure levels were almost similar over the 2 treatment periods, and it is doubtful that the impressive reduction in AF burden could be explained by a small difference in diastolic blood pressure, but even if the reduction in diastolic blood pressure is an important contributor to the effect of moxonidine, this would not lessen the importance of the observed clinical benefit (should the latter be confirmed by further and larger studies).

Finally, this was a small study, whose main aim was to prove the principle that pharmacologic modulation of the central sympathetic tone may be of therapeutic use in patients with paroxysmal AF. Its results should not be extrapolated to the general population of patients with AF (for example, patients with impaired ventricular function were excluded according to the results of the Moxonidine in Congestive Heart Failure [MOXCON] trial, in which moxonidine was found to have a deleterious effect in patients with heart failure and an ejection fraction of <0.35). However, we believe that this evidence justifies further investigation of the potential role of moxonidine in AF and its potential to reduce AF recurrences in relevant patient populations, including those undergoing left atrial ablation treatment (actually, in view of the present results, our group has such a protocol under way; ClinicalTrials.gov Identifier: NCT01791699).

Disclosures

The authors have no conflicts of interest to disclose.

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