Coronary Artery Disease

Coronary Slow Flow is Associated with Depression and Anxiety

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Background: There is an established relationship between depression/anxiety disorders and cardiovascular morbidity and mortality which has been previously documented. However, there has been no study evaluating coronary slow flow in association with depression and anxiety.

Methods and Results: A total of consecutive 90 patients were included in the study. All patients completed scoring scales for depression [Hamilton Rating Scale for Depression (HAMD)] and anxiety (STAI-1, State anxiety subscale of State-Trait Anxiety Inventory; STAI-2, Trait anxiety subscale of State-Trait Anxiety Inventory). Thereafter, they underwent selective coronary angiography and 2 groups were formed: coronary slow flow (n = 42), and normal coronary flow (n = 48). The two groups had comparable baseline characteristics. However, significant differences were found between coronary slow flow and normal coronary flow groups regarding depression (13.1 ± 8.2 and 6.9 ± 6.7, $p < 0.001$ for HAMD, respectively) and anxiety (46.2 ± 15.0 vs. 32.6 ± 9.9, $p < 0.001$ for STAI-1 and 51.0 ± 16.7 vs. 43.0 ± 10.7, $p = 0.009$ for STAI-2, respectively) scores. There were also significant positive correlations between depression/anxiety scores and TIMI frame counts of all major epicardial coronary arteries. In addition, after adjustment for smoking, hypertension, scoring scales, and the presence of depressive mood, all scoring scales and depressive mood were found to be independent risk factors for coronary slow flow in multivariable logistic regression analysis.

Conclusions: Significant association was found among coronary slow flow, depression/anxiety scores and depressive mood.

Key Words: Anxiety • Coronary slow flow • Depression • Scale

Coronary slow flow (CSF) with otherwise normal epicardial coronary arteries can be observed in patients presenting with anginal chest pain. Tambe et al. first described CSF in six patients with angina pectoris.[1] The exact mechanism associated with this interesting phenomenon remains obscure, although the most probable underlying mechanism seems to be microvascular dysfunction.[2-4]

The thrombolysis in myocardial infarction (TIMI) frame count is a simple, reproducible, objective, and quantitative index of coronary blood flow.[5] In this method, the number of cineangiographic frames from initial contrast material opacification of the proximal portion of the coronary artery to opacification of the distal arterial landmarks with contrast material is counted.

Epidemiologic studies have shown that depression or anxiety disorder can predict the incidence of coronary artery disease in healthy populations.[6] Several other studies have reported that patients who had chest pain and normal coronary arteries exhibited more psychiatric illnesses than did patients with definitive coronary artery disease.[7-9]

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In the present study, we aimed to demonstrate any association between CSF and depression/anxiety.

METHODS

Study population

All patients (n = 992) admitted to the study center for suspected coronary heart disease and whose medical management included coronary angiography were possible candidates for inclusion in the study between January 2012 and September 2012. Before diagnostic coronary angiography was administrated, all participants completed 3-step scoring scales (described below). Among them, patients who had angiographically proven CSF and normal coronary flow (NCF) (as control group) without atherosclerosis were candidates for inclusion in the study. A total of 90 consecutive patients (mean age, 51 $\pm$ 7 years, age range, 39-71 years, 65 male and 25 female) were recruited. All patients were questioned as to any cardiovascular risk factors including diabetes and smoking. Transthoracic echocardiography was performed on all patients to detect diastolic dysfunction and left ventricular hypertrophy. Scoring scales were performed on all study participants to detect their depression and anxiety levels before undergoing selective coronary angiography. Exclusion criteria included the following: refusal to participate in the study; known coronary artery disease; LV dysfunction (LVEF < 50%); unstable ischemic conditions (unstable angina pectoris and myocardial infarction); valvular heart disease; rhythm other than sinus; metabolic syndrome; renal or hepatic dysfunction (creatinine > 1.2 mg/dl, AST and ALT more than twice the upper limit of normal, respectively); chronic obstructive pulmonary disease; systemic diseases; detection of coronary atherosclerotic lesion after selective coronary artery angiography; follow-up visits or medical treatment for chronic psychosis; recent medical treatment for depression; insufficient cooperation; incomplete study forms; and all coronary anomalies including myocardial bridging and coronary-pulmonary artery fistula which may lead to slow coronary flow. The Institutional Ethics Committee approved the study protocol and all patients gave informed consent to participate in the study.

