Happiness and Stress Alter Susceptibility to Cardiac Events in Long QT Syndrome

Richard D. Lane, M.D., Ph.D.,* Harry T. Reis, Ph.D.,† Derick R. Peterson, Ph.D.,‡ Wojciech Zareba, M.D., Ph.D.,§ and Arthur J. Moss, M.D.§

*From the *Department of Psychiatry, University of Arizona, Tucson, AZ; †Department of Psychology, University of Rochester, Rochester, NY; ‡Department of Biostatistics and Computational Biology, University of Rochester, Rochester, NY; and §Department of Medicine, University of Rochester, Rochester, NY*

Objective: We sought to determine whether the circumstances preceding an arrhythmic event differed from those preceding a prior control occasion in patients with Long QT Syndrome (LQTS), a well-characterized genetic disorder that puts affected individuals at risk for sudden cardiac death.

Methods: Thirty-eight patients (89% female) with LQTS completed a "case-crossover interview" in which each patient served as his/her own control by reporting on circumstances preceding an arrhythmic event (syncope, aborted cardiac arrest, or defibrillator discharge) and preceding a control occasion (the next-to-last birthday). On average the interview was conducted 17 months after the cardiac event and control occasion.

Results: During the 24-hour period preceding the cardiac event compared to the day before the control occasion, psychological stress was elevated, peak happiness was reduced, and peak exertion was not significantly different. Rated for the 6-month intervals preceding the event and control occasions, none of these three variables was significantly associated with events.

Conclusions: Happiness is associated with a reduction in the 24-hour risk of cardiac events in patients with LQTS, with stress having an opposite effect. To our knowledge, this is the first report indicating that positive emotion may have a protective effect on life-threatening ventricular arrhythmias. This study lends further support to the role of emotions in influencing cardiac events in arrhythmia-prone patients.

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Sudden cardiac death (SCD) is the leading cause of death in the Western world, accounting for over 300,000 deaths per year in the United States alone.[1] SCD typically occurs in the context of structural heart disease, particularly coronary artery disease (CAD).[2] Although SCD was once thought to be an inevitable result of the progression of the underlying disease, current thinking is that SCD results from an arrhythmia that occurs due to an interaction between a vulnerable substrate and a trigger, and that if the arrhythmia can be prevented or reversed, the potential victim can live many more years.[3] This has propelled research on resuscitation methods and led to the use of implanted defibrillators in high-risk patients.[4] At the same time, our understanding of the types of triggers that can induce SCD is advancing, and the evidence indicates that emotional states such as depression[5] and psychological stress[6] are associated with greater rates of cardiac mortality in the context of CAD compared to nondepressed or nonstressed controls. However, relatively little work has been done on psychological resilience or protective factors that can reduce the risk of SCD in individuals with heart disease.

One of the challenges for research in this area is that the cardiac substrate in CAD is very heterogeneous.[2] This is because the severity of occlusion of the coronary arteries varies a great deal

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Address for correspondence: Richard D. Lane, M.D., Ph.D., Department of Psychiatry, University of Arizona, 1501 N. Campbell Ave., Tucson, AZ 85724-5002. Fax: 520-626-6050; E-mail: lane@email.arizona.edu

from patient to patient, as does the location and extent of the lesions in the myocardium in those patients who have sustained a myocardial infarction (MI). Moreover, there are a variety of physiological mechanisms that can contribute to cardiac events in CAD patients, including ischemia, volume overload, and/or autonomic factors. This heterogeneity makes it necessary to study large numbers of patients in order to detect triggering or protective factors that influence outcome.

Long QT Syndrome (LQTS), by contrast, has been described as a Rosetta Stone for ventricular tachyarrhythmias.[7] LQTS is a genetic disorder caused by mutations of genes adversely affecting ion-channel function in the cellular membranes of cardiac myocytes.[8] Numerous mutations involving 10 different genes have been identified as causing this disorder, with 90% of the identified mutations involving the KCNQ1 (LQT1), KCNH2 (LQT2), or SCN5A (LQT3) genes that result in reduced repolarizing IKs (LQT1) and IKr (LQT2) currents or augmented late depolarizing current in LQT3.[9] The lengthened repolarization, detected in prolongation of the QT interval on the ECG, creates a vulnerability to ventricular tachyarrhythmias due to transient torsade de pointes or SCD from torsade de pointes that deteriorates into ventricular fibrillation. LQTS is considered an especially interesting naturally occurring model because the contractile heart muscle, coronary arteries, and conduction pathways are entirely normal, and because the nature of the arrhythmic vulnerability is well characterized. As a result, triggering and protective factors for cardiac events are easier to detect with smaller samples compared to the more complex substrate in CAD.

