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Tendency to Angry Rumination Predicts Stress-Provoked Endothelin-1 Increase in Patients with Coronary Artery Disease

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Abstract

Objectives—To determine whether a tendency to angry rumination predicts anger recall stress provoked increase in ET-1 among patients with coronary heart disease (CHD).

Methods—Patients with chronic stable CHD (n=105) completed a 5-item measure of tendency to angry rumination (DAB-VR) and underwent a laboratory anger-recall stress protocol (15-min resting baseline [BL], 8-min anger recall [AR]). Blood samples drawn at end of BL and AR were assayed for ET-1. Change in ET-1 from BL to AR (increase vs. decrease/no change) was treated dichotomously in multivariate logistic regression models including DAB-VR score and potential confounders to evaluate the contribution of DAB-VR to the prediction of change in ET-1.

Results—In the multivariate model, DAB-VR score significantly predicted ET-1 increase (OR=1.34, 95% CI [1.10–1.63], p=0.004), controlling for age, history of diabetes, hypercholesterolemia, rate pressure product, use of β -blockers, and statins.

Conclusions—A tendency to angry rumination independently predicted AR stress provoked ET-1 increase among CHD patients. Given the involvement of ET-1 in plaque rupture, anger rumination tendency may identify vulnerability to anger triggered ACS through prolongation of initial anger mobilization. The contribution of ruminative thinking to sustained post-stress ET-1 elevation, and the synergistic relationship of ET-1 during emotional stress with norepinephrine and nitric oxide, remains to be explored.

Keywords

Anger; Rumination; Endothelin-1; Mental Stress; Coronary Heart Disease

INTRODUCTION

Trait anger - the tendency to respond to stressful situations with angry affect (1) - has been prospectively associated with a greater than 3-fold increased risk of incident coronary heart disease (CHD) (2). Furthermore, Mittelman et al (3) have shown that the experience of moderate to extreme anger in response to environmental provocation can trigger myocardial

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infarction (MI), with a 2.3-fold increased risk for a 2-hour hazard period after the provocation. In a recent replication (4) and extension (5) of the Mittelman et al findings, patients with anger-triggered acute coronary syndrome (ACS) showed *delayed recovery* of physiological responses after the termination of a laboratory psychological stressor, in comparison to patients whose ACS was not triggered by anger. These findings suggest that the pathophysiology underlying anger triggered events may entail not only physiological elements associated with acute coronary events (e.g., plaque rupture), but psychological elements that prolong the experience of anger after a discrete provocation and define a 2-hour period wherein vulnerability for ACS persists.

Delayed post-stress recovery and the processes underlying this phenomenon have been the focus of recent efforts, with angry rumination receiving considerable attention. Angry rumination is defined as the propensity to repetitively think about past situations that provoked anger at the time. During angry rumination, anger is re-provoked by the repeated focus on the causes and consequences of an anger provoking incident (6,7). Research has shown that individuals prone to angry rumination evidence delayed recovery of physiological stress responses in the laboratory after the termination of standard psychological stress tasks (e.g., mental arithmetic with harassment, anger recall), and reactivation of these responses when the individual is prompted to think about a prior laboratory stress session (8,9). We have also shown that CHD patients who are predisposed to *re-experience* anger in the lab during their description of a past anger provoking incident are at greater risk for transient myocardial ischemia, and potentially fatal arrhythmias (1,10,11). Thus rumination, by prolonging and/or repeating the experience of anger and the associated physiological responses after a stressful episode, may play a key role in anger provoked coronary syndromes. Furthermore, the tendency to engage in angry rumination may identify a vulnerability marker for these triggered events.

In addition to a potentially important role for angry rumination, the link between anger and triggered coronary syndromes may in part be mediated by vascular dysfunction. For example, we and others have shown that laboratory psychological stress - including anger recall -can provoke epicardial and coronary microvascular vasoconstriction (12–14), and peripheral endothelial dysfunction that lasts for greater than 90-minutes after the stress is terminated (15,16). This phenomenon appears to be at least partially mediated by endothelin-1 (ET-1) (15,17), the most potent endogenous vasoconstrictor (18). While ET-1 is normally secreted by endothelial cells, in the arterial substrate defined by CAD research has shown that it is also secreted by activated macrophages, the primary inflammatory cells found in atherosclerotic lesions (17,19–22). It is through this pathway that ET-1 contributes to the atherosclerotic process (20) and to the enhanced vasoreactivity (19–22) that links ET-1 to coronary plaque rupture (23,24) and the triggering of ACS events (18,25).

