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Behavioral influences on cardiac arrhythmias

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Abstract

Stress can trigger both ventricular and atrial arrhythmias, as evidenced by epidemiological, clinical, and laboratory studies, through its impact on autonomic activity. Chronic stress also increases vulnerability to arrhythmias. Novel therapies aimed at decreasing the psychological and physiological response to stress may decrease arrhythmia frequency and improve quality of life.

Introduction

Arrhythmogenesis requires an anatomic substrate and an immediate trigger. While not all arrhythmias can be traced to an identifiable trigger, evidence continues to mount that in at least some circumstances, emotional stress, with its attendant autonomic perturbations, can serve as a proximate trigger for both atrial and ventricular arrhythmias. Further, chronic psychological stressors, such as depression and hostility, can increase susceptibility to both atrial and ventricular arrhythmias, through long-term changes in autonomic function. Early evidence suggests that therapies aimed at decreasing both the experience of negative emotion, and physiological impact of negative emotion, may decrease arrhythmia frequency in individuals with an anatomic substrate for atrial or ventricular arrhythmias as evidenced by a history of these entities.

I. Ventricular Arrhythmias and Sudden Death

Acute stress as a trigger for ventricular arrhythmia

The concept that stress can trigger sudden death seems familiar anecdotally, and reports of stress-induced sudden cardiac death (SCD) go back decades.[1] The first convincing scientific evidence that psychological stress can trigger sudden death came with epidemiological reports of increases in SCD at times of devastating population disasters such as earthquake or war. [2, 3] For example, on the day of the Northridge earthquake in 1994, there was a 6-fold increase in sudden cardiac deaths compared to days prior to and following the disaster. [2] Only 3 of the 24 SCDs occurred during physical exertion such as cleaning debris, suggesting it was psychological rather than physical effects of the disaster which were responsible for the increase in mortality. Around the same time, Meisel et al

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reported increases in mortality during the Iraqi missile crises in Israel in 1981, which were not related to physical injuries[3] (A somewhat similar study showed increases in acute myocardial infarction in England following the loss by England to Argentina in a World Cup soccer match, apparently a population disaster for at least a segment of the British population). [4] From these reports on sudden death, it cannot be determined whether stress was activating primarily ischemic or primarily arrhythmic pathways. Stress has long been known to precipitate ischemia and infarction, through platelet activation, vasoconstriction, and other mechanisms. However, Steinberg et al reported an increase in ICD-treated ventricular arrhythmias at one center in New York City in the month following the World Trade Center attacks of 9/11/2001[5] (Figure 1) which suggests that autonomic changes due to stress may directly modulate arrhythmogenesis.

Prospective studies of triggering factors in patients with ICDs have provided further evidence of emotional triggering of arrhythmia. We[6] asked ICD patients to record in a diary their activities and emotions in the 15 minutes and 2 hours prior to any ICD shocks they received over the course of a year's follow-up. Subjects ranked their levels of anger and other emotions on a 5-point likert scale, and reported what they were doing. They then filled out a similar diary one week later at the same time of day. 107 shocks were reported by 42 patients. Higher levels of anger, dichotomized at level 3 or above, were more common pre-shock, occurring 15% of the time, were reported in just 3% of diaries during control periods. Anger was significantly associated with the 15 minutes preceding shock.[6] Anger-triggered arrhythmias, defined as those preceded by an anger level of 3 or above, were more likely to be polymorphic, PVC-initiated, and pause-dependent, than those not preceded by anger.[7] (Figure 2) Anger is known to increase PVC burden in animals[8] and humans, [9] and it is likely that anger triggered the PVCs which then triggered polymorphic VT. As these characteristics are associated with more malignant arrhythmias, this suggests that anger not only increases the frequency, but the lethality, of ventricular arrhythmia. Preliminary data from the TOVA trial, or "Triggers of Ventricular Arrhythmia," a multicenter study evaluating potential triggering factors which is currently in the analysis phase, have also demonstrated that anger can precipitate ventricular arrhythmias.[10]

Chronic stress increases susceptibility to ventricular arrhythmia

Psychopathological states such as depression and anxiety, forms of chronic stress, may also predispose to ventricular arrhythmias over the long-term. In the Nurses' Health Study, depressive symptoms doubled the risk of SCD[11], also seen in other populations.[12] SCD may be due to acute coronary occlusion, or arrhythmia in the setting of ischemic cardiomyopathy, and associations of depression, and other negative emotional states such as stress and hostility, with outcomes in atherosclerotic disease are well described. [13] [14] These associations may be due to impact of negative emotion on risk factors such as hypertension, or on behavioral changes such as poor adherence or on health-related habits, such as physical inactivity. [15]

However, data from patients with ICDs suggest that negative emotion can impact arrhythmia even in the absence of new ischemia or structural change. In the TOVA trial, depression was associated with an increased risk of appropriate ICD shock for ventricular arrhythmia, even

after controlling for clinical variables.[16] (Figure 3) Individuals experiencing high anxiety after ICD implantation are twice as likely to experience ventricular arrhythmias [17] and the combination of anxiety and the “Type D” personality-- the tendency to experience emotional and social distress in combination with emotional nonexpression-- may be particularly arrhythmogenic. [18] In our diary study, individuals with psychological profile characterized by anger or anxiety were more likely to experience triggering of arrhythmias by these emotions.[19]

Potential electrophysiological pathways linking emotion and ventricular arrhythmia

The first step in the pathway from stress to arrhythmia lies in the autonomic changes attendant with strong emotion. Negative emotion increases catecholamine levels[19] and decreases vagal output.[20] Chronic stressors such as depression alter long-term autonomic balance.[21] Multiple experimental studies have demonstrated that these autonomic changes-- sympathetic activation and vagal withdrawal--are arrhythmogenic. In animal models of infarction, direct sympathetic stimulation of the ventricles via stellate ganglion stimulation induces fibrillation,[22] demonstrated as early as 1964 by Han et al, and higher levels of vagal activity are protective against ischemic arrhythmias.[23]

In humans, investigators have looked at effects of stress on ventricular repolarization. Toivonen[24] was among the first to look at effects of an acute sympathetic output on repolarization, using a human model of acute stress—the on-call medical resident. Residents were asked to wear holters while on-call, and record the times of pages that awakened them from sleep. They found that the QT interval was relatively longer for a given HR during stress periods of returning pages, than during the same HR in the absence of stress.

We used a laboratory mental stress protocol (anger recall and mental arithmetic) to evaluate effects of mental stress on three surface measures of heterogeneity of repolarization, well-known to be an important factor in arrhythmogenesis. T-wave alternans, (TWA), T-wave amplitude and area, using time-domain methodology. In this study, 33 patients with ICDs and a history of ventricular arrhythmias underwent a mental stress protocol including mental arithmetic and anger recall. TWA increased from 22 at baseline to 29 uV during mental stress ($p<0.001$) All other measures of heterogeneity also increased with stress. In a similar study by Kop et al, mental-stress was also seen to increase TWA. This group performed simultaneous SPECT-perfusion imaging, and so were able to confirm that the effect of anger on TWA was independent of ischemia.[25] In our study, the increase in TWA correlated with increases in catecholamines, but there was minimal increase in heart rate with mental stress, suggesting a direct autonomic effect on TWA. Prior studies have also suggested that sympathetic activation may increase TWA beyond the effects of heart rate. Experimentally, stellectomy abolishes, while stellate ganglion stimulation increases, TWA.[26] In clinical studies, intravenous betablockade[27] decreased the magnitude of TWA, and TWA induced with exercise is greater than that with atrial pacing at the same heart rate.[28]

The effect of anger on TWA in the laboratory was predictive of arrhythmias in real life. In a follow-up of our study of anger and TWA,[29] we found that anger-induced TWA was a significant predictor of arrhythmia, with likelihood of ICD-treated ventricular arrhythmia for those in the top quartile of anger-induced in the lab of over 10 times that of other patients

(CI 1.6–113, $p < 0.05$.) (Figure 4) Anger-induced TWA remained predictive after controlling for standard predictors of arrhythmia such as ejection fraction, prior clinical arrhythmia, and wide QRS. Prior studies of the predictive value of TWA have shown mixed results, and a recent consensus study concludes that “there is as yet no definitive evidence that it can guide therapy”. [30] Our study was limited by size, inclusion of mainly men, and using treated arrhythmias as an outcome in an era prior to current evidence-based programming. [31] However, the high predictive value seen here raises an intriguing possibility-- Laboratory mental stress-invoked TWA may be a better probe arrhythmia-risk, as this modality measures the interaction of trigger and substrate which may lead to arrhythmogenesis (rather than substrate alone).

The most physiologically detailed data on the impact of stress on repolarization comes from a recent study by Child, Taggart, et al, in which they measured activation recovery intervals, in patients undergoing invasive electrophysiology studies (for SVTs), at rest and during a stressful movie (“Vertical Limit”). Pacing ensured no change in heart rate, and breathing at rest was calibrated to respiratory rate during stress. Activation recovery intervals, a surrogate for action potential duration, decreased during stress, with regional difference between right and left ventricles. [32] This study was performed in subjects with normal ventricles, but it is highly likely that this decrease in repolarization time would be non-uniform in those with structurally and thus electrically abnormal hearts, perhaps increasing baseline heterogeneity as suggested by the TWA studies.

In a landmark study published in 1973,[33] Lown investigated the possibility that mental stress could facilitate induction of ventricular arrhythmias. Using a protocol conceptually similar to electrophysiologic programmed stimulation in a dog model, he found that in rested animals, only 1 PVC could be induced, and required a high output of 35 mA. In a dog stressed by being lifted in a sling conditioned to be a noxious experience, 2 PVCs were induced, using just 5mA. (figure 5.) In a similar study in humans, we later evaluated the effects of mental stress on induced arrhythmias in patients with a history of known ventricular arrhythmias and ICDs.[34] All patients had had VT which was terminated with anti-tachycardia pacing at previous EP studies. Some patients had VT induced earlier in the protocol, using fewer extra-stimuli, although this was not significant. However, arrhythmias induced during mental stress were faster than those induced at rest, and were harder to terminate. In some cases, an identical VT which had been pacer-terminated in the baseline state required shock for termination during anger-recall, (figure 6) suggesting that autonomic changes due to the anger had altered properties of conduction and refractoriness of the VT circuit, eliminating the excitable gap. Further understanding of the electrophysiological underpinnings of stress-induced arrhythmogenesis is an important avenue of future research. It will also be important to investigate whether there are interactions between gender and stress in impacting ventricular arrhythmias. As in most defibrillator studies, women are under-represented in all the above studies.

Stress and Ventricular Arrhythmias in Genetic Arrhythmic Disorders

The above data describe the impact of stress on ventricular arrhythmogenesis in patients with the most common cardiac diseases—ischemic and non-ischemic cardiomyopathy.

There are also several genetic arrhythmic disorders in which stress may play a role, in some cases through well-understood effects of catecholamines on the underlying channelopathies. Amongst LQTS patients, 26–43% of arrhythmic events have reportedly been preceded by emotional triggers, varying with genotype [35], with stress doubling the risk of an event in one study. [36] The sudden arousal by a loud noise can trigger arrhythmias, particularly in LQT2, [37] [38] In this genotype, with the underlying HERG mutation, beta-stimulation can lengthen the action potential with resultant development of the early afterdepolarizations which give rise to torsades. [38] In catecholaminergic polymorphic ventricular tachycardia, adrenergic stimulation exacerbates the mutated ryanodine-receptor gain-of-function, and this disease often first manifests as emotion (or exertion) related syncope. [39] Beta-adrenergic blockade is the cornerstone of therapy for both of these disorders.

Implications for novel therapies

In a recent American Heart Association Scientific Statement, Dunbar et al reviewed educational and psychological interventions to improve outcomes for ICD patients. [40] A number of studies have used a variety of psychoeducational methods—groups, phone interventions, cognitive behavioral therapy—and most have found improvements in psychosocial outcomes such as anxiety and quality of life. Intriguingly, several have also found improvements in arrhythmia frequency. In one small study, Chevalier[41] evaluated whether cognitive behavioral therapy, administered in small groups for three months after ICD implant, could reduce shock incidence, randomizing 70 patients to therapy or usual care. In the treatment group, anxiety was lower at 3 and 12 months in the treatment group, decreasing in the treated group, but increasing in the untreated. Heart rate variability was also higher, and heart rate lower, in the therapy-treated patients. Shock incidence was less at 3 and 12 months, although the 12 month comparison did not reach significance, likely due to the small numbers enrolled. In another small study, Toise et al randomized ICD patients to yoga classes, versus usual care, and found that yoga improved anxiety and patient acceptance of the ICD, and may reduce shock frequency. [42] Our group has recently completed follow-up in the RISTA trial—Reducing Vulnerability to Implantable Cardioverter Defibrillator Shock-Treated Ventricular Arrhythmias [43]—which randomized 300 ICD patients to an eight-week stress reduction program or usual care, to determine if reducing negative emotion can reduce arrhythmia frequency, and data analysis will begin shortly. This study is also evaluating whether stress reduction can attenuate the increases in TWA with laboratory stress which we have previously described (data analysis underway). Further research is needed to determine most effective stress-reducing modalities, whether complementary modalities such as yoga, or traditional modalities such as cognitive behavioral therapy, for reducing arrhythmia-frequency in patients with ICDs.

II. Atrial Fibrillation

While the links between stress and ventricular arrhythmias are now well-documented, as described above, data linking stress and atrial arrhythmias are just beginning to emerge.

Acute stress as a trigger for atrial fibrillation

Small case-series dating back 50 years have suggested that stressful stimuli may acutely trigger AF. Anecdotally reported emotional triggers have included a death or injury in the family, and awakening to an alarm. [44] 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.[45, 46] 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.

We have recently reported the first prospective study of emotional triggering of AF. [47] In this year-long, prospective, electronic-diary (eDiary)-based study, 95 patients with intermittent AF recorded their heart rhythm on event-monitor at the time of symptoms, and completed an eDiary query of their emotions (e.g., anger, anxiety, sadness, stress, happiness), 1) for the preceding (proximal) 30 minutes, (Figure 7) and 2) at the end of each day, summarizing their emotions for that day. Patients also underwent monthly 24-hour holter-monitoring, completing an eDiary twice per waking hour. Emotions reported on eDiary for the 30 minutes proximal to AF were compared to those reported during 24-hr holter monitoring during sinus rhythm. Similarly, end-of-day emotion summaries for days preceding a day with AF were compared to the end-of-day emotion summaries preceding a day without AF. Overall, 228 symptomatic AF episodes were reported by 40 subjects. There were 163 episodes (34 subjects) with associated proximal emotion reports on eDiary, 11,563 emotion reports during holter-confirmed sinus rhythm, 112 end-of-day summary emotion reports preceding days with episodes of AF (31 subjects), and 14663 end-of-day summary emotion reports preceding days without AF. Negative emotions (sadness, anxiety, anger, stress) increased the likelihood of an AF episode 2–5 fold (all $p < 0.01$.) Happiness decreased AF likelihood by 85% ($p < 0.001$). Anger and stress reported on end-of-day emotion summaries similarly increased the likelihood of AF the following day (HRs 1.69 and 1.82, $p < 0.05$). (Tables 1a and 1b).