The clinical characteristics of patients with different LQTS mutations have many similarities,[10] although the frequency of various triggering factors for cardiac events may differ somewhat in the various forms of LQTS. Exercise and exertion are important triggering factors in LQT1, abrupt loud noise with startle are frequently initiating factors in LQT2, and cardiac events frequently occur during inactivity in LQT3.[11] Emotional stress with sudden or sustained activation of the sympathetic nervous system and accompanying catecholamine stimulation of the heart have been hypothesized as important physiologic mechanisms for triggering cardiac events in patients with LQTS.[12] Antiadrenergic therapies with beta-blockers or surgical left cervicothoracic sympathetic ganglionectomy have been a mainstay in the management of patients with this disorder.[13,14]

These LQTS-related treatments, as well as other primary, secondary, and tertiary prevention methods, have led to a decline in SCD due to LQTS, making prospective studies more difficult and expensive. An alternative approach is to focus on arrhythmogenic cardiac events and use each patient as his/her own control, using a method called the "case-crossover" interview.[15] Here the patient describes the circumstances preceding an event of interest as well as those preceding a specified control date in that patient's life. Anger,[16] exertion,[17] and sexual activity[18] have all been shown to increase the risk of acute MI using this methodology. Two previous case-crossover studies in recipients of implantable cardioverter-defibrillators (ICDs) have examined life-threatening arrhythmias as an outcome and found positive associations with emotional stress and physical exertion.[19,20] No previous case-crossover study has demonstrated an association between positive emotion or other potentially protective factors and any health outcome in any population, and none have been performed in LQTS patients.

METHODS

We studied 38 well-characterized patients with LQTS with a case-crossover interview. Due to the relative rarity of the disorder (1 in 5000) and the infrequency of cardiac events (less than 10% in 5 years), we performed telephone interviews with LQTS patients located across the United States.

Patients were identified from the International Long QT Syndrome Registry and from the practices of several other cardiologists. We selected LQTS patients who experienced a verified cardiac event within 3 years of our initial contact with them. Eligibility for enrollment included age between 14 and 80 years, a verified clinical or genetic diagnosis of LQTS, no evidence of neurologic or cognitive abnormality that would interfere with successful completion of the interview, and signed informed consent. The cardiac event, verified by study cardiologists, consisted of syncope, aborted cardiac arrest, or discharge of an implanted defibrillator. The control time period used for comparison purposes was the next-to-last birthday, as we sought a universally occurring occasion on a specific date approximately midway in the 3-year time window

that was likely to be remembered. Since a few patients had more than one cardiac event during the 3-year window, we selected the earliest of these cardiac events for this analysis. To facilitate recall, subjects were asked in advance to check their diaries and calendars to determine what was happening in their lives during the time periods of interest.

Telephone interviews were recorded. After a general description of the circumstances associated with the cardiac event, subjects were asked specific questions about the circumstances preceding the cardiac event or control date during the preceding 6 months, 1 month, and 1 day. For the cardiac event, the 1-day window for exertion, startle and happiness consisted of the time from when the subject awoke on the day of the event until the onset of the cardiac event, and for stress the 1-day window consisted of the entire 1-day period ending with onset of the cardiac event. For the control occasion (the day prior to the birthday), the 1-day window for all four variables consisted of the day before the birthday. Definitions of the variables being rated were provided verbally along with an advance hard copy of the rating form. For the control occasion and cardiac event, for each time window, subjects rated the following four variables on a 7-level intensity scale: highest level of exertion, most intense feeling of happiness, most intense startling event, and the level of stress/negative emotion. To ensure that the respondent understood how stress and/or negative emotions were to be rated, the interviewer described stress in four sentences followed by the statement "other negative emotions may include anger, sadness, grief, anxiety, depression, fear, guilt or loneliness." Other ratings included the number of startling events and the general level of happiness for the time period. Due to an administrative error, 1-month data for stress were not obtained.

Patient characteristics are listed in Table 1. Most patients were female and among those in this sample who had been genotyped, the distribution of genotypes was comparable to that of the LQTS population. Those not genotyped were diagnosed based on clinical criteria. Most patients were on beta-blockers both at the time of the interview and the control time period. Patients were evenly divided between those in whom the cardiac event preceded and those in whom it followed the control occasion, and the duration of these time intervals did not differ: mean (SD) = 320 (106) days for the 20 participants in whom the control date followed the event date and mean SD = 366 (157) days for the 18 participants in whom the control date preceded the event date. On average, the interview occurred 17 months after both the cardiac event and control occasion.

Table 1. Characteristics of the 38 Patients in the Study Population

	Value
Female, percent	89.5
QTc (ms)	0.51 ± 0.06
LQTS genotype, percent	
LQT1 (n = 8)	21.1
LQT2 (n = 7)	18.4
LQT3 (n = 3)	7.9
Unknown (n = 20)	52.6
Cardiac event	
Age at cardiac event, year	32.5 ± 17.2
1st cardiac event, percent	21.1
Number of cardiac events	6.3 ± 7.0
Cardiac event type	
Syncope (n = 24)	63.2
Aborted cardiac arrest (n = 1)	2.6
ICD shock (n = 13)	34.2
Chronology of event date and control date	
Control before event, percent	52.6
Days between event date and control date (absolute value)	342 ± 133
Number of days from interview	
Control occasion (mean)	515 ±179
Control occasion (median)	481
Cardiac event (mean)	520 ± 340
Cardiac event (median)	510
Beta-blockers, percent	
Day of cardiac event	60.5
Control occasion	60.5

Plus-minus values are mean ± standard deviation.

RESULTS

The prespecified primary analysis was to use conditional logistic regression, 1:1 matched by subject (nonparametrically controlling for all subject-specific time-independent covariates). This analysis modeled the binary 1-day event outcome as a function of four predictors: stress, peak exertion, peak startle, and peak happiness. Since the majority of patients failed to report whether or not they had been startled, this variable was excluded from the models. The primary null hypothesis that both stress and peak happiness are unrelated to cardiac events, adjusted for peak exertion, was tested via

Table 2. One-to-One Subject-Matched Multivariable Conditional Logistic Regression Analyses of Cardiac Event versus Control as a Function of Peak Happiness, Stress and Peak Exertion

	Adjusted Odds Ratio	95% Confidence Interval	P-Value
Within 24 hours of the cardiac event or control occasion[a]			
Peak happiness	0.60	(0.32, 0.95)	0.03
Stress	1.87	(1.03, 4.12)	0.04
Peak exertion	1.28	(0.74, 2.58)	0.38
6 months prior to the cardiac event or control occasion[b]			
Peak happiness	0.71	(0.31, 1.41)	0.33
Stress	1.08	(0.61, 1.96)	0.78
Peak exertion	1.32	(0.72, 2.58)	0.37

Adjusted odds ratio <1.0 indicates a reduced level of the variable prior to the cardiac event relative to the control occasion, with values >1 indicating the reverse.
[a]n = 34; four subjects ignored due to missing values.
[b]n = 36; two subjects ignored due to missing values.

the 2-df likelihood ratio test (LRT); the results (P = 0.0002) indicate that one or both of these variables is related to cardiac events. Follow-up 1-df LRTs of each individual predictor appear in Table 2. Both stress (OR = 1.87 per unit, P = 0.04) and peak happiness (OR = 0.60 per unit, P = 0.03) influence the risk of cardiac events, adjusted for one another and for peak exertion, while there is insufficient evidence of any relationship between peak exertion and cardiac events (OR = 1.28 per unit, P = 0.39). The odds ratio (OR) results imply that if a subject were to rate his own stress on the 0–6 scale at three times as 0, 1, and 3 (or, equivalently, 3, 4, and 6), then his odds of an event at time 3 would be 6.5 (1.87^3) times that at time 1, and 3.5 (1.87^2) times that at time 2, whereas the odds ratio for time 2 versus time 1 would be 1.87. Similarly, for each unit increase (decrease) in happiness, his odds of an event would decrease by 40% (increase by 1.67-fold), irrespective of whether he typically rated himself high or low on the happiness scale. The differences (event minus control) in peak happiness and stress were negatively correlated (r = −0.40, P = 0.02). Peak happiness and general happiness ratings were strongly correlated (r = 0.88, P < 0.001). No interactions were present between beta-blocker use and the effect of stress, peak exertion, or peak happiness. In Table 3, a comparison of general happiness and peak happiness during the 6-month, 1- month, and 1-day time periods indicates that peak happiness appeared unusually low on the day of the cardiac event. Stress was also significantly greater during the 24 hours prior to the cardiac event, relative to the day prior to the control occasion. Parallel analyses for the 6-month intervals prior to the event and control occasions were also performed, and the results appear in Tables 2 and 3. For the 6-month window, there was insufficient evidence of any association of stress or peak happiness (P = 0.40 for the 2-df LRT), adjusted for peak exertion, nor was peak exertion significant (OR = 1.32, P = 0.37).

Table 3. Ratings of Peak Happiness, General Happiness, Stress, and Peak Exertion at Different Time Intervals Prior to the Cardiac Event and Control Occasion

	Control Occasion Mean (SD)	Cardiac Event Mean (SD)	Difference Mean (SD)	95% Confidence Interval	P-Value
Peak happiness ≤ 1 day	4.35 (1.14)	3.08 (2.01)	−1.22 (2.12)	(−1.92, −0.51)	0.001
Peak happiness ≤ 1 month	4.92 (0.89)	4.55 (1.37)	−0.32 (1.13)	(−0.70, 0.05)	0.09
Peak happiness ≤ 6 months	5.03 (1.07)	4.92 (1.04)	−0.11 (1.05)	(−0.46, 0.24)	0.56
General happiness ≤ 1 day	3.62 (1.40)	2.68 (1.96)	−0.89 (2.23)	(−1.64, −0.15)	0.02
General happiness ≤ 1 month	3.74 (1.03)	3.45 (1.48)	−0.29 (1.61)	(−0.82, 0.24)	0.29
General happiness ≤ 6 months	3.68 (1.19)	3.43 (1.17)	−0.27 (1.47)	(−0.76, 0.22)	0.20
Stress ≤ 1 day	1.44 (1.13)	2.42 (1.59)	0.89 (1.58)	(0.35, 1.42)	0.001
Stress ≤ 6 months	3.32 (1.45)	3.46 (1.41)	0.14 (1.32)	(−0.30, 0.57)	0.51
Peak exertion ≤ 1 day	2.83 (1.12)	2.73 (1.76)	−0.03 (1.82)	(−0.66, 0.60)	0.93
Peak exertion ≤ 1 month	3.66 (1.02)	3.82 (1.18)	0.16 (1.26)	(−0.26, 0.57)	0.44
Peak exertion ≤ 6 months	4.03 (1.20)	4.11 (1.16)	0.08 (1.17)	(−0.31, 0.46)	0.74

The 7-point scale used for rating peak happiness, general happiness, and stress was: 0-none; 1-mild; 2-somewhat; 3-moderate; 4-quite a bit; 5-very much; 6-extreme. The 7-point scale used for rating exertion (17) was: 0-sleeping, reclining; 1-very light; 2-light (e.g., normal breathing); 3-moderate (e.g., deep breathing); 4-vigorous (e.g., panting); 5-heavy (e.g., gasping, much sweating); 6-extreme (e.g., extremely heavy gasping and sweating).

DISCUSSION

We believe that these results in LQTS patients provide further support for the influence of emotion-related factors on cardiac events in arrhythmia-prone patients. Although a number of case studies have reported that emotional stress precedes cardiac events in some LQTS patients,[11,12] none of these previous reports was controlled. The current study used the case-crossover method in which each patient served as his or her own control. This study is unique not only because it demonstrates in a controlled study that emotional stress is associated with arrhythmogenic cardiac events in patients with LQTS; it also, for the first time, demonstrates that positive emotion (happiness) is associated with reduced susceptibility for these events.

