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TRAIT ANGER, HOSTILITY, SERUM HOMOCYSTEINE, AND RECURRENT CARDIAC EVENTS AFTER PERCUTANEOUS CORONARY INTERVENTIONS

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Abstract

Background—Trait anger, hostility, and serum level of homocysteine are associated with recurrent cardiac events after percutaneous coronary interventions. However, whether trait anger or hostility influences the association between serum level of homocysteine and recurrent cardiac events is unknown.

Objectives—To examine the relationships among trait anger, hostility, serum level of homocysteine, and recurrent cardiac events after percutaneous coronary interventions.

Methods—This prospective study included 135 consecutive patients (68% male, mean age 61 [SD, 10] years) undergoing percutaneous coronary interventions during an index hospitalization. Trait anger and hostility were measured with the Spielberger Trait Anger Scale and the Cynical Hostility Scale, respectively. Blood samples were obtained to measure serum levels of total cholesterol, triglycerides, high- and low-density lipoprotein cholesterol, and homocysteine. Recurrent cardiac events (emergency department visits and rehospitalization) were noted for 6 months after discharge and confirmed by review of hospital records. Hierarchical Cox hazard regression was used for statistical analysis.

Results—Trait anger (hazard ratio = 1.11, 95% confidence interval = 1.03–1.20) and homocysteine level (hazard ratio = 1.10, 95% confidence interval = 1.01–1.21) were independent predictors of recurrent cardiac events after other risk factors were controlled for. Patients with high trait anger (score ≥ 24) and high serum level of homocysteine (≥ 11.3 μmol/L) had the shortest time to recurrent cardiac events ($P = .01$).

Conclusion—Trait anger had a combined effect on the link between serum level of homocysteine and recurrent cardiac events. Interventions to reduce trait anger may improve health outcomes by influencing both trait anger and homocysteine level.

The mortality rate of patients with coronary artery disease (CAD) has steadily decreased, thanks to advances in percutaneous coronary interventions (PCIs).¹ However, in South Korea, cardiovascular disease, including myocardial infarction, remains a major cause of

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FINANCIAL DISCLOSURES

None reported.

death.² Restenosis rates after PCIs vary widely from less than 10% to 60%.^{1, 3, 4} In addition, the rate of recurrence of cardiac events (eg, emergency department visits and rehospitalization due to restenosis) within 6 months after PCIs is almost 15%,⁵⁻⁷ and recurrence of cardiac events confers a higher risk of fatal myocardial infarction. Therefore, secondary prevention of recurrent cardiac events remains important, and research to identify factors that may contribute to recurrent cardiac events among patients with CAD after PCI is essential.

Previous investigators have identified characteristics of patients, including sex, age, hypertension, smoking, serum level of cholesterol, obesity, diabetes, and lack of physical activity, as predictors of development and progression of CAD.⁷⁻⁹ Recently, serum level of homocysteine has also been identified as a risk factor for development and progression of CAD^{10, 11} and restenosis in patients undergoing PCIs.^{12, 13} Homocysteine is an intermediate metabolite of methionine.¹⁴ High concentrations of homocysteine markedly increase the risk for development and progression of CAD by damaging vascular endothelial cells and stimulating prothrombin responses and proliferation of smooth muscle cells.¹⁵⁻¹⁷ Behavioral pathways that may link high serum levels of homocysteine to CAD (eg, lack of physical activity and smoking) have been suggested.^{18, 19} However, these behavioral mechanisms do not explain fully the association between serum level of homocysteine and recurrent cardiac events.

As a result, interest in the relationship among psychosocial factors, biological factors, and development of CAD is growing.²⁰ Hostility has a positive correlation with serum levels of homocysteine.^{21, 22} High levels of hostility are predictive of CAD²³ and restenosis in patients who undergo PCI.²⁴ People with a higher level of hostility tend to experience more intense and frequent feelings of anger than do people with a lower level of hostility.^{21, 25} Anger is predictive of the occurrence of CAD⁹ and recurrent cardiac events after successful PCIs.²⁶ The potential link among trait anger, hostility, and serum level of homocysteine in patients with CAD after PCIs as a tentative mechanism leading to recurrent cardiac events has not been fully explored.

The purpose of this study was to examine the relationship among trait anger, hostility, serum level of homocysteine, and recurrent cardiac events in patients undergoing PCIs. The following 5 hypotheses were proposed.

Hypothesis 1: The risk of recurrent cardiac events will be higher in patients with higher trait anger once age, sex, body mass index, regular exercise, smoking behavior, and serum levels of total cholesterol, triglycerides, and high- and low-density lipoprotein cholesterol are controlled for.

