Effect of Atrial Fibrillation and an Irregular Ventricular Response on Sympathetic Nerve Activity in Human Subjects

Stephen L. Wasmund, PhD; Jian-Ming Li, MD, PhD; Richard L. Page, MD; Jose A. Joglar, MD; Robert C. Kowal, MD, PhD; Michael L. Smith, PhD; Mohamed H. Hamdan, MD

Background—Although the hemodynamic changes associated with atrial fibrillation (AF) have been extensively studied, the neural changes remain unclear. We hypothesized that AF is associated with an increase in sympathetic nerve activity (SNA) and that the irregular ventricular response contributes to this state of sympathoexcitation.

Methods and Results—In 8 patients referred for an electrophysiological study, SNA, blood pressure (BP), central venous pressure (CVP), and heart rate were recorded during 3 minutes of normal sinus rhythm (NSR) and 3 minutes of induced AF. In 5 of 8 patients who converted to NSR, right atrial (RA) pacing was performed for 3 minutes in atrial pacing triggered by ventricular sensing mode triggered by playback of an FM tape previously recorded from the right ventricle during AF (RA-irregular) and atrial pacing inhibited by atrial sensing mode at a rate equal to the mean heart rate obtained during AF (RA-regular). SNA data were expressed as percentage of baseline during NSR. SNA increased in all 8 patients during induced AF compared with NSR (171±40% versus 100%, respectively; P<0.01). This was associated with a trend for a decrease in BP and an increase in CVP (P=0.02). Similarly, SNA was significantly higher during RA-irregular pacing compared with RA-regular pacing (124±24% versus 91±20%, respectively; P=0.03). BP and CVP were not significantly different between the 2 pacing modes.

Conclusions—Induced AF results in a significant increase in SNA, which is in part attributable to the irregular ventricular response. Our findings suggest that restoring NSR or regularity might be beneficial, particularly in patients with heart failure. (Circulation. 2003;107:2011-2015.)

Key Words: atrium ■ fibrillation ■ nervous system

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Most studies seem to suggest that AF is associated with increased mortality. This increase in mortality is thought to be attributable to the cardiovascular conditions associated with AF. However, a recent study from the Framingham cohort showed that AF per se was associated with a 1.5- to 1.9-fold increase in mortality risk, even after adjusting for the preexisting cardiovascular conditions associated with AF. Although the hemodynamic changes associated with AF have been extensively studied, the neural changes resulting from this arrhythmia remain unclear. An understanding of the effect of AF and in particular the effect of an irregular ventricular response on sympathetic activity may shed some light on the etiology behind the reduced survival in patients with AF. To our knowledge, such work has not been done.

The purpose of the present study was to determine the effect of induced AF on sympathetic nerve activity (SNA). We hypothesized that AF is associated with an increase in SNA and that the irregular ventricular response contributes to this state of sympathoexcitation.

Methods

Study Patients

The study was performed at the Dallas Veterans Affairs Medical Center and was approved by the local institutional review board. Informed consent was obtained from all patients, and all procedures were in accordance with institutional guidelines. All patients with a history of supraventricular tachycardia or paroxysmal atrial flutter referred for an electrophysiological study were screened. Patients who were not in normal sinus rhythm at the time of the study were excluded. A total of 10 patients were enrolled in the study. Successful nerve recordings were obtained in 8 patients. The data from these 8 patients form the material of this study.

Electrophysiological Studies

Patients were studied in the drug-free postabsorptive state after informed consent was obtained. Three quadripolar catheters were inserted percutaneously and positioned in the high lateral RA, RV apex, and across the tricuspid valve for His-bundle recording. Atrial and ventricular pacing thresholds were measured and pacing was performed at twice diastolic pacing threshold.

Measurements

Efferent, postganglionic muscle SNA was recorded from the left peroneal nerve, as previously described. Briefly, a sterile microelec-
fibular head. The nerve signals were amplified, filtered (700 to 2000 Hz), rectified, and discriminated. Raw nerve signals were integrated (time constant, 0.01 seconds) to produce a mean voltage display for quantitative analysis. Muscle sympathetic nerve bursts during sinus rhythm were readily recognized by their tight temporal relationship to the sinus cardiac cycle, their increasing frequency during Valsalva maneuvers, the occurrence of large bursts accompanying premature ventricular beats, and the failure to respond to arousal stimuli or stroking of the skin in the region of innervation. The SNA was quantified as the total activity derived from the sum of the area of the SNA bursts for a given time period. Area was used for these analyses, because, compared with the burst amplitude, it more appropriately reflects the changes in SNA associated with the wide variations in arterial BP that can occur during AF. SNA data were expressed as a percentage of baseline burst area during normal sinus rhythm (NSR) before AF induction and RA pacing. Arterial blood pressure (BP) was directly recorded with a 5F catheter inserted into the right femoral artery. Central venous pressure (CVP) was continuously recorded with a catheter placed in the right atrium via the right femoral vein. Heart rate (HR) was derived from continuous ECG recording of at least 2 leads (typically leads II and V1).

Experimental Protocol
After obtaining acceptable recordings of SNA, BP, CVP, and HR, the following protocol was performed. Three minutes of data during NSR were recorded (NSR). AF was then induced with rapid atrial pacing or atrial premature stimulation, and 3 minutes of AF data were recorded (AF). During AF, the bipolar electrogram from the RV catheter was recorded onto a frequency-modulated (FM) tape using an analog data recorder for subsequent use (see below). After obtaining NSR and AF data, patients were monitored for 15 minutes. If AF persisted, they underwent electrical cardioversion, and no additional data were recorded in these patients. In those who had spontaneous cardioversion, right atrial (RA) pacing was performed for 3 minutes in an AVT mode triggered from the previous FM tape recordings (RA-regular) and in an AAI mode at a rate equal to the baseline RA pacing (RA-irregular). RA-irregular and RA-regular pacing were done at random with a 1-minute recovery time and 1-minute baseline in between.

In summary, patients who required electrical cardioversion had recordings during NSR and AF (n=8), and those who converted spontaneously had recordings during NSR, AF, RA-irregular, and RA-regular pacing (n=5). Data analysis in all patients was performed during the last minute of the 3-minute recordings.

Statistics
All data are presented as mean±SEM. All data sets were tested for normality using a Kolmogorov-Smirnov test. Group comparisons of NSR versus AF and RA-regular versus RA-irregular were performed with a paired t test. A signed-rank sum was used for comparisons in which normality failed. For all analyses, significance was set at an α level of 0.05.

Results
Clinical Characteristics
All patients were men, with a mean age of 64±2 years. Four patients had the diagnosis of atrial flutter, 3 atrioventricular nodal tachycardia, and 1 atrial tachycardia. All patients were in NSR at the time of the electrophysiological study. The clinical characteristics of all subjects are summarized in the Table.

Atrial Fibrillation Compared With Normal Sinus Rhythm
Atrial fibrillation was successfully induced in all 8 patients. Figure 1 is a representative tracing of SNA, BP, and CVP during NSR and AF in 1 subject. A summary of the hemodynamic and SNA changes associated with AF compared with NSR is provided in Figure 2. SNA was significantly higher during AF compared with NSR (171±40% versus 100%, respectively; *P<0.01*). The increase in SNA was associated with a trend for a decrease in BP, which was not statistically significant. On the other hand, a significant increase in CVP was noted during AF compared with NSR (13±1 versus 11±1 mm Hg, respectively; *P=0.02*).

RA-Irregular Pacing Compared With RA-Regular Pacing
Regular and irregular RA pacing was performed in 5 of 8 patients who converted spontaneously to NSR. In the remaining 3 patients, electrical cardioversion was required. In these patients, no additional data were acquired because of the drugs used during anesthesia. Figure 3 illustrates a sample tracing of SNA, BP, and CVP during RA-regular and RA-irregular pacing in 1 subject. A summary of the hemodynamic and SNA changes associated with RA-regular and RA-irregular pacing is provided in Figure 4. SNA was significantly higher during RA-irregular pacing compared with
RA-regular pacing (124±24% versus 91±20%, respectively; P=0.03). BP and CVP were not significantly different between the 2 pacing modes.

**Discussion**

The main findings from this study are that induced AF results in a significant increase in sympathetic activity compared with normal sinus rhythm and an irregular ventricular response is associated with a higher sympathetic activity compared with a regular ventricular response. To our knowledge, this is the first study to assess the effect of AF and irregularity on sympathetic activity in human subjects.

**Effect of AF on Morbidity/Mortality**

Carson et al analyzed, retrospectively, the data from the Veterans administration Heart Failure Trial (V-HeFT) studies and found no difference in mortality in patients with AF compared with NSR. On the other hand, in the largest study to date combining data from the Studies Of Left Ventricular Dysfunction (SOLVD) trials, Dries et al found AF to be associated with an increased risk for all-cause mortality in patients with mild to moderate CHF. Similarly, a recent study from the Framingham cohort showed that AF was associated with a 1.5- to 1.9-fold increase in mortality even after adjusting for the preexisting cardiovascular conditions with which AF was associated. The mechanism for this increased mortality independent of other risk factors is unknown. A possible explanation could be the autonomic changes that accompany AF.