A key issue in the study of positive emotion and sudden death is whether high arousal positive emotions can have a deleterious effect on outcome. The literature is rife with anecdotes of patients who have died suddenly in the context of reunions, celebrations, special recognition, and the like.[21] To test for such a phenomenon, we included peak happiness in our prespecified model but anticipated a result in the opposite direction. Contrary to these anecdotes, in this controlled study our results instead demonstrated a protective effect of peak happiness. This result may have occurred because peak happiness on the day of the index event was correlated with average happiness over the course of the day and because the absolute level of peak happiness was moderate. It is therefore possible that strong positive emotion associated with very high arousal might yield a different result.

An intuitive concern might be that birthdays are intrinsically happy events and that our choice of a control event was biased accordingly. If that were the case, one might expect that the difference between the cardiac event and the control occasion would be due to elevated happiness scores prior to the birthday, yet such an elevation is not apparent in Table 3. In fact, Table 3 suggests that peak happiness was unusually low during the day of the cardiac event, consistent with the relative absence of a protective factor in that context, not an elevation of happiness prior to the birthday. Consistent with this finding, recent evidence indicates that birthdays are associated with elevated rates of MI, stroke, and transient ischemic attacks,[22] suggesting that in adulthood birthdays can themselves be stressful.

The protective effect of positive emotion that we observed in LQTS patients may be applicable to the broader context of SCD in patients with CAD. Higher levels of trait positive emotion are associated with decreases in: (1) the incidence of CAD,[23] (2) adverse cardiac outcomes (angina, recurrent MI, and cardiac mortality) in patients with established CAD,[24] (3) rehospitalization following coronary artery bypass graft surgery,[25] (4) all-cause mortality in patients with CAD,[26] and (5) cardiac mortality in patients with CAD.[27,28] Conversely, (6) reduced state positive emotion was associated with elevated rates of recurrent MI and cardiac mortality during the 2 years following implantation of coronary-artery stents.[29]

Research on cardiovascular correlates of positive emotion has been sparse, but current evidence is consistent with our findings. Positive emotion tends to be associated with heart rate decreases as compared to heart rate increases associated with negative emotion, faster recovery times following cardiovascular activation,[32] lower blood pressure,[33] and increases in the high-frequency (vagal) component of heart rate variability.[34] These findings are consistent with greater parasympathetic activity counteracting sympathetic effects. In the context of CAD, vagal tone and reflexes are known to be protective against SCD.[35]

Strong evidence that aversive emotions trigger ventricular tachycardia-ventricular fibrillation (VT-VF) has been provided by a new generation of studies in patients with implanted cardioverter-defibrillators (ICDs). These studies have demonstrated that depression[36] and the stress associated with the terrorist attacks on September 11, 2001 increased the propensity for life-threatening arrhythmias in the New York area.[37] The current study extends findings from the latter studies by examining patients with structurally normal hearts who have a well-defined genetic/metabolic substrate. This study adds to this impressive body of work that together provides strong evidence that aversive emotions increase the propensity for life-threatening cardiac events in the context of a pre-existing cardiac substrate.

Unlike studies of patients with CAD or idiopathic VT-VF,[38] we did not find an association between emotion variables during the 6 months preceding the cardiac event, and we did not find evidence for exertion as a trigger. These results should not

be taken as proof that such phenomena do not exist, however, as power was limited with this relatively small sample. However, the significant findings in this study suggest that emotional factors are associated with arrhythmogenic cardiac events in LQTS patients. They also highlight the need to study negative emotions as aggravating factors and positive emotions as salutary factors that influence the propensity for fatal arrhythmias in LQTS as well as other cardiac conditions associated with SCD. Our findings are consistent with extensive evidence showing that positive and negative emotions vary independently as two unipolar variables, not as a single bipolar variable.[39]

Case-crossover studies typically have a shorter time lag between the interview and the events being recalled. Indeed, our original plan was to study patients within six weeks of their cardiac events. Due to the rarity of LQTS and the challenges of identifying patients after events had occurred, we expanded the event time window in order to capture an adequate number of patients, as has been done in a study of patients who sustained cardiac arrest secondary to idiopathic VT-VF.[38]