Hypothesis 2: The risk of recurrent cardiac events will be higher in patients with higher levels of hostility once traditional risk factors are controlled for.

Hypothesis 3: The risk of recurrent cardiac events will be associated with higher serum levels of homocysteine once traditional risk factors are controlled for.

Hypothesis 4: Patients with high trait anger and high homocysteine level will have the shortest time to recurrent cardiac events after traditional risk factors are controlled for.

Hypothesis 5: Patients with high hostility and high homocysteine level will have the shortest time to recurrent cardiac events once traditional risk factors are controlled for.

Methods

Patients and Setting

A prospective study design was used. Participants were recruited from 2 university tertiary referral hospitals in Seoul, South Korea, between August 1, 2005, and December 2005. Both hospitals have acute and critical coronary care units.

The sample size of this study was estimated by using a power analysis suggested by Erdfelder et al.²⁷ According to previous studies,^{5–7} the recurrence rate for cardiac events within 6 months after PCIs is almost 15%. Twelve independent variables were included in this study. According to the G*Power 3 program²⁸ (effect size $f^2 = 0.15$, $\alpha = 0.05$, 95% power, using 12 predictors), a sample size of at least 127 was required.

Inclusion criteria were (1) CAD diagnosed by 2 cardiologists and confirmed via coronary angiography, (2) patients hospitalized for percutaneous transluminal coronary angioplasty with or without a stent.

Exclusion criteria were (1) history of a cognitive disorder, (2) cancer, (3) current psychiatric problems such as schizophrenia, bipolar disorder, or antisocial personality disorder, (4) thyroid disease, (5) chronic renal disease, and (6) taking vitamin supplements including folate and vitamins B₆ or B₁₂. Environmental factors such as disease and taking vitamin supplements are known to influence homocysteine level.²⁹ One hundred forty-two patients were eligible for this study. Three patients refused to participate, 2 patients withdrew, and 2 patients were lost to follow-up. Thus, a final total of 135 patients were included.

Instruments and Measurements

The Spielberger Trait Anger Scale (STAS), a self-rated tool for evaluating intensity and frequency of feelings of anger, was used to measure trait anger.³⁰ The STAS, a 10-item instrument, is rated on a 4-point scale ranging from 1 (not at all) to 4 (very much). The total score range is 10 to 40, with higher scores indicating the predisposition toward quick unprovoked anger, a fiery temper, and aroused anger in response to unfair treatment and negative critique. The reliability of the STAS was previously supported by Cronbach α 's from 0.74 to 0.85.^{30, 31} The Cronbach α for the Korean version of the STAS was 0.86.³² In this study, the Cronbach α for all 10 items was 0.91. The STAS correlated positively with the Multidimensional Anger Inventory widely used for measuring angry temperament and angry reaction^{33, 34} among middle-aged Korean men and women.³⁵

Hostility was measured with the Cynical Hostility Scale, a 24-item instrument for evaluating cynical and mistrustful attitudes toward others.³⁶ Subjects responded on a scale ranging from 1 to 4 (1, not at all; 2, some; 3, much; 4, very much). The total score range is 24 to 96, and higher scores indicate a higher level of hostility. The initial Cronbach α for the total 24 items of the Korean version of the Cynical Hostility Scale was 0.77.³⁷ In this study, the Cronbach α for the total 24 items was 0.91. The convergent and discriminant validity of the Cynical Hostility Scale had been previously established, with the higher score indicating more suspiciousness, severe resentment, frequent hassles and cynical distrust, less hardiness, and less satisfaction with others.³⁸

A blood sample was obtained from fasting patients at the time of enrollment to measure serum levels of total cholesterol, triglycerides, high- and low-density lipoprotein, and homocysteine. Data on each patient's age, sex, body mass index, smoking, and regular exercise behavior were collected from patients' medical records and interviews.

The outcome variable for this study was the combined end point of recurrent cardiac events, which were defined as emergency department visits or rehospitalization for myocardial infarction, repeat percutaneous coronary intervention, or coronary artery bypass graft surgery. As specified in the updated guidelines for PCIs from the American College of Cardiology/American Heart Association,⁷ a 6-month follow-up after PCI served as the standard period for evaluating outcomes. Data on the time, date, and cause of all recurrent cardiac events were collected for 6 months and confirmed by review of hospital records.