While the tendency to re-experience anger that has been previously experienced - angry rumination - is related to a range of stress-provoked physiological consequences that include coronary microvascular dysfunction and transient myocardial ischemia, it is not known whether ET-1 plays a contributing role in this relationship. The purpose of the present study was therefore to explore whether angry rumination is associated with an increase in ET-1 in response to laboratory “anger recall” in patients with CHD.

METHODS

Subjects

Patients with chronic stable CHD (n=105), documented by history of ACS, surgical or percutaneous revascularization, and/or positive exercise myocardial perfusion study were recruited from the Cardiology outpatient clinics at Yale University Medical Center and VA Connecticut Healthcare System from January 2004-February 2008. Patients with a diagnosis

of myocardial infarction or unstable angina within 3-months of the study, surgical or percutaneous revascularization within 6-months of the study, major cardiac arrhythmia or use of a pacemaker or implantable cardioverter defibrillators, uncompensated congestive heart failure, incapacitating or life-threatening illness, major psychiatric disorder, substance abuse disorder (by history), cognitive impairment, pregnancy, and/or inability to speak or read English were excluded. The population enrolled was homogeneous with regard to severity of CHD as demonstrated by perfusion imaging, and all patients fell into NY Heart Association Class I–II. The study was approved by the Institutional Review Board at both medical facilities.

Medical chart review and patient interview were used to obtain demographic information and determine cardiovascular risk profile. Participants with a recent history of systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg, or currently taking medication for high blood pressure were classified as hypertensive, while those with total cholesterol $\geq$ 200 mg/dl, LDL $\geq$ 130 mg/dl, or taking cholesterol lowering medications were classified as having hypercholesterolemia. Use of beta-blockers, statins, angiotensin converting enzyme inhibitors, aspirin and calcium channel blockers was documented. Tobacco use was also determined. Patient characteristics are described in Table 1.

Procedures

As part of a larger investigation concerning the effects of emotional stress on vascular performance, patients reported to the Cardiovascular Behavioral Medicine research laboratory at 9AM on the morning of study. Participants were asked to eat a light breakfast and take their normal medications. On arrival they completed the 5-item Destructive Anger Behavior Verbal Rumination (DAB-VR) questionnaire, a measure of tendency to engage in angry rumination that has been used in previous studies (9). The items describe responses to anger situations that are self-focused (e.g., “I feel compelled to discuss the situation that made me angry, over and over again”, “I continue to dwell on it”, “I hold a grudge”). Patients rate each item on a 1–4 scale that indicates how often the individual feels or acts in the manner described (total score range 0–20). Cronbach’s alpha for this scale on this sample was 0.73 with inter-item correlation ranging from 0.67–0.74. This is comparable to other samples on which adequate test-retest reliability was also established (9).

After completing the questionnaire, an indwelling intravenous catheter was placed in the patient’s non-dominant arm for collection of blood samples. Patients were then placed in a relaxed recumbent position, and a 30-minute rest period was initiated to allow for return of vascular biologic mediators to resting levels subsequent to catheter placement. This 30-minute rest period was followed by a standard psychological stress protocol (14,26) that included a 15-min resting baseline condition (BL), followed by an 8-min anger recall condition (AR). The time of initiation and end for each of these conditions (rest, BL, AR) was recorded.

During BL, the patient was instructed to close their eyes and imagine being in a restful setting. Approximately 10-min into this condition two blood samples of 4mL each (for catecholamine and ET-1 assay) were collected into refrigerated vacuum tubes containing potassium EDTA as an anticoagulant, mixed by gently inverting the tube for 30 seconds, and placed on ice. After completion of BL, the AR condition was initiated. Participants were instructed to recall a recent incident that had made them irritated, aggravated, or frankly angry. They were then instructed to describe this incident in detail to the interviewer. Follow-up questions designed to make the experience of anger more vivid were asked throughout the condition. Approximately 2-min into the condition, a 4mL blood sample for catecholamine analysis was collected into refrigerated tubes containing reduced glutathione and placed on ice. The timing of the 2-minute sample was based on previously published data from our laboratory concerning onset and peak of cardiovascular effects associated with laboratory emotional stress (27). In the last minute of AR a final blood sample for ET-1 assay was collected into a refrigerated vacuum tube

containing potassium EDTA, mixed by gently inverting the tube for 30 seconds, and placed on ice. Upon completion of the AR condition, the catheter was removed, and patients were de-instrumented and released.