We sought to maximize the likelihood of accurate recall in our design because the primary findings in this study involved recall of past experiences. A potential concern is that subjects who experience a cardiac event may fill an explanatory vacuum about the cause of the event by fabricating a story about stress when in fact none exists. There are several reasons why we believe that that is unlikely. First, patients were discriminating in their answers and stated that they did not know when they could not recall. For example, we asked about specific instances of startle in each time period, but the results were inconclusive because many patients could not confidently recall occurrences of startle. Second, if reports of stress were fabricated, the results would likely reflect what is known or typically believed about stress and cardiac events for both 1-day and 6-months before the event, yet no preferential association was observed between the cardiac event and stress during the preceding 6-month period. Third, it is commonly believed that happiness and stress are reciprocally related, yet we found them to make independent contributions. Had these reports been fabricated, they likely would have been redundant. Fourth, the day prior to the birthday was not associated with elevated levels of happiness, as might be expected based on conventional notions of birthdays as happy occasions. If recall bias is present in these data, then, it is likely to be more subtle than gross fabrication out of whole cloth.

The particular type of recall involved in this study consisted of the unique personal experiences of each subject, which is called "autobiographical memory" in the literature. It is now well established that emotion enhances encoding and retrieval of personal experiences,[40] consistent with the evolutionary advantages of remembering life-threatening circumstances. This memory enhancement occurs for both emotionally positive and negative events,[41] which is an important observation given our findings. It is also notable that women tend to have more detailed emotion-related memory than men[42] and most of the subjects in this study were women. In the case of ICD shock, which accounted for one-third of cases, memory may also have been enhanced through mechanisms related to classical conditioning.[43] By contrast, the control occasion was typically neutral in emotional content and likely was less well remembered. Therefore, one potential source of bias is that recall for the cardiac event may have been more accurate than recall for the control occasion.

It is therefore important to consider what such a bias would mean for the current findings. If specific details were lacking in the recall of the control occasion (compared to recall of the cardiac event), the subject likely reported a general estimate of what would be true for her or him on a typical day. If that were the case then that itself would be a suitable control period, in that it permits comparison of emotions experienced on the day of a life-threatening event with emotions experienced on a typical day. Thus, recall for the control is either accurate or is a general estimate of what is typical and would in either case constitute a useful and informative comparison relative to the cardiac event.

In conclusion, these preliminary findings, together with others indicating a cardioprotective effect of positive emotions,[23–29] suggest the need for new research on the cardiovascular correlates of positive emotion and on whether trait-like characteristics such as optimism and extraversion, both of which facilitate positive emotional experiences, are protective against SCD. They raise the question of whether the degree of anhedonia in depression,[44] as distinguished from the level of distress in depression, is an important predictor of mortality in individuals at risk for SCD, and whether

inactivity associated with heart disease contributes to reduced positive emotion as a consequence of a reduction in behavioral activation. They also suggest that interventions to increase positive emotion, such as scheduling enjoyable activities, being active, helping others, meditation, improving the quality of close relationships, enhancing a sense of self-efficacy, or cultivating a sense of purpose in life may have beneficial effects on longevity in those known to be at risk for life-threatening cardiac events.