Procedure

Approval was granted by the institutional review boards at the 2 university hospitals before patients were recruited for this study. After the investigator explained the study, written informed consent and permission to review hospital records for any subsequent hospitalization were obtained from the patients. Patients received the questionnaires to complete within 3 or 4 days of hospital admission. The status of all patients was followed by outpatient contact or by monthly telephone contact for 6 months after discharge. If a patient was rehospitalized or visited an emergency department, a trained research assistant reviewed the hospital record to confirm that the reason for the visit was a cardiac event and to verify the date.

Statistical Analysis

Statistical analyses were performed by using SPSS for Windows 16.0 (SPSS Inc, Chicago, Illinois). Frequencies, percentages, means, and standard deviations were used to describe patients' characteristics depending on the level of the measurement. After traditional risk factors including patient's age, sex, body mass index, regular exercise, smoking behavior, and levels of total cholesterol, triglycerides, and high- and low-density lipoprotein cholesterol were controlled for in the first step, homocysteine, trait anger, and hostility were entered in the second step.

A hierarchical Cox proportional hazards regression model was used to test proposed hypotheses 1, 2, and 3. A hazard ratio for recurrent cardiac events was obtained for all independent variables along with 95% confidence intervals. For testing of hypotheses 4 and 5, patients were stratified into 4 groups by median value of trait anger and serum level of homocysteine, and 4 groups by median value of hostility and serum level of homocysteine. Hierarchical Cox proportional hazards regression with survival curve was used to determine whether the association between serum level of homocysteine and recurrent cardiac events differed by level of trait anger or hostility in patients with CAD. Normality assumed for multiple regression analysis was verified by using skewness, kurtosis, and histogram. Multicollinearity among all independent variables was evaluated by Pearson correlation with r less than 0.52. The significance level for all statistical analyses was set a priori at $P < .05$.

Results

Characteristics of the Sample

The mean age of patients in this study was 61 (SD 10) years, and approximately one-third were women (Table 1). Most patients were of normal weight. Less than 40% of the patients engaged in regular exercise, and about a quarter were current smokers. In accordance with the guidelines of the National Cholesterol Education Program's Adult Treatment Panel III,³⁹ 70% of patients met the desirable criterion for total serum cholesterol (<200 mg/dL; to convert to millimoles per liter, multiply by 0.0259) and 64% had the normal range of triglyceride (<150 mg/dL; to convert to millimoles per liter, multiply by 0.0113). Only 9% had high levels of high-density lipoprotein cholesterol (<60 mg/dL) and 30% had an optimal level of low-density lipoprotein cholesterol (<100 mg/dL). The overall level of

homocysteine had a normal distribution, and a homocysteine level greater than 15 $\mu\text{mol/L}$ was documented in 25% of patients. About 40% of patients met the ideal goal for serum level of homocysteine ($<10 \mu\text{mol/L}$) suggested by Gerhard and Duell.⁴⁰ Trait anger was moderate (24.5) as was hostility (58), with scores ranging from 10 to 40 and 24 to 78, respectively.

Recurrent Cardiac Events

During the 6-month follow-up period, 18 patients (13%) were rehospitalized or visited emergency departments for complaints of chest pain or shortness of breath. Five patients had restenosis in the same lesions, and 4 patients had stenosis at new lesions. Six patients received anticoagulants and vasodilators for reperfusion, and 3 patients underwent coronary artery bypass graft surgery.

Independent Predictors of Recurrent Cardiac Events

After patient's age, sex, body mass index, regular exercise, smoking behavior, serum levels of total cholesterol, triglycerides, and high- and low-density lipoprotein cholesterol were controlled for, only 2 factors were significantly associated with recurrent cardiac events in the hierarchical Cox proportional hazard regression (Table 2): trait anger and serum level of homocysteine. Therefore, hypotheses 1 and 3 were supported, but hypothesis 2 was not supported. The risk of recurrent cardiac events increased by 11% for each 1 unit increase in the STAS score and by 10% for each 1 unit increase in the serum level of homocysteine.

Association Between Serum Level of Homocysteine and Recurrent Cardiac Events by Trait Anger or Hostility

When stratified into 4 groups by median value of trait anger and serum level of homocysteine, patients with high trait anger (STAS score ≥ 24) and high homocysteine level (serum level of homocysteine $\geq 11.3 \mu\text{mol/L}$) had the shortest time to recurrent cardiac events ($P = .01$) after age, sex, body mass index, regular exercise, smoking behavior, and serum levels of total cholesterol, triglycerides, and high- and low-density lipoprotein cholesterol were controlled for (see Figure). Therefore, hypothesis 4 was supported.