Measures

Blood samples for catecholamine analysis were brought to the Yale General Clinical Research Center within 60-min where they were spun and stored at -70°C until analysis. Catecholamines were analyzed by high-performance liquid chromatography, (ESA Inc, Chelmsford, MA) using electrochemical detection (Coulchem II) after alumina extraction. Sensitivity of the assays for both epinephrine and norepinephrine are at least 5 pg/ml.

Blood samples for ET-1 assay were centrifuged at 3000g for 15 min to separate plasma. Aliquots of plasma were then stored at -70°C until analysis. Enzyme-linked immunosorbent assay (ELISA) was used for assessment of ET-1 using a colorimetric sandwich kit generating absorbance at 450 nm (Biomedica Gruppe, Austria). The kit has a detection limit of 0.02 fmol/ml (0.05 pg/ml). Specificity of the antibody used in this kit has previously been described (28), as has its use in a previous study in humans (29). All samples from a single subject were analyzed in one assay to insure against inter-assay variation.

Statistical Analysis

The distribution of ET-1 at baseline and anger recall was not normal, nor did logarithmic transformation contribute to normality (all Shapiro-Wilks p-values were <0.0001). ET-1 is a physiologically active and dynamically secreted protein. While research examining the effect of psychological stress on level of ET-1 in relatively young and healthy samples has treated ET-1 as a continuous variable (30–32), the current sample was defined by the presence of active CAD, and all patients were taking medications with cardiovascular effects. These two factors substantially alter the underlying vascular substrate and the bio-distribution, availability, and kinetics of ET-1 (19–25). The non-normality of our distribution is therefore not unexpected. Furthermore, other researchers have found that a very a low threshold of ET-1 increase is related to triggered ACS (25) and post-ACS prognosis (33,34). Given the exploratory nature of the current study and the demonstration in these latter findings that even a small increase in ET-1 can be risk related, change in ET-1 (in fmol/ml) from BL to AR was treated dichotomously (increase vs. no change/decrease). We then examined the contribution that DAB-VR score makes to the likelihood of an increase in ET-1 from BL to AR, vs. no change/a decrease.

Baseline indices (e.g., age, left ventricular function) as a function of ET-1 change were compared with t-tests or sign rank tests as appropriate. Change from BL to AR for cardiovascular (heart rate, systolic blood pressure, diastolic blood pressure, rate pressure product) and neuroendocrine (epinephrine, norepinephrine) indices were tested for the total cohort and as a function of change in ET-1. DAB-VR score was treated as a continuous variable and logistic regression was used to determine its contribution to change in ET-1 from BL to AR. This model was adjusted for variables whose selection was based on previous research. These variables included age, based on marked increased microvascular dysfunction with age (35) and on a stronger association of ET-1 with CHD in elderly individuals (36); diabetes, based on the association of endothelial dysfunction in that patient population (37); hypertension, based on higher ET-1 levels documented in hypertensive individuals (38); β -blocker use, based on literature supporting a role for β -blockers in a decrease production and secretion of ET-1 (39); and statins based on their potential to affect endothelial function and ET-1 synthesis (40,41). We also controlled for rate pressure product, due to its known contribution to sheer stress, which could serve as a potential mediator in the secretion of ET-1 (42). All tests were two-sided, and analyses were performed using SAS version 10.1 (43).

RESULTS

The average age of the study cohort was 67 years (± 8.9 years), with 1.9% female and 11% non-white. Most patients had a history of hypertension (86%) and 13% were active smokers. Mean LVEF was greater than 52%. With regard to medications, 55% were on ACE inhibitors, 78% were on β -blockers, 28% on calcium channel blockers and 90% on statins. (Table 1). The mean DAB-VR score for the cohort was 7.9 ± 2.5 , with participants evidencing an increase in ET-1 from BL to AR ($n = 54$) scoring higher (8.5 ± 2.6) than those evidencing a decrease ($n = 47$) or no change ($n = 4$) (7.3 ± 2.4 , $p = 0.02$). There was a significant increase from BL to AR in all cardiovascular and neuroendocrine indices, thereby demonstrating the effect of the AR condition, with no difference as a function of change in ET-1. (Table 2).

The multivariate logistic regression model showed a significant Odds Ratio of 1.34 (95% CI [1.10–1.63], $p = 0.004$) for risk of an increase in ET-1 from BL to AR attributable to DAB-VR score. (Table 3). Among the patients who experienced an increased in ET-1, 71% were on β -blockers; compared to 86% in the group with a decrease/no change ($p = 0.049$). The interaction between beta blockers and DAB-VR score was tested and found however, to not be significant ($p = .81$).