Scoring scales

Eligible participants completed a 17-item Hamilton rating scale for Depression (HAMD), which is the most commonly used observer-rated depressive symptom rating scale. Items with quantifiable severity were ranked on a scale of 0-4 and those measuring symptoms that are difficult to assess reliably were ranked on a scale of 0-2. The range of the 17-item scale was 0-50, with 14 considered to be the cut-off point of this scale; higher scores indicated more severe depression. According to HAMD, patients were classified into 2 groups of depressed (score $\geq$ 14) and non-depressed (score < 14).[10]

Anxiety was measured by means of the State-Trait Anxiety Inventory (STAI).[11] This self-report questionnaire consists of two subscales each containing 20 items. The state anxiety subscale (STAI-1) measures the anxiety at the moment of scoring. State anxiety is conceptualized as a transient emotional condition of the individual, characterized by subjectively experienced feelings of tension, together with a heightened activity of the autonomous nervous system. Trait anxiety (STAI-2) measures dispositional anxiety or anxiety in general. Trait anxiety refers to anxiety proneness; that is, relatively stable individual differences in the tendency to react with a more intense state anxiety in situations that are perceived as threatening. The items are summed per scale and transformed into scores between 20 and 80. Higher scores on the STAI indicate a higher intensity of anxiety. The Turkish version of the STAI has been validated previously.[12]

Cardiac catheterization

All patients in the study underwent selective coronary artery angiography after appropriate patient preparation. Femoral artery and sometimes radial or brachial artery cannulation were used for the arterial access site and Judkins system was applied for cannulation of the left and right coronary arteries. All angiograms were evaluated by two experienced physicians blinded to the study. Angiograms without stenotic lesions in any major epicardial coronary arteries including left main (LM), left anterior descending (LAD), left circumflex (LCx), and right coronary arteries (RCA) were considered normal angiograms. CSF was investigated by using the TIMI frame count method described by Gibson et al. TIMI

frame count was used for the quantification of coronary blood flow for each major coronary artery in each individual. The first frame is the initial frame in which a column of contrast material extends across the entire width of coronary artery, touches both borders of the artery, and moves antegradely. The last frame is the frame when contrast material first enters the distal landmark. The distal bifurcation of coronary artery is used for the distal landmark in the LAD (the "mustache," "pitchfork," or "whale's tail"). In the LCx, the distal landmark is distal bifurcation of the longest coronary arterial segment which is dyed by contrast material. The distal landmark for the RCA is the first branch of the posterolateral artery. Corrected TIMI frame count was calculated via dividing TIMI frame count by 1.7 for the LAD, since this coronary artery is generally longer than the others. Previously published normal TIMI frame counts were 21.1 ± 1.5 frames for LAD (after correction), 22.2 ± 4.1 frames for LCx, and 20.4 ± 3.0 frames for RCA.[5] For a given artery, any value above this published range was considered as CSF. It should be mentioned that TIMI frame measures mainly "flow rate" rather than "total flow amount". TIMI frame correlates with coronary flow only when in the same subject, such as before/after percutaneous coronary intervention. Therefore, it is surely associated with slow "flow rate", but not necessarily with slow "flow amount".

Statistical analysis

Data were analyzed with the SPSS software version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Non-normal continuous variables were presented as median (50^{th}) values and interquantile ranges (25^{th} and 75^{th}). The Kolmogorov-Smirnov test was used to assess the normality distribution of continuous variables. Student's *t*-test was used for variables with normal distribution and Mann-Whitney U test for non-normal continuous variables. The $\chi 2$ test was used to compare categorical variables. Pearson correlation was performed to analyze any association among scoring scales and TIMI frame counts for all major coronary arteries. A two-tailed p-value of < 0.05 was considered statistically significant. Multivariable logistic regression analysis was used to evaluate the independent associates of the risk of CSF. Parameters with a p-value of less than 0.1 in univariate analysis were included in the model. The odds ratios (OR) and 95% confidence intervals (CI) were calculated.

RESULTS

The baseline demographic, clinical, laboratory, echocardiographic, and angiographic characteristics of both groups were summarized in Table 1. The two groups were similar regarding demographic, clinical, laboratory and echocardiographic characteristics, except for smoking that was higher in the study group. Age, sex, major clinical risk factors for coronary artery disease including hypertension, diabetes, hyperlipidemia, and smoking, laboratory and echocardiographic parameters were similar in patients with and without CSF (p > 0.05).

As expected, TIMI frame count values were significantly higher in CSF patients compared to NCF patients (p < 0.001 for all 3 major epicardial coronary arteries).

Significant differences were found between the 2 study groups regarding depression and anxiety scores. The mean Hamilton rating scale for Depression (HAMD) score was 13.1 ± 8.2 and 6.9 ± 6.7 in CSF and NCF groups, respectively (p < 0.001). In addition, there was a significant difference between the 2 groups regarding depressive mood [21 (50%) and 4 (8%), p < 0.001, respectively]. Similarly, STAI-1 and STAI-2 scores were significantly different between the 2 groups (46.2 ± 15.0 vs. 32.6 ± 9.9, p < 0.001 for STAI-1 and 51.0 ± 16.7 vs. 43.0 ± 10.7, p = 0.009 for STAI-2, respectively).

In male patients, significant differences were obtained between CSF and NCF patients regarding HAMD (13.6 ± 8.7 and 7.6 ± 6.9, p = 0.003), STAI-1 (48.1 ± 13.8 and 33.1 ± 10.6, p < 0.001) and STAI-2 (52.8 ± 14.4 and 45.5 ± 8.8, p = 0.019) scores, respectively.

In female patients, however, there were no significant differences noted between both groups regarding anxiety scoring systems (40.9 ± 17.4 vs. 31.2 ± 8.1, p = 0.089 for STAI-1 and 46.2 ± 21.6 vs. 36.8 ± 12.7, p = 0.198 for STAI-2), respectively. In the HAMD scores, significance was found (11.8 ± 7.2 vs. 5.0 ± 6.0, p = 0.018, respectively).

In correlation analysis, significant positive correlations were found between scoring scales and TIMI frame

Table 1. Demographic, clinical, echocardiographic, laboratory and angiographic characteristics of the study population

Characteristics	Normal flow group (n = 48)	Slow flow group (n = 42)	p value
Age (years)	50 ± 7	52 ± 7	0.192
Male	35 (73%)	30 (71%)	0.875
Hypertension	28 (58%)	16 (38%)	0.055
Hyperlipidemia	36 (75%)	28 (67%)	0.384
Diabetes	14 (29%)	12 (29%)	0.950
Smoking	4 (8%)	12 (29%)	0.012
Systolic BP (mmHg)	120 ± 14	124 ± 12	0.170
Diastolic BP (mmHg)	72 ± 11	75 ± 8	0.102
Heart rate (bpm)	76 ± 10	75 ± 11	0.865
Cardiac work (systolic BP x heart rate)[#]	9355 ± 1780	9934 ± 1372	0.096
LV ejection fraction (%)*	62 (57-65)	63 (59-65)	0.590
Diastolic dysfunction	24 (50%)	26 (62%)	0.257
LV hypertrophy	8 (17%)	6 (14%)	0.756
Total cholesterol (mg/dL)	187 ± 37	187 ± 44	0.931
LDL cholesterol (mg/dL)	112 ± 33	108 ± 31	0.567
HDL cholesterol (mg/dL)	44 ± 11	41 ± 9	0.097
Triglyceride (mg/dL)*	136 (100-170)	168 (104-301)	0.128
Fasting plasma glucose (mg/dL)*	95 (83-107)	102 (84-127)	0.088
Vascular diameter (mm)	3.10 ± 0.60	3.20 ± 0.50	0.391
Coronary slow flow presence			
LAD	-	30 (71%)	-
LCx	-	20 (48%)	-
RCA	-	28 (67%)	-
TIMI frame counts*			
LAD	19 (16-23)	38 (31-46)	< 0.001
LCx	20 (13-23)	33 (24-42)	< 0.001
RCA	18 (14-21)	36 (20-40)	< 0.001