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REFERENCES

1. Zipes DP,Wellens HJ. Sudden cardiac death. Circulation 1998;98:2334–2351.
2. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Epidemiology, transient risk, and intervention assessment. Ann Intern Med 1993;119:1187–1197.
3. Lown B, Desilva RA, Reich P, et al. Psychophysiologic factors in sudden cardiac death. Am J Psychiatry 1980;137:1325–1335.
4. Wellens HJ, Gorgels AP, de Munter H. Sudden death in the community. J Cardiovasc Electrophysiol 2003;14:S104–S107.
5. Lesperance F, Frasure-Smith N, Talajic M, et al. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002;105:1049–1053.
6. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med 1996;334:413–419.
7. Zipes DP. The long QT interval syndrome. A Rosetta stone for sympathetic related ventricular tachyarrhythmias. Circulation 1991;84:1414–1419.
8. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136–1144.
9. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes: KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2000;102:1178–1185.
10. Moss AJ. Long QT syndrome. JAMA 2003;289:2041–2044.
11. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: Gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
12. Schwartz PJ, Zaza A, Locati E, et al. Stress and sudden death. The case of the long QT syndrome. Circulation 1991;83:II71–II80.
13. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000;101:616–623.
14. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circulation 2004;109:1826–1833.
15. Maclure M. The case-crossover design: A method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144–153.
16. Mittleman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial infarction onset by episodes of anger. Circulation 1995;92:1720–1725.
17. Mittleman MA, Maclure M, Tofler GH, et al. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. N Engl J Med 1993;329:1677–1683.
18. Muller JE, Mittleman MA, Maclure M, et al. Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. JAMA 1996;275:1405–1409.
19. Fries R, Konig J, Schafers HJ, et al. Triggering effect of physical and mental stress on spontaneous ventricular tachyarrhythmias in patients with implantable cardioverter-defibrillators. Clin Cardiol 2002;25:474–478.
20. Lampert R, Joska T, Burg MM, et al. Emotional and physical precipitants of ventricular arrhythmia. Circulation 2002;106:1800–1805.
21. Engel GL. Sudden and rapid death during psychological stress. Ann Intern Med 1971;74:771–782.
22. Saposnik G, Balbergenova A, Dang J, et al. Does a birthday predispose to vascular events? Neurology 2006;67:300–304.
23. Kubzansky LD, Thurston RC. Emotional vitality and incident coronary heart disease: Benefits of healthy psychological functioning. Arch Gen Psychiatry 2007;64:1393–1401.
24. Kubzansky LD, Sparrow D, Vokonas P, et al. Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. Psychosom Med 2001;63:910–916.
25. Scheier MF, Matthews KA, Owens JF, et al. Optimism and rehospitalization after coronary artery bypass graft surgery. Arch Intern Med 1999;159:829–835.
26. Brummett BH, Boyle SH, Siegler IC, et al. Ratings of positive and depressive emotion as predictors of mortality in coronary patients. Int J Cardiol 2005;100:213–216.
27. Giltay EJ, Kamphuis MH, Kalmijn S, et al. Dispositional optimism and the risk of cardiovascular death: The Zutphen Elderly Study. Arch Intern Med 2006;166:431–436.
28. Giltay EJ, Geleijnse JM, Zitman FG, et al. Dispositional optimism and all-cause and cardiovascular mortality in a prospective cohort of elderly Dutch men and women. Arch Gen Psychiatry 2004;61:1126–1135.
29. Denollet J, Pedersen SS, Daemen J, et al. Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents. J Intern Med 2008;263:203–211.
30. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
31. Bardy BH, Lee K, Mark D, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
32. Fredrickson BL, Levenson RW. Positive emotions speed recovery from the cardiovascular sequelae of negative emotions. Cogn Emot 1998;12:191–220.
33. Steptoe A, Gibson EL, Hamer M, et al. Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire. Psychoneuroendocrinology 2007;32:56–64.
34. Brosschot JF, Thayer JF. Anger inhibition, cardiovascular recovery, and vagal function: A model of the link

between hostility and cardiovascular disease. Ann Behav Med 1998;20:326–332
35. La Rovere MT, Bigger JT Jr, Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes after Myocardial Infarction) Investigators. Lancet 1998;351:478–484.
36. Whang W, Albert CM, Sears SF, et al. Depression as a predictor for appropriate shocks among patients with implantable cardioverter-defibrillators: Results from the Triggers of Ventricular Arrhythmias (TOVA) Study. JACC 2005;45:1090–1095.
37. Steinberg JS, Arshad A, Kowalski M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. JACC 2004;44:1261–1264.
38. Lane R, Laukes C, Marcus F, et al. Psychological stress preceding idiopathic ventricular fibrillation. Psychosom Med 2005;67:359–365.
39. Watson D, Clark LA, Tellegan A. Development and validation of brief measures of positive and negative affect: The PANAS scales. J Pers Soc Psychol 1988;54:1063–1070.
40. McGaugh JL, Cahill L, Roozendaal B. Involvement of the amygdala in memory storage: Interaction with other brain systems. Proc Natl Acad Sci USA 1996;93:13508–13514.
41. LaBar KS, Cabeza R. Cognitive neuroscience of emotional memory. Nat Rev Neurosci 2006;7:54–64.
42. Cahill L. Sex-related influences on the neurobiology of emotionally influenced memory. Ann NY Acad Sci 2003;985:163–173.
43. Sears SF Jr, Todaro JF, Lewis TS, et al. Examining the psychosocial impact of implantable cardioverter defibrillators: A literature review. Clin Cardiol 1999;22:481–489.
44. Pizzagalli DA, Oakes TR, Fox As, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatr 2004;9:325, 393–405.