DISCUSSION

The experience of moderate to extreme anger in response to a stressor significantly increases risk for triggered ACS, with a prolonged post-stress hazard period (3,5). This finding, which is mirrored by prolonged endothelial dysfunction after laboratory psychological stress that appears mediated by ET-1 (15), has led researchers toward the identification of factors that underlie both the anger-triggering of the event and the prolonged hazard period. In the current study, the tendency to angry rumination among CHD patients significantly predicted an increase in ET-1 provoked by anger recall stress. The measure used to assess tendency to angry rumination has previously been linked to delayed recovery of physiological responses after termination of laboratory stress and to re-activation of these responses upon recall of that laboratory session several weeks later (8,9). Considering that the immediate experience associated with most anger episodes lasts for merely a few minutes, the relatively longer hazard period for anger-triggered ACS demonstrates that processes unleashed by the initial episode are paramount. The results of the current study suggest that a tendency to angry rumination may be a vulnerability marker for anger-triggered ACS events. These results may suggest two complementary processes by which an episode of anger can trigger ACS at 2-hours remove: first, due to rumination about the anger provoking episode subsequent to that episode, and secondly by the effect of rumination on the secretion of ET-1. It is important to note however, that we did not utilize an extended recovery period. Thus we did not assess whether research participants engaged in ruminative thinking after the AR condition during which they described the episode that previously provoked anger, or whether this ruminative thinking had a prolonged effect on ET-1. Therefore a demonstration of whether these two complementary processes are engaged as a function of anger recall stress among CHD patients with a high tendency to angry rumination remains for future research.

ET-1 is a potent vasoconstrictor with actions in both the peripheral and cardiac circulations (17,19–21,23,44). It is abundantly present in the intima of atherosclerotic coronary arteries (17,21,23,44), contributing significantly to reactive tone in the coronary microvascular bed (21), and during laboratory psychological stress, to peripheral endothelial dysfunction (15). Of perhaps greatest importance for the current findings, ET-1 has been linked to plaque rupture and subsequent ACS (18,25) and increased levels are found throughout the intima of atherosclerotic arteries, particularly in areas with significant macrophage infiltration (23). Furthermore, in studies that examined the independent contribution of ET-1 to plaque rupture

(25) and to post-myocardial infarction prognosis (33,34), a low threshold increase was found to significantly predict early death and cardiovascular complications. Of note, the average increase in response to anger recall stress seen in the current study among those patients grouped accordingly (0.58 fmol/ml) was within the range for the median level of ET-1 that in these earlier studies was associated with prognosis (range 0.25 fmol/ml to 1.16 fmol/ml). Thus, the increase in ET-1 that we observed in association with recollection of a previous anger provoking incident may explain an important part of an overarching process which promotes an increased vulnerability for those patients inclined to angry rumination.

The processes by which anger provoking stress and subsequent angry rumination might modulate ET-1 release are not fully understood. Previous work from our group (45) suggests that a decrease in parasympathetic tone during anger recall stress may disinhibit infiltrated macrophages, thereby accelerating their production and/or release of ET-1, while Lerman et al (46) using an animal model, have reported a strong correlation between acetylcholine-induced coronary vasoconstriction and elevated plasma ET-1. Indeed, it may be this process that contributes to the paradoxical epicardial vasoconstriction and coronary microvascular dysfunction observed by our group and others in studies of mental stress with CHD patients (12–14). Similarly, ET-1 has been shown to synergistically sensitize the vasculature to norepinephrine, a known vasoconstrictor that is increased in the circulation during mental and emotional stress (47). Thus, research should be directed toward the elucidation of the complex pathway(s) by which emotional stress contributes to ET-1 secretion and ultimately to triggered coronary syndromes.

The current study is not without limitations. The population was relatively small and predominantly male, which may skew the results since levels of ET-1 are generally lower in pre-menopausal females, possibly due to protective effects of estrogen (48). In addition, the dichotomous treatment of ET-1 raises known statistical issues, though the exploratory nature of the current study and the non-normal distribution of ET-1 in the current sample provide some justification for this approach. We also did not measure ruminative angry thoughts or ET-1 during an extended, post-stress recovery period. The DAB-VR only served to assess a participant's tendency to angry rumination, while ET-1 was measured only before and at the end of the AR stress. Therefore, the current findings neither indicate the degree of angry rumination that may have taken place after the stressor was removed nor the effects of this rumination on ET-1. Future studies should include both self-reported angry rumination and ET-1 levels during an extended recovery period so as to provide for a more direct test of whether angry rumination is linked to prolonged elevation of ET-1.

