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Anxiety is a better predictor of platelet reactivity in coronary artery disease patients than depression

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Aims Depression and anxiety are linked to coronary events but the mechanism(s) remains unclear. We investigated the associations of depression and anxiety with serotonin-mediated platelet hyperactivity in coronary artery disease (CAD) patients in a cross-sectional study.

Methods and results Three months after an acute coronary event, stable CAD patients ($n = 83$) on aspirin and clopidogrel were evaluated for depression (beck depression inventory) and anxiety (hospital anxiety and depression scale), and their platelet reactivity was measured (optical aggregometry and flow cytometric fibrinogen binding in response to adenosine diphosphate (ADP = 5 μM) and two serotonin + epinephrine doses [5HT:E (L) = 4 μM + 4 μM and 5HT:E (H) = 10 μM + 4 μM]. Platelet reactivity was significantly higher in *depressed and anxious* than in *depressed only* or *non-depressed-and-non-anxious* patients. Aggregation (mean ± SE) was 41.9 ± 2.6% vs. 32.2 ± 2.6% vs. 30.4 ± 3.7% with 5HT:E (L) and 46.9 ± 2.7% vs. 35.6 ± 2.7% vs. 31.7 ± 3.8% with 5HT:E (H) ($P < 0.05$ for both). Differences in ADP aggregations were not significant, perhaps because of clopidogrel therapy. Flow cytometry findings were similar. In a multivariate linear regression model adjusted for age, body mass index, and each other, anxiety symptoms independently predicted all 5HT:E-mediated platelet reactivity measures, whereas depression predicted none.

Conclusion Anxiety is associated with elevated serotonin-mediated platelet reactivity in stable CAD patients and symptoms of anxiety show strong, independent correlations with platelet function.

Keywords Anxiety • Coronary artery disease • Depression • Myocardial infarction • Platelets

Introduction

Coronary artery disease (CAD) and its thrombotic manifestations remain the leading cause of morbidity and mortality in the industrialized nations. The importance of psychosocial factors as contributors to the incidence and progression of CAD has been the focus of a concerted research effort over the years.[1–8] For example, the INTERHEART study,[9] a case–control examination of modifiable risk factors in 52 countries, found that a composite variable comprises exposure to depression, perceived life stress, low control, and major life events carried an adjusted 2.67-fold increased risk of acute myocardial infarction (AMI). Indeed, the contribution of depression and anxiety to increased likelihood of recurrent coronary events after AMI and bypass surgeries,[2,10–13] and transient depressed and anxious mood as trigger acute cardiac events and potentially fatal arrhythmias is well documented.[14–16] The risk associated with depression in these populations, where its prevalence can be up to 10 times greater than in the healthy groups,[17,18] is comparable to that of smoking, hypertension or diabetes, and independent of such traditional cardiovascular risk

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factors such as left ventricular ejection fraction, history of myocardial infarction or Killip class.[19–22] On the basis of this literature, an American Heart Association science advisory has recommended screening for depression in CAD patients.[23]

Anxiety is also highly prevalent in cardiac populations, with estimates ranging from 28 to 44% in younger groups and from 14 to 24% in older groups.[24,25] Furthermore, anxiety is a frequently encountered co-morbidity of depression.[26] Though the aetiologies, mechanisms, and sequelae of anxiety and depression share many commonalities,[27,28] there are many distinctions as well.[29] The impact of depression on cardiac events has been extensively investigated.[19] The few studies that have evaluated the prognostic value and individual contribution of depression and/or anxiety towards CAD outcomes show that when evaluated concurrently, anxiety frequently carries the cardiac risk alone,[30–33] although this observation is not universal.[34]

Increased platelet reactivity is one of several mechanisms postulated in explaining the link between psychosocial factors and CAD.[35–37] A recent review by Bruce and Musselman[38] found considerable evidence linking depression to increased platelet activation in both groups with extant CAD and those with only CAD risk factors. Others have found greater platelet responsiveness and prolonged platelet activation among individuals characterized by hostility and chronic psychological stress.[39–41] Acute psychological stress can similarly affect platelet function,[42] particularly among those prone to anxiety.[43]

Platelets are activated by their interaction with various circulating agonists (including serotonin and catecholamines) via separate and specific receptors in the platelet membrane. Serotonin (5HT) is considered an important element in psychopathology and psychopharmacology and specific 5HT2A receptors have been reported to play a role in platelet aggregation.[44] A higher 5HT-mediated platelet reactivity has been described in depressed patients compared with healthy, non-depressed adults.[45] Alternatively, catecholamines activate platelets via stimulation of platelets' α-2 receptors.[46,47] As the two agonists act through different pathways, a synergistic effect between 5HT and epinephrine on platelets has been observed;[48] levels of autonomic activity and circulating catecholamines are elevated in patients with anxiety,[49] which could lead to the activation of platelets in these patients. Given the link of depression and anxiety with increased risk of cardiovascular events, we investigated their associations with platelet reactivity in patients with stable CAD.

Methods

Study population and design

The study was conducted using a cross-sectional design on CAD patients admitted to the Mount Sinai Medical Center in New York for acute coronary syndrome (ACS), including AMI and unstable angina from April 2005 to March 2008. Patients were recruited ($n = 83$) during their first week of admission for ACS and scheduled for follow-up visit 3 months later to allow any post-ACS changes in platelet function to subside and for the platelet reactivity to stabilize. During 3-month follow-up visit, patients were assessed for symptoms of depression and anxiety, and their platelet reactivity was measured by investigators blinded to the results of these assessments (*Figure 1*). All subjects were on daily aspirin (81 mg) and clopidogrel (75 mg) therapy at the time of platelet testing.

The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of Mount Sinai Medical Center. A written informed consent was obtained from each patient before initiating any study-related procedures.

Inclusion criteria

Patients 18 years and older were eligible if they had been hospitalized for an ACS event—either AMI with or without ST-elevation or unstable angina.

Exclusion criteria

Active suicidal or homicidal ideation (these patients require and were provided immediate referral for further evaluation); antidepressant treatment within 6 weeks prior to study enrolment; current alcohol or other substance abuse disorders; any current psychotic disorder; history of psychotic, bipolar or serious personality disorders; diagnosis of a terminal non-cardiac illness; inability to communicate in English or Spanish; levels of cognitive impairment indicative of dementia.

Assessment of depression and anxiety symptom severity

Patients completed the beck depression inventory (BDI)[50] and the anxiety subscale of the hospital anxiety and depression scale (HADS-A),[51] each of which measure symptom severity. These scales are commonly used in research and clinical practice, and scores have been linked to post-ACS prognosis in prior research.[34]

For categorical analysis, patients were classified as depressed if they had a BDI score of ≥ 10. Although this threshold is not specific for major depression, it is clinically meaningful, and prior research has found this threshold to carry increased risk for post-ACS recurrent cardiac events.[19] Patients were similarly classified as anxious, if they had a HADS-A score of ≥ 8, using previously published cutoffs for identifying individuals with clinically meaningful levels of anxiety.[52,53] This classification yielded four groups: (i) *non-depressed and non-anxious*, (ii) *depressed only*, (iii) *anxious only*, and (iv) *depressed and anxious*.

Blood sampling

Platelet reactivity was measured during the office visit scheduled 3 months after the ACS event. Steps were taken to standardize blood collection procedures as much as possible, including scheduling the blood sampling around the same time of day (early afternoon) and collