



## Role of Stress in Cardiac Arrhythmias

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### Abstract

Stress is a major trigger of cardiac arrhythmias; it exerts profound effects on electrophysiology of the cardiomyocytes and the cardiac rhythm. Psychological and physiological stressors impact the cardiovascular system through the autonomic nervous system (ANS). While stressors vary, properties of the stress response at the level of cardiovascular system (collectively referred to as the autonomic cardiovascular responses) are similar and can be studied independently from the properties of specific stressors. Here, we will review the clinical and experimental evidence linking common stressors and atrial arrhythmias. Specifically, we will describe the impact of psychological and circadian stressors on ANS activity and arrhythmogenesis. We will also review studies examining relationships between autonomic cardiovascular responses and cardiac arrhythmias in ambulatory and laboratory settings.

### Introduction

Stress is a major trigger of cardiac arrhythmias; it exerts profound effects on electrophysiology of the cardiomyocytes and the cardiac rhythm.<sup>1-3</sup> Psychological and physiological stressors impact the cardiovascular system through the autonomic nervous system (ANS). While stressors vary, properties of the stress response at the level of cardiovascular system (collectively referred to as the autonomic cardiovascular responses) are similar and can be studied independently from the properties of specific stressors.<sup>4</sup>

### Psychological Stress and Arrhythmias

While the associations of psychological stress and ventricular arrhythmias are well-established,<sup>5-7</sup> data linking stress and atrial arrhythmias are just beginning to emerge. Small case-series dating back 50 years have suggested that stressful stimuli may acutely trigger atrial fibrillation (AF). Anecdotally reported emotional triggers have included a

death or injury in the family, and awakening to an alarm.<sup>8</sup> One older case-series reported a patient with a first AF episode during involvement in a motor vehicle accident, and a next episode four years later on hearing a collision.<sup>9</sup> Other small series have reported both sympathetic and vagal precipitants. From 2% to 30% of AF episodes have been described during "emotional or physical exhaustion" and from 1-30% after coughing, vomiting, eating, or sleeping.<sup>10,11</sup> These small observational studies have suggested that vagal and sympathetic stimuli may separately trigger occurrence of AF through the autonomic effects on atrial electrophysiology described below.

More recently, preliminary prospective data from our group has supported the concept of stress-induced AF. In this prospective, controlled, electronic-diary-based study of emotions preceding AF, 75 patients with a history of paroxysmal or persistent AF recorded their rhythm on event-monitor at the time of AF symptoms, and completed a diary entry querying mood states and

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also completed diaries on a nightly basis. The likelihood of an AF episode was increased five times immediately following an episode of anger as well as by other negative emotions, and was decreased by happiness. Anger reported the night before the event was associated with a 50% increase in likelihood of AF the following day.<sup>12</sup>

In addition to triggering of AF by acute stressors, stress may also increase likelihood of AF over time. Several long term stressors, which also impact autonomic function chronically, have been associated with development of AF. In a Danish study, Sterndorf et al. found that patients with any cardiac disease, including AF, scored higher on measures of impatience, competitiveness, and job involvement, than did controls.<sup>13</sup> Among patients with AF, those with greatest degree of somatization had the greatest frequency of symptoms of recurrence.<sup>14</sup> In one small study of 54 AF patients undergoing cardioversion, 85% of those scoring high in depression, compared with 39% of those without depression, had a recurrence over the two month follow-up period.<sup>15</sup> In the Framingham study, measures of anger, hostility and tension predicted development of AF over ten years in men, although not in women.<sup>16,17</sup>

In a more recent analysis of the Womens Health Study (Whang/Albert JAHA), while measures of global distress as measured by the SF-36 did not predict development of AF, happiness did prove to be protective, similar to the findings from our group. In laboratory studies of provoked mental stress, happiness attenuates stress-induced increases in fibrinogen,<sup>19</sup> and blood pressure, and in daily life, happiness is associated with lower daily heart rate and cortisol,<sup>18</sup> all mechanisms which over time could be protective against AF.

### Circadian Mechanisms of Stress and Arrhythmias

The 24-hour light/dark cycle is a powerful modulator of the central nervous system and ANS activity,<sup>20</sup> with well-documented decreases in sympathetic activity and increases in vagal activity<sup>21,22</sup> during the night, which adjusts sensitivity of stress response to fit environmental demands. In addition to the circadian variations of

ANS activity, recent experimental studies have demonstrated circadian changes in the peripheral receptor responsiveness to autonomic influences,<sup>23</sup> which suggests that the circadian pattern to ventricular tachyarrhythmia is likely a result of interaction between ANS activity, central and peripheral circadian molecular mechanisms. Indeed approximately 2-8% of all cardiac gene transcripts demonstrate a circadian pattern of expression.<sup>24,25</sup>

The circadian timing system is organized in a hierarchy of multiple circadian oscillators with the circadian “master” clock consisting of cells located in the suprachiasmatic nuclei (SCN) of the hypothalamus.<sup>26</sup> The master clock is entrained by the light-dark cycle via retinohypothalamic tract and possibly other pathways. The “slave” oscillator clocks are scattered throughout the body, including the heart; importantly, they can sustain 24-hour oscillations independently of the master clock for at least several days.<sup>27</sup> The cardiomyocyte circadian clock regulates diurnal variation in heart rate, contractile function, responses to adrenergic stimulation and increased workload.<sup>27</sup> Mice with cardiomyocyte-specific overexpression of a dominant negative Clock (a “core” circadian clock-controlled gene) mutant have attenuated diurnal variations of heart rate and bradycardia; the hearts of these mice exhibit bradycardia both in vivo and ex vivo, in the absence of conduction defects or neurohormonal influences.<sup>27</sup>

The circadian pattern of gene expression has been documented for two K<sup>+</sup> channels: Kv1.5 (associated with the rapidly activating slowly inactivating current) and Kv4.2 (associated with the transient outward current, I<sub>to</sub>) with the rest of the K<sup>+</sup> channels remaining constant during a 24-hour period in rats. The circadian rhythms of Kv1.5 and 4.2 mRNA have relatively large magnitudes, with the peak being ~ 2-fold greater than that during the opposite phase of the circadian cycle.<sup>28</sup> A circadian pattern of activity also has been reported for the L-type Ca<sup>2+</sup> current in the suprachiasmatic nucleus (the location of the “master” circadian clock in the brain).<sup>28</sup> However, the question whether Ca<sup>2+</sup> channels in the heart also exhibit circadian pattern of activity remains unexplored.

Importantly, the greatest differences between hypertrophied and normal hearts with respect to the

expression of cardiac clock genes (Per2, Per3, and DBP) were observed immediately before or at the beginning of active (dark) phase of the circadian cycle in rodents, coinciding with the peak of arrhythmia frequency in genetic mouse models of heart failure and arrhythmias.<sup>29</sup> In humans with heart failure, there is a similar association between the circadian peak of ventricular arrhythmia occurrence and the onset of activity period (in the morning), despite the 12-hour shift in the cycle between rodents and humans.<sup>5</sup> A number of studies have documented circadian patterns of ventricular arrhythmia.<sup>30,31</sup> This cyclical variation of environmental demands and responsiveness to environmental stressors is also associated with circadian patterns of atrial arrhythmias.<sup>32</sup>

### Circadian Patterns of Paroxysmal Atrial Fibrillation

Gillis et al. have studied the patterns of paroxysmal AF in patients with implanted dual-chamber pacemakers and found that longer AF episodes (>2 hours) had a single morning peak, whereas shorter episodes (<2 hours) had two peaks, both in the morning and evening time.<sup>33</sup> Similarly, Viskin et al., analyzing emergency phone calls related to 9989 episodes of paroxysmal AF, have found that the time of AF onset showed two peaks, one in the morning and another one in the evening.<sup>34</sup> Kupari et al. also reported two peaks (in the morning and evening time) in the occurrence of sustained supraventricular tachyarrhythmias.<sup>35</sup> Yamashita et al. in Holter recordings from 150 patients with paroxysmal AF have also observed that the initiation of arrhythmias had two peaks, although the peaks occurred later in the 24-hour cycle (at 1 pm and midnight).<sup>36</sup> Clair et al. have examined the first recurrence of symptomatic paroxysmal atrial tachycardia or AF in 150 ambulatory patients using transtelephonic ECG transmitted by the patients and found a daytime peak of occurrence of paroxysmal AT (2-8 pm) but a random 24-hour distribution of AF.<sup>37</sup>

To explain the differences in the circadian patterns of AF reported in different populations, Gillis et al. have suggested that the 24-hour distributions are modulated by the disease burden (i.e. the frequency and duration of arrhythmias as well as the presence of structural heart disease).<sup>33</sup> Recently,

our group has shown, in a large group of patients with implantable devices, which allow continuous collection of the event data over prolonged periods of time (16,130 atrial tachycardia/AF events were recorded in 236 patients over a period of 12 months), that the total arrhythmia burden is the major determinant of the circadian pattern of AF. In patients with rare arrhythmias (<4 atrial tachycardia/AF episodes over the follow up period), the events are distributed randomly over 24-hour period. However, patients with more frequent arrhythmias are more likely to develop atrial tachycardia/AF at night. A nocturnal peak emerges in patients with more frequent atrial tachycardia/AF episodes and grows as a function of the total number of arrhythmias. This strong relationship between the nighttime peak of atrial tachycardia/AF initiation and total arrhythmia burden is present in both absolute and patient-normalized units. It is observed in patients of different age groups, genders, irrespective of the level of left ventricular ejection fraction, presence of coronary artery disease and pharmacological treatment (including beta-blockers). It is likely that some patients in our study had abnormal autonomic nervous system activity, which is typical for patients with implantable cardioverter-defibrillator. Because the heart rate variability and other autonomic markers were not available to us, further research is needed to examine the relationship between nighttime surges in vagal activity, sleep-disordered breathing, oxygen saturation and patterns of atrial tachycardia/AF.

Summarizing, circadian periodicity of the AF initiation confirms the important role of the ANS activity and the ANS-mediated stress response in triggering the arrhythmia. However, the exact mechanisms and “weights” of the participating factors are not uniform in different patient groups and even in the same patient over different periods of time; the mechanisms linking circadian patterns of stress, ANS activity, behavior and arrhythmogenesis are subjects of ongoing research studies.

### Ambulatory Studies of Autonomic Nervous System Activity and Atrial Arrhythmias

Specific contributions of vagal and sympathetic ANS effects to atrial arrhythmogenesis, as well

as the accuracy of estimating those effects in a clinical setting, are still under debate. In the early 1990s, Coumel suggested that AF is an electrical abnormality of the atrium exposed by autonomic stimuli and proposed to classify all AF episodes as “vagal” or “sympathetic”, depending on the relative balance between the two systems<sup>38</sup> He pointed out that vagal AF episodes usually happen at night or at rest in the setting of relatively slow heart rates, whereas sympathetic events usually occur during day time, in the setting of heightened sympathetic activity, such as emotional or physical stress, accompanied by heart rate acceleration. Further support for this classification has been provided by the findings of: i) immediate changes in the heart rate variability indexes corresponding to vagal/ sympathetic ANS effects prior to the vagal/ sympathetic AF events,<sup>39-42</sup> and ii) increased heart rate variability (HRV) indexes of parasympathetic activity (the high-frequency power and the root-mean-square of the successive differences between consecutive RR intervals) in patients with vagal AF.<sup>43</sup> Coumel also noted that vagal AF usually occurs in relatively young, <50 year-old, men without a history of structural heart disease.<sup>44</sup> He observed that in those patients, vagal maneuvers can provoke AF, whereas exercises prevent it when patients experience the sensation of an impending arrhythmia (frequent atrial extrasystoles). In addition, he noted frequent co-existence of atrial flutter and AF in these patients, which led him to suggest that AF could be associated with an acceleration of the flutter due to the vagally induced shortening of the atrial refractory period.<sup>45</sup>

According to Coumel’s classification, the 2nd type of AF is adrenergic (sympathetic); it often occurs in the morning or day time, during exercise or emotional stress in patients with structural heart disease but with no age or sex predominance.<sup>46</sup> In contrast to vagal AF, the heart rate and the low-frequency (partially sympathetically-mediated) oscillations of cardiac rhythm increase prior to the onset. Moreover, the arrhythmia is often associated with hyperadrenergic state and can be reproduced by administering  $\beta$ -adrenergic agonists. Long-lasting beta-blockers, such as nadolol, can reduce the AF burden in these patients.<sup>4</sup>

Several studies provided experimental support for Coumel’s classification of AF episodes. Huang

et al. analyzed changes in heart rate variability (HRV) in patients before the onset of sustained (>30 s) AF.<sup>47</sup> Most patients who did not have structural heart disease (64%), had the vagal type of AF (increased high-frequency HRV and decreased low/high frequency power ratio), whereas most patients with structural heart disease (67%), had adrenergic AF (decreased high-frequency HRV and increased low/high frequency power ratio). Dalal et al. investigated HRV during 20 min before the onset of AF and were able to demonstrate an increase in vagally-mediated high-frequency HRV power prior to the onset of AF at night but not during day time.<sup>48</sup> Sasabe et al. classified AF using HRV analysis into predominantly sympathetic and vagal ones and reported that ventricular rate was higher before the onset of adrenergic AF.<sup>49</sup> Furthermore, beta-blockers were effective in suppressing 37% of adrenergic AF episodes vs. only 5% of vagal AF events.

Other studies have reported a more complex interplay of autonomic activity preceding AF. Tanabe et al. reported that high-frequency power was reduced 20-30 min before the event but increased during the last 5 min before the event. The authors concluded that an increase in sympathetic modulation is followed by an increase in vagal tone shortly before the onset.<sup>50</sup> Zimmermann and Kalusche also found that sustained AF is preceded by an increase in sympathetic modulation followed by an increase in the vagal tone immediately before the onset. A large-scale clinical study, which included more than five thousand patients with AF from 35 European countries, could not identify the ANS triggers of arrhythmias in 2/3 of the studied patients.<sup>52</sup> The study has shown that a majority (79%) of arrhythmic events cannot be classified as purely vagal or sympathetic. Moreover, the study has found that clinical and demographic characteristics (age, gender, presence of structural heart disease) cannot discriminate between these two types of arrhythmias. Yet, this large-scale, multicenter investigation has confirmed one important clinical implication of Coumel’s theory that beta-blockers applied in patients with the vagal type of atrial tachycardia/AF may promote arrhythmogenesis and increase the frequency of arrhythmic events.

A gradual increase in the number of premature atrial contractions has been consistently observed prior to the onset of AF both in ambulatory setting

and during the course of a clinical electrophysiologic study, which could be attributed to the adrenergically mediated increase in the atrial cell automaticity.<sup>1,12,53</sup> Vikman et al. reported that the number of atrial ectopic beats increased in the last 40 min before the onset of paroxysmal AF in patients without structural heart disease. The authors also observed that approximate entropy (a nonlinear measure of cardiac rhythm regularity)<sup>54</sup> and beta1-scaling exponent (a modified root-mean-square estimate of the short-time (<11 beats) correlation properties of the cardiac rhythm)<sup>55</sup> decreased before the onset. However, changes in high and low-frequency HRV power before the events were not uniform, suggesting involvement of mixed vagal and adrenergic mechanisms. Experimental studies in ambulatory canines have provided direct evidence that AF episodes are preceded by both sympathetic and vagal discharges (although the generalizability of these findings to the clinical setting remains to be determined).<sup>57,58</sup> Nevertheless, this novel experimental approach has shown that paroxysmal atrial tachyarrhythmias are invariably preceded by increased intrinsic cardiac nerve activity, including that in ganglionated plexi and the ligament of Marshall.<sup>58</sup>

To summarize, the ANS effects play a major role in the initiation of AF events; however, most events usually involve complex changes in the ANS activity and probably cannot be classified as purely vagal or sympathetic. Whether a “finer”, quantitative assessment of such complex ANS changes is feasible using direct measurements of the neural activity remains to be established.

### Laboratory Studies of Autonomic Effects on Atrial Electrophysiology

Psychological stressors such as anxiety, anger, and fear have profound effects on the autonomic nervous system. In the laboratory setting, mental challenge and distress, increase both epinephrine and norepinephrine,<sup>6,59-63</sup> and decrease heart rate variability suggesting vagal withdrawal.<sup>64</sup> These autonomic perturbations in turn impact atrial electrophysiology in ways that may be arrhythmogenic.

The atria are innervated by sympathetic and

vagal nerves, but their spatial distribution is not uniform. Vagal nerve endings are predominantly located in the endocardium, whereas the sympathetic terminals could be found both in the endocardium and epicardium.

### Parasympathetic Effects

In experimental studies, vagal stimulation has long been known to aid in the provocation of AF by causing hyperpolarization of atrial fibers, shortening of atrial effective refractory period and action potential duration,<sup>68,69</sup> and creating local conduction inhomogeneity.<sup>70,71</sup> In normal human atrial cells, an acetylcholine-like agent ouabain increases the maximal diastolic potential, the action potential amplitude and the upstroke depolarization velocity and at the same time, decreases the action potential duration and automaticity.<sup>72,73</sup>

Stimulation of the vagus (in the cervical region or the third fat pad of the right pulmonary artery) caused shortening of the effective refractory period and increased its inter-site dispersion in canine atria.<sup>74</sup> The enhanced dispersion was attributed to the inhomogeneity of vagal nerve distribution and relatively higher concentration of acetylcholine near the nerve endings.<sup>26</sup> Both the shortening of the refractory period and the increase in dispersion are pro-arrhythmic, because an early ectopic impulse can propagate along an irregular path, encountering areas in various states of excitability.<sup>26</sup> Catheter ablation of atrial parasympathetic nerve terminales abolished these effects and eliminated AF that could be induced by vagal stimulation before the ablation.<sup>39</sup> Although more recent clinical studies have confirmed the feasibility of local modification of the cardiac vagal effects; they did not find any measurable impact on the outcome (clinical recurrence of AF).<sup>75</sup>

In human studies, baroreceptor stimulation provides a noninvasive tool to evaluate parasympathetic effects. Prystowsky et al. increased vagal activity by carotid baroreceptor stimulation in humans (using neck collar suction) and observed shortening of atrial effective refractory periods.<sup>76</sup> Chen et al. reported that higher baroreflex sensitivity and enhanced atrial effective refractory period dispersion correlated with the occurrence of paroxysmal AF.<sup>77</sup> The same group studied in-

ducibility of AF during atrioventricular pacing with varying intervals. Again, patients with AF had greater atrial dispersion and higher baroreflex sensitivity than patients without AF<sup>78</sup> however, no differences in heart rate variability were found between patients with and without AF. These findings suggest that the high baroreflex sensitivity could be one of the components of the “AF-prone” ANS-phenotype.

### Sympathetic Effects

Sympathetic activity also alters atrial electrophysiology in ways which may predispose to AF. Most,<sup>79-82</sup> although not all,<sup>69</sup> studies, have shown that sympathetic stimulation decreases atrial effective refractory period (AERP), and acts synergistically when combined with vagal stimulation.<sup>79-82,79,80,81,82</sup> In a study evaluating diurnal variation of AERPs through non-invasive programmed stimulation in patients with pacemakers, Huikuri found the shortest AERPs in the morning, the time of highest catecholamine levels.<sup>83</sup> Beta-blockers lengthen both AERP and action potential duration. Heterogeneity of the atrial sympathetic innervation (that could be enhanced by rapid pacing or epicardial application of phenol) promotes dispersion of atrial refractoriness and creates a substrate for sustained AF.<sup>85,86</sup>

Isoproterenol may provoke AF originating from the pulmonary veins, suggesting that increased sympathetic tone may enhance local automaticity in this area and thus facilitate AF.<sup>87</sup> In addition, sympathetic stimulation with isoproterenol may lead to proarrhythmic shortening of the atrial refractoriness and intra (inter)-atrial conduction times.<sup>88</sup> For this reason, beta-blockers suppress initiation of arrhythmia in this setting.

Our group has examined longer-term (>10 min) changes in the cardiac rhythm dynamics preceding the onset of AF in human subjects undergoing electrophysiologic study.<sup>89</sup> After infusion of isoproterenol (5-10mg), the cycle length significantly shortened during 3-6 min before the onset, but no changes occurred in the last 2 min before AF. The cycle length shortening, which develops gradually, minutes before the onset of AF, suggested the predominant role of the adrenergic mechanisms in this group of patients.

### Interaction Between Vagal and Sympathetic Branches of the Autonomic Nervous Systems

The parasympathetic and sympathetic nervous system activities may affect each other both locally and at the level of the central nervous system.<sup>90</sup> Acetylcholine released from vagal nerve endings diminishes release of norepinephrine in adjacent sympathetic nerves.<sup>91</sup> However, the latency and duration of physiological responses to vagal and sympathetic stimulation are different. The responses to cholinergic stimulation occur within a few milliseconds, whereas those to adrenergic stimulation are approximately three orders of magnitude slower for target activation.<sup>38</sup> Thus, the spatial inhomogeneity of the autonomic nerve distribution as well as the differences in the functional response times may set the stage for pro-arrhythmic conduction irregularities.<sup>92-94</sup> Because the centers of sympathetic and parasympathetic control are located in the brainstem in a close proximity to each other and are connected by multiple links, stress-induced ANS changes are rarely confined to pure sympathetic or vagal effects.<sup>90</sup> For example, direct stimulation of the rootlets of the vagus nerve in the brainstem increases heart rate and decreases the amplitude of electrocardiographic T wave, possibly acting via the closely connected sympathetic centers.<sup>90</sup>

### Conclusions

In “Pathophysiology and Prevention of Atrial Fibrillation”, published 12 years ago, an international expert group has pointed out that analysis of the ANS activity must be considered as an integral component of any preventive AF strategy. Although a large number of studies have been conducted over the last 12 years to elucidate the links between ANS activity and atrial arrhythmias, no effective preventive methods have emerged thus far from either pharmacologic or non-pharmacological approaches to autonomic modulation. Recent technological advancements, however, create new opportunities for personalized assessment and management of daily stressors and excessive autonomic responses, which could be proarrhythmic. These include: (i) miniaturized sensors, which track cardiac rhythm and ANS activity, and (ii) mobile devices, which collect physiological data, run stress-assessment software, and provide

feedback as well as communication platform for patients and healthcare providers. It remains to be seen whether these technological advancements will lead to practical benefits in stress management and prevention of cardiac arrhythmias.

## Disclosures

No disclosures relevant to this article were made by the authors.

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