This study may provide the first prospective proof of the triggering effect of emotion on arrhythmia in a real-world setting. Triggering of clinical cardiac events has been difficult to confirm, due to recall-bias, as previous studies have all queried emotion after the cardiac event had occurred. Conclusions drawn from these post-event, retrospective interview studies are tempered by several potential reporting biases, including memory decay, greater salience for emotional experiences just prior to and following event onset, and cognitive attempts to ‘explain’ symptoms *post-hoc*. [48] The electronic diary used in this study eliminates many of these confounding influences. Even more important, however, temporal associations were seen between emotions reported on end-of-the-day diaries and symptomatic AF on the following day, eliminating the possibility of recall-bias as an explanation.

Chronic stress increases susceptibility to atrial fibrillation

In addition to triggering of AF by acute stressors, chronic 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 the Framingham study, measures of anger, hostility and tension predicted development of AF over ten years in men, although not in women.[49, 50] 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. [51] In a more recent analysis of the Women's Health Study[52], measures of global distress as measured by the SF-36 did not predict development of AF. Interestingly, negative emotion has different physiological effects in women than men. Men show greater hemodynamic and neuroendocrine response to laboratory stressors than women, although specific patterns of activation by gender vary depending on the stressor. [53] Brain activation in response to stress also differs between the sexes. [54] Further, estrogen attenuates tachycardia-induced AERP-shortening, [55] which could lead to gender differences in propensity to AF with stress.

While distress did not predict AF in the Women's Health Study, 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,[56] and blood pressure, [57] and in daily life, happiness is associated with lower daily heart rate and cortisol, [56] all mechanisms which over time could be protective against AF.

Potential electrophysiological pathways linking emotion and atrial fibrillation

Negative emotions such as anger alter autonomic tone, increasing sympathetic and decreasing vagal activation. Experimental manipulations of the autonomic nervous system can perturb the electrical system of the atrium, shortening the effective refractory period (AERP),[58]and increasing heterogeneity of conduction and repolarization,[59] each of which facilitate AF. Most, [59] although not all,[60] studies, have shown that sympathetic stimulation decreases AERP. Shortest AERPs are found in the morning, coinciding with highest diurnal catecholamine levels.[61] As measured by heart rate variability, sympathetic activation[62] may precede AF.

Further, clinical effects of sympathomimetic drugs suggest a pro-fibrillatory effect of sympathetic stimulation. Isoproterenol, (alone or in combination with programmed electrical stimulation,) has been used to purposefully induce AF in patients undergoing AF ablation. [63]. Dobutamine also can cause AF, as an unintended side effect, when used for stress echocardiography[64] or maintenance of cardiac output.[65]

It is also possible that these sympathetic stimuli may provoke a vagal response, which may contribute to AF. The impact of vagal stimulation on atrial electrophysiological properties is also well described, shortening the AERP as well as the action potential duration,[59, 60] in a non-uniform distribution,[59] which correlates with duration of induced AF[59]. Further, vagal stimulation facilitates induction of AF with programmed stimulation.[66] Ambulatory monitoring studies analyzing heart rate variability have also shown a primary adrenergic increase followed by a vagal response may precede AF, supporting this concept.[67]

In addition to direct electrophysiologic effects, emotion could trigger AF indirectly, via acutely increased blood pressure (BP), which subsequently increases atrial pressure. In both

experimental[68, 69] and human[70] studies, increasing atrial pressure shortens AERP[68, 70], and/or increases dispersion of atrial refractoriness[69], (mechanoelectrical feedback,) which in turn correlates with new inducibility of AF by programmed stimulation.[68, 69] Further studies should address potential physiological mechanisms underlying the associations between negative emotion and AF.

Implications for novel therapies

Several small studies have evaluated the efficacy of complementary therapies, which increase relaxation, at decreasing AF burden and improving symptoms and quality of life for patients with AF. Lakireddy enrolled 52 patients with PAF in twice-weekly, three month yoga training program, and found that the yoga reduced symptomatic and asymptomatic AF episodes, as well as improving quality of life and decreasing anxiety and depression, compared to the period prior to yoga training. [71] In a small randomized study, acupuncture significantly decreased recurrence of AF after cardioversion compared to sham-acupuncture or usual-care groups. [72] Larger, randomized studies of yoga and other complementary therapies are needed, as are studies of traditional psychoeducational modalities, which have not thus far been investigated in AF patients.