* Median values (50th) and interquantile ranges (25th and 75th) were presented; [#] Crude estimate of cardiac work.
BP, blood pressure; HDL, high-density lipoprotein; LAD, left anterior descending; LCx, left circumflex; LDL, low-density lipoprotein; LV, left ventricular; RCA, right coronary artery.

counts of all major epicardial coronary arteries (Table 2).

In univariate analysis, hypertension (OR 2.28, 95% CI, 0.98-5.31, p = 0.057), smoking (OR 0.23, 95% CI, 0.07-0.77, p = 0.018), depressive mood (OR 7.39, 95% CI, 2.28-23.99, p = 0.001), and all 3 scoring scales (OR 1.12, 95% CI, 1.05-1.19, p = 0.001 for HAMD; OR 1.08, 95% CI, 1.04-1.13, p < 0.001 for STAI-1; OR 1.04, 95% CI, 1.01-1.07, p = 0.012 for STAI-2) were found to be independent risk factors for CSF. However, other possible determining factors of coronary flow including heart rate (OR 0.97, 95% CI, 0.90-1.04, p = 0.361), left ventricular ejection fraction (OR 1.04, 95% CI, 0.94-1.15, p = 0.421), systolic/diastolic blood pressures (OR 0.98, 95% CI, 0.93-1.02, p = 0.296/OR 0.96, 95% CI, 0.90-1.02, p = 0.142, respectively), cardiac work (OR 1.00, 95% CI, 0.99-1.00, p = 0.198), and vascular diameter (OR 0.71,

Table 2. Correlation analyses between anxiety/depression scores and TIMI frame counts of 3 major epicardial coronary arteries

Characteristics	r value	p value
HAMD score and LAD TIMI count	0.381	< 0.001
HAMD score and LCx TIMI count	0.267	0.011
HAMD score and RCA TIMI count	0.339	0.001
STAI-1 score and LAD TIMI count	0.458	< 0.001
STAI-1 score and LCx TIMI count	0.343	0.001
STAI-1 score and RCA TIMI count	0.363	< 0.001
STAI-2 score and LAD TIMI count	0.320	0.002
STAI-2 score and LCx TIMI count	0.295	0.005
STAI-2 score and RCA TIMI count	0.236	0.023

HAMD, Hamilton rating scale for Depression; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; STAI-1, State anxiety subscale of State-Trait Anxiety Inventory; STAI-2, Trait anxiety subscale of State-Trait Anxiety Inventory.

95% CI, 0.24-2.13, p = 0.540) were not independent risk factors. After including significant variables of smoking, hypertension and scoring scales in multivariable logistic regression analysis, scoring scales were found to be independent risk factors for CSF (Table 3).

DISCUSSION

Our findings showed significant differences regarding depression and anxiety between CSF and NCF patients, and significant and independent associations were found between CSF and depression/anxiety. In a finding limited to the female subgroup, there were no significant differences between both groups regarding anxiety scoring systems, although anxiety seemed to be more prevalent in females. This insignificant difference can be related to the small sample size of females in the study.