The difference in time to recurrent cardiac events among 4 groups stratified by median value of hostility and serum level of homocysteine was not significant ($P = .06$) after age, sex, body mass index, regular exercise, smoking behavior, serum levels of total cholesterol, triglycerides, and high- and low-density lipoprotein cholesterol were adjusted for. Therefore, hypothesis 5 was not supported.

Discussion

This study is the first to demonstrate that trait anger and serum level of homocysteine are predictive of recurrent cardiac events and that trait anger and serum level of homocysteine may be linked with recurrent cardiac events in Korean patients with CAD following PCIs.

Trait anger remained an independent predictor of recurrent cardiac events among patients with CAD who underwent PCI even after other traditional risk factors were controlled for in this study. This finding is consistent with results of previous studies,^{9, 41–44} which showed that intense and frequent feelings of anger or an angry temperament were predictive of development of CAD. This prior research,^{9, 41–43} however, was focused on development of CAD among people who had been free of CAD. Our study extended these findings to demonstrate that anger remains an independent predictor of recurrent cardiac events in patients with CAD who undergo PCI.

Prior research^{43, 44} demonstrated that a higher level of anger was associated with development of CAD only in men, but both men and women were included in this study. Interestingly, our findings indicate that patients with a higher level of trait anger who undergo PCI have a higher risk for recurrent cardiac events than do patients with a lower level of trait anger who undergo PCIs. Therefore, patients with the disposition to anger may be ideal candidates for risk reduction programs after PCIs. Early intervention focusing on anger management may be an important part of secondary prevention of CAD. Identification and treatment of trait anger should be emphasized in clinical areas.

Our data suggested that Korean patients with CAD express high levels of trait anger. Approximately 8% of middle-aged residents in communities in the United States who did not have CAD had high trait anger scores from 22 to 40,⁹ whereas approximately 60% of patients in our study had scores in this range. The mean score for trait anger was 24.5 in this study, whereas the mean score of trait anger was 19.1 for healthy men and 18.6 for healthy women in Korea⁴⁵ and 16.0 for US residents without CAD.⁹ Thus, the overall level of trait anger was higher in this study than has been reported in other studies. This result indicates that Korean patients with CAD expressed angry feelings more intensely and more often than did healthy Koreans without CAD and US residents with CAD when they experienced a stressful event. This finding was supported by prior studies of a Korean culture-bound syndrome called *Hwa-byung*.^{46, 47} It was categorized as an anger syndrome in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,⁴⁸ and the symptoms include anger and chest discomfort.⁴⁹

Homocysteine was also an independent predictor of recurrent cardiac events after other traditional risk factors were adjusted for. This result is similar to results of prior studies,^{13, 50} in which high concentrations of homocysteine were positively associated with an increased risk of restenosis after successful PCIs. Malinow et al⁵¹ reported that normal serum levels of homocysteine in fasting patients are between 5 and 15 $\mu\text{mol/L}$. However, a recent meta-analysis⁵² demonstrated that different cutoff levels for homocysteine (including median, quartiles, or treatment as a continuous variable) were used, with a range from 10.7 to 12.9 $\mu\text{mol/L}$. The median value of 11.3 $\mu\text{mol/L}$ used as the cutoff point in our study falls in the middle of this range. Thus, our study supports the finding of Humphrey et al⁵² that homocysteine values currently considered to be in the normal range are associated with risk for recurrent cardiac events. Most intervention studies^{53–55} have targeted reducing serum levels of homocysteine through increased intake of folate, vitamin B₆ or vitamin B₁₂ to reduce homocysteine levels and prevent occurrence of CAD. However, not enough evidence is available to support what amount of folic acid, vitamin B₆ or vitamin B₁₂ is required for patients with CAD. The standard guideline for intake of vitamin supplements should be determined through prospective and experimental studies in the future.

Our most compelling finding was the demonstrated link between serum levels of homocysteine, anger levels, and recurrent cardiac events. We showed that homocysteine levels were only a significant risk factor for recurrent cardiac events when coupled with high levels of trait anger. This finding suggests a biological mechanism through which anger influences development and progression of CAD. One hypothesis suggests that excessive sympathetic arousal with release of catecholamines induced by higher levels of anger may damage the endothelium, thus promoting the progression of atherosclerotic lesions. This hypothesis is understood from the framework in which anger works as a trigger to disrupt vulnerable atherosclerotic plaques. During anger, coronary vasoconstriction,⁵⁶ transient myocardial ischemia,⁵⁷ autonomic nervous system stimulation,⁶ and neuroendocrine activation⁵⁸ all occur. Although a biological mechanism linking anger and homocysteine levels was not investigated in this study, the positive association between these 2 variables has been supported by several investigators.^{21, 59, 60} Therefore, a putative biological

pathway is supported by our findings; the link between homocysteine level and recurrent cardiac events seems to be stronger in patients with a high level of trait anger.