We have previously shown that arterial baroreflexes play a major role in mediating sympathoexcitation during supraventricular and ventricular tachycardias. In the present study, we found that SNA was increased during AF with a trend for a decrease in BP, suggesting again a primary role of the arterial baroreflexes. In addition, we found that irregular pacing was associated with an increase in sympathetic activity compared with regular pacing, suggesting that the irregular ventricular response during AF may play a role in mediating sympathoexcitation. The relative role of the arterial and cardiopulmonary baroreflex gain and other potential mechanisms of sympathoexcitation in the control of SNA during AF remains unclear.

**The Detrimental Effects of an Irregular Ventricular Response**

The detrimental effects of an irregular ventricular response have been highlighted in several elegant studies. Clark et al assessed the hemodynamic effects of an irregular ventricular cycle length in 16 patients with AF referred for atrioventricular junctional ablation. Compared with an irregular sequence of RR intervals, VVI pacing at the same average rate as AF resulted in a significant increase in cardiac output and a significant decrease in pulmonary capillary wedge pressure and right atrial pressure. A limitation of that study was that comparison was made between intrinsically conducted beats (AF) and RV paced beats. Nevertheless, this
study clearly showed that a regular ventricular response resulted in better hemodynamics compared with the irregularity seen during AF. The importance of a regular ventricular response is additionally evidenced by the results of a study by Kubac et al.\textsuperscript{12} that showed improvement in left ventricular function after cardioversion, even in patients with a previously well-controlled ventricular rate. Therefore, most studies seem to suggest that the hemodynamic changes associated with an irregular ventricular response are detrimental. To our knowledge, the neural changes associated with an irregular ventricular response have not been assessed.

In the present study, we found that an irregular ventricular response was associated with a higher sympathetic activity compared with a regular ventricular response. Our findings complement the results of the previously mentioned studies. Therefore, the relationship between AF and congestive heart failure seems to be even more intriguing than previously thought. In addition to tachycardia-induced cardiomyopathy,\textsuperscript{13,14} AF could theoretically lead to impairment in left ventricular function as a result of the irregular ventricular response. This hypothesis, however, remains to be proven.

**Clinical Implications**

Elevated levels of sympathetic activity have long been shown to be detrimental, particularly in patients with left ventricular dysfunction. Our findings of increased sympathetic activity during AF suggest that restoring sinus rhythm might be beneficial in patients with paroxysmal or persistent AF. On the other hand, the increase in SNA during irregular pacing compared with regular pacing suggests that in addition to rate control, restoring regularity might be important in patients with permanent AF. The relative role of rate and irregularity in mediating sympathoexcitation at different rates and the long-term effects of restoring a regular ventricular response in patients with clinical AF remain to be seen.

**Study Limitations**

This study has limitations. First, our findings may not apply to patients with clinical AF. Patients with clinical AF may have impairment of the cardiopulmonary baroreflex gain, and, as such, the neural changes in these patients might be different. However, we believe our findings are likely to be true in these patients, because impairment of the cardiopulmonary baroreflex gain should result in less sympato-inhibition and thus even a greater elevation of SNA during AF. Second, we did not assess the effect of AF and an irregular ventricular response on SNA at different rates. Therefore, our findings of a higher SNA during AF compared with NSR may not be true at faster or slower rates. Close analysis of the data, however, suggests that the increase in SNA was primarily attributable to the irregularity and not the tachycardia rate. Indeed, RA-regular pacing at a rate equal to the AF rate (112 ± 8 bpm) resulted in a decrease in SNA compared with baseline (91 ± 20% of baseline). This finding suggests that the increase in HR associated with AF in this study did not play a major role in mediating the sympathoexcitation associated with AF. We predict that the detrimental effect of irregularity is likely to decrease as the ventricular rate increases. The relative role of rate and irregularity on the hemodynamic and neural changes remains to be evaluated. Finally, the number of subjects we studied is small. Although a larger number of patients might have yielded different results, we think this is unlikely, because every patient (8 of 8) had an increase in SNA during AF compared with NSR.

**Conclusion**

In summary, we have shown for the first time that AF is associated with an increase in sympathetic activity and that an irregular ventricular response is associated with a higher sympathetic activity compared with a regular ventricular response. Therefore, our findings may help explain why AF, and in particular an irregular ventricular response, is detrimental in patients with congestive heart failure. The effect of restoring sinus rhythm and a regular ventricular response on sympathetic activity in patients with clinical AF remains to be determined.

**Acknowledgments**

This work has been supported by a National Institutes of Health grant (R01 HL-65490-01) to Dr Hamdan.

**References**


Effect of Atrial Fibrillation and an Irregular Ventricular Response on Sympathetic Nerve Activity in Human Subjects

Stephen L. Wasmund, Jian-Ming Li, Richard L. Page, Jose A. Joglar, Robert C. Kowal, Michael L. Smith and Mohamed H. Hamdan

Circulation. 2003;107:2011-2015; originally published online April 7, 2003;
doi: 10.1161/01.CIR.0000064900.76674.CC

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/15/2011

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/