Major depressive disorder is associated with coronary heart disease incidence and mortality, but results are heterogeneous across the previous studies.[13,14] However, a recent study of patients with stable coronary heart disease found little association between major depressive disorder and systolic or diastolic function, inducible ischemia, or wall motion abnormalities.[15]

There are also conflicting results regarding coronary circulation and depression. The results of the study performed by Yang et al. have demonstrated that depression is not associated with coronary endothelial dysfunction in men and women without significant coronary artery disease.[16] In another study conducted with flow-mediated dilation of the brachial artery, vascular endothelial dysfunction has been found in coronary heart disease patients with depressive symptoms.[17] In our study, we have found a significant difference and association between CSF and depression.

Patients with depression generally have a high sympathetic tone, increased cortisol and catecholamine levels, abnormal platelet activation including enhanced platelet reactivity and release of platelet products such as platelet factor 4 and b-thromboglobulin,[18,19] increased inflammatory markers, and endothelial dysfunction. Importantly, these physiological derangements are present in depressed patients who do not have cardiac disease; and even when not actively depressed, patients with a history of depression have at least some of these abnormalities as compared with patients who are not depressed.[20]

Stress has been shown to be one of the most potent triggers of depression.[21] With stress, the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenomedullary system are activated. Persistent activation of these 2 systems leads to the observed downstream abnormalities in platelet function, autonomic tone, inflammation, and endothelial function.

In addition, reduced heart rate variability[22] and impaired vagal control[23] have been reported among depressed patients.

Similar to depression, patients with anxiety show increased cardiovascular mortality and morbidity. In a large, prospective cohort study of females who were free from cardiovascular disorder at baseline, anxiety was associated with an increase in risk of sudden cardiac death and fatal coronary heart disease but not for nonfatal myocardial infarction in age-adjusted and multivariable models that excluded potential biological mediators.[24] Most notably, 3 large-scale community-based studies have reported a significant relationship between anxiety disorders and cardiac death.[25-27]

Table 3. Univariate and multivariable logistic regression for CSF

Characteristics	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Hypertension	2.28 (0.98-5.31)	0.057	1.73 (0.68-4.43)	0.251
Smoking	0.23 (0.07-0.77)	0.018	0.22 (0.05-1.06)	0.058
STAI-1	1.08 (1.04-1.13)	< 0.001	1.08 (1.03-1.13)	0.001
STAI-2	1.04 (1.01-1.07)	0.012	1.04 (1.01-1.08)	0.016
HAMD	1.12 (1.05-1.19)	0.001	1.14 (1.06-1.22)	0.001

HAMD, Hamilton rating scale for Depression; STAI-1, State anxiety subscale of State-Trait Anxiety Inventory; STAI-2, Trait anxiety subscale of State-Trait Anxiety Inventory.

Similar pathophysiologic mechanisms seem responsible for similar results. A recent study has reported reduced baroreflex control of the heart in patients with anxiety.[28] Stress impairs endothelium-independent and nitric oxide-mediated coronary relaxation, but without causing visible endothelial damage.[29] In accordance with these studies, a significant difference and association was found between CSF and anxiety (except for female subjects) in our study, probably due to the small size of the female study population.

Coronary flow usually meets cardiac metabolic needs and coronary flow will increase fivefold in the heart during exercise without significant ischemia. Therefore, slow flow may reflect small cardiac metabolic demands rather than a state of impaired coronary endothelial function or poor neuroregulation,[30] although Canga et al. showed that circulating inflammatory cells and low-grade inflammation were significantly and independently related to CSF.[31] This can partly explain why current study results are conflicting.

LIMITATIONS

The most important limitation of the present study was small sample size which could affect the results. Secondly, the scoring scales are based on subjective assessment methods to evaluate the level of depression and anxiety. Therefore, the subjective evaluation methods became limited in value if patients failed to provide reliable answers. Third, by its nature, our study is a cross-sectional and observational study and thus cannot show a definite causal relationship between CSF and depression or anxiety disorder.

CONCLUSIONS

For the first time, we have demonstrated that depression and anxiety scores were higher in patients with CSF compared to patients with NCF. In addition, significant correlations were found between CSF and these scores and depressive mood. Therefore, we reasonably have speculated that depression, stress and related pathophysiologic mechanisms appear related to CSF.

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