Inconsistent with results of other studies,^{21, 22} hostility was not a significant predictor of recurrent cardiac events, and, moreover, the association between serum level of homocysteine and recurrent cardiac events did not differ with the level of hostility once other traditional risk factors had been controlled for. Because hostility may result in late restenosis,^{24, 61} long-term follow-up for 12 months may be needed to examine the association between hostility and recurrent cardiac events. In addition, a low hostility has been associated with noncompliance to exercise programs in patients with heart disease.⁶² Therefore, study of the relationship among serum level of homocysteine, hostility, and behavioral factors such as exercise is needed.

Study limitations are acknowledged. Serum level of homocysteine, trait anger, and hostility were measured only once during hospitalization and not over time. Thus, caution should be used in concluding that the relationship among these variables is stable over time. Another potential limitation of this study is the relatively small sample. However, this study was adequately powered to test proposed hypotheses among patients following PCIs. A study that uses a larger sample and includes additional putative risk factors such as adherence to exercise and medication should be done to increase understanding of the effects of trait anger and homocysteine level on recurrent cardiac events in CAD patients after PCI.

Conclusions

Patients with CAD who have a high level of trait anger and a high serum level of homocysteine are at increased risk for recurrent cardiac events after PCI. Trait anger strengthens the association between serum level of homocysteine and recurrence of cardiac events among patients undergoing PCI. Early intervention should be focused on patients who experience angry feelings as a personality trait in addition to other risk factors. Interventions to reduce trait anger may improve health outcomes via their influence on both trait anger and serum levels of homocysteine.

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Figure.
Differences in the association between serum level of homocysteine and recurrent cardiac events by level of trait anger.

Table 1Characteristics of 135 patients with coronary artery disease^a

Characteristic	Value
Age, mean (SD), y	60.8 (10.4)
Sex	
Male	92 (68.1)
Female	43 (31.9)
Body mass index ^b	
Underweight (<18.5)	3 (2.2)
Normal weight (18.5–24.9)	88 (65.2)
Overweight (25.0–29.9)	40 (29.6)
Obesity (≥30.0)	4 (3.0)
Regular exercise	
None	83 (61.5)
Yes	52 (38.5)
Smoking	
None	62 (45.9)
Quit smoking	37 (27.4)
Current smoker	36 (26.7)
Total cholesterol, mean (SD), mg/dL	180.6 (38.4)
Triglycerides, mean (SD), mg/dL	144.8 (88.3)
High-density lipoprotein, mean (SD), mg/dL	48.2 (22.0)
Low-density lipoprotein, mean (SD), mg/dL	107.0 (31.2)
Homocysteine, mean (SD), μmol/L	12.1 (4.8)
Trait anger, mean (SD)	24.5 (6.6)
Hostility, mean (SD)	58.0 (9.8)

SI conversion factors: To convert total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259. To convert triglycerides to millimoles per liter, multiply by 0.0113.

^aValues are No. (%) of patients unless otherwise specified.

^bCalculated as weight in kilograms divided by height in meters squared. Mean was 24.2 (SD 2.7) for all 135 patients.

Table 2

Independent predictors of risk for recurrent cardiac events among 135 patients after percutaneous coronary interventions

Characteristic	Adjusted Hazard ratio	95% Confidence Interval	<i>p</i>
Age, y	1.06	1.00 – 1.13	.06
Sex			
Male	1.00		
Female	2.38	0.65 – 8.80	.19
Body mass index ^a	0.95	0.79 – 1.14	.59
Regular exercise			
None	1.00		
Yes	0.97	0.32 – 2.92	.96
Smoking			
None	1.00		
Quit smoking	0.87	0.20 – 3.88	.85
Current smoker	1.83	0.32 – 10.5	.50
Total cholesterol, mg/dL	0.99	0.98 – 1.01	.58
Triglycerides, mg/dL	0.99	0.99 – 1.00	.39
High-density lipoprotein, mg/dL	0.98	0.93 – 1.03	.42
Low-density lipoprotein, mg/dL	1.01	0.99 – 1.03	.46
Homocysteine, μ mol/L	1.10	1.01 – 1.21	.04
Trait anger	1.11	1.03 – 1.20	.01
Hostility	0.97	0.93 – 1.02	.24

SI conversion factors: To convert total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259. To convert triglycerides to millimoles per liter, multiply by 0.0113.

^a Calculated as weight in kilograms divided by height in meters squared.