Conclusion

Currently, neither ablation nor pharmacology offer a definitive cure for arrhythmias. Managing arrhythmia-frequency remains imperative for improving quality of life in patients with atrial and ventricular tachyarrhythmias. Based on extensive data clearly demonstrating links between negative emotion and atrial and ventricular arrhythmias, and preliminary data that complementary and traditional stress management techniques may be beneficial at reducing arrhythmias, it is important to make patients aware of these options.

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Figure 1. Incidence of ventricular arrhythmias terminated by an implantable cardioverter-defibrillator in the months prior to and following the World Trade Center attacks of 9/1/2001
From Steinberg et al, JACC 2004 (ref 5), with permission

Figure 3. Time to first appropriate implantable cardioverter-defibrillator (ICD) discharge by presence of depression according to Centers for Epidemiologic Studies-Depression scale score 16 ($p = 0.02$, log-rank test)

From Whang, et al, JACC 2005, (ref 11) with permission

Figure 4. Kaplan-Meier curves depicting survival from ICD-treated arrhythmias in patients with anger-induced TWA in the top quartile compared to the other quartiles
From Lampert, et al JACC 2009 (ref 24) with permission

From Lown, et al, Science, 1973

Figure 5. Sequential R/T pulsing in the conscious dog

In the cage, where dogs were never stressed, 35 ma in S_a elicits but a single repetitive response indicated by Letter R. However, in the sling where animals had received an electrical shock on the previous day, the threshold is reduced to 5 ma and now a dual repetitive response is elicited (RR). The heart rate was maintained constant at 200 beats per minute by ventricular pacing. From Lown et al, Science, 1973, with permission (ref 25)

Figure 6. Alteration of VT termination by anger

Top, in the resting-awake state, VT of CL 360ms is induced and terminated by ATP.

Bottom, During anger recall, an identical VT is induced but is accelerated by ATP into a zone requiring shock.

From Lampert, *Circulation* 2000, (ref 26), with permission

Figure 7. Electronic Diary

a Proximal emotions and atrial fibrillation			
	Unadjusted OR Adjusted OR	95% CI	P value
HAPPINESS	0.15	0.09 0.25	<.0001
	0.12	0.06 0.22	<.0001
SADNESS	5.39	3.11 9.34	<.0001
	5.59	3.2 9.75	<.0001
ANGER	3.94	2.12 7.34	<.0001
	4.46	2.38 8.36	.004
STRESS	2.92	1.52 5.59	.001
	3.07	1.53 6.13	.002
IMPATIENCE	2.92	1.52 5.59	.001
	3.07	1.53 6.13	0.002
ANXIETY	4.27	1.85 9.83	.0008
	4.41	1.8 10.78	.001
HUNGER	0.93	0.64 1.36	0.72
	0.98	0.68 1.4	0.90

b End-of-day emotion summary and next-day atrial fibrillation			
	Unadjusted OR/ Adjusted OR	95% CI	P value
GOOD MOOD	0.82	0.53 1.27	0.38
	0.81	0.54 1.21	0.36
SADNESS	1.22	0.78 1.89	0.39
	1.25	0.78 2	0.36
ANGER	1.69	1.01 2.81	0.05
	1.73	1.04 2.9	0.04
STRESS	1.82	1.16 2.84	0.009
	1.88	1.18 3.02	0.008
IMPATIENCE	1.44	0.98 2.11	0.07
	1.48	0.99 2.23	0.06
WORRY	1.37	0.88 2.15	0.17
	1.44	0.89 2.34	0.14

Odds ratios quantify the likelihood of AF following time-periods during which patients endorsed, compared to those during which they did not endorse, a particular emotion. Multivariable models adjusted for age, gender, use of beta blockers, simultaneous alcohol intake, time of day, day of week (weekday/weekend), and season, and included all emotions

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