In the current study 45% of the participants experienced a *decrease* in ET-1 with AR stress, and these individuals were more likely to be on β -blockers. Indeed, the multivariate model demonstrated a 70% reduction in risk of an increase in ET-1 with AR stress (95% CI [0.09–0.99], $p=0.05$). This observation is consistent with the known effects of β -blockers on ET-1 (39,49), though prior work by our group has also shown β -blocker use to be associated with increased risk of psychological stress provoked ischemia (50).

It is also possible that individuals demonstrating a decrease in ET-1 from BL to AR experienced some degree of anticipatory stress during the rest and baseline conditions. This anticipatory stress may have increased the level of ET-1 observed during BL. With the onset of the stressor and the opportunity to respond, these patients may have experienced some degree of “relief” with an associated decrease in ET-1. We did not measure subjective levels of stress or anger for each condition in this study, so it is not possible to determine whether this was indeed the case. It is important to note however, that regardless of change in ET-1, there was a significant increase in both the cardiovascular and neuroendocrine indices from BL to AR. ET-1 production and secretion is complex, involving a range of factors. Future studies should be

devoted toward a more complete elucidation of these processes as they relate to emotional stress-triggered pathophysiological processes.

In summary, the tendency to engage in angry rumination among CHD patients predicted ET-1 increase during the recall of a previously anger provoking incident. We speculate that angry rumination and its effects on endothelial cell and macrophage function after a psychological stress may accelerate and prolong the release of ET-1 after the initial stimulus is no longer present. Therefore, angry rumination may link anger episodes to acute cardiac events. These results represent a new finding that needs to be corroborated by larger studies.

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List of abbreviations

CHD	coronary heart disease
ACS	acute coronary syndrome
MI	myocardial infarction
ET-1	endothelin-1
DAB-VR	destructive anger behavior verbal rumination
BL	baseline
AR	anger recall

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Table 1

Patient Characteristics

Variable	ET-1		
	Overall Cohort (N=105)	Increase (n=54)	Decrease/ NC (n=51)
Age	66.5(8.9)	67.9(8.7)	65.0(9.0)
Female	1.9%	3.7%	0%
Non White Race	11.4%	11.1%	11.8%
History of Hypertension	85.7%	83.3%	88.2%
Active smokers	13.3%	13.0%	11.7%
LVEF	52.2(9.4)	52.7(9.7)	51.7(3.1)
Obesity (BMI >30)	46.2%	42.6%	50.0%
Diabetes	31.4%	31.5%	31.4%
Medications			
Ace inhibitors	55.2%	50.0%	60.8%
Beta-Blockers *	78.1%	70.4%	86.3%
Aspirin	67.6%	70.4%	64.7%
Calcium Channel Blocker	27.6%	29.6%	25.5%
Statins	90.5%	87.0%	94.1%

*
p-value = 0.049

Values are percent of group, or group mean (standard deviation)

Table 2

Physiologic Response to Anger Recall*

ET-1			
	Overall Cohort (n=105)	Increase (n=54)	Decrease / NC (n=51)
Δ HR (bpm)	9.9 (6.5)	10.5 (6.4)	9.2 (6.6)
Δ SBP (mm Hg)	29.0 (13.9)	29.3 (14.9)	28.7 (13.0)
Δ DBP (mm Hg)	12.8 (9.1)	14.2 (8.2)	11.3 (9.9)
Δ Epinephrine (pg/ml)	12.6 (25.3)	17.5 (28.2)	7.1 (20.5)
Δ Norepinephrine (pg/ml)	11.4 (113.2)	6.2 (125.0)	17.3 (99.0)

* - Values are provided as mean change (SD)

Table 3

Logistic Regression Predicting ET-1 Increase From BL to AR

Variable	Point Estimate	95% Wald Confidence Limits		P-Value
Rumination	1.34	1.10	1.63	0.004
Use of Beta-Blockers	0.30	1.00	1.10	0.05
Diabetes	0.73	0.27	2.01	0.55
Age	1.045	1.05	1.00	0.08
Use of Statins	0.72	0.14	3.72	0.70
Hypertension	0.44	0.12	1.67	0.23
Change in RPP	1.01	0.99	1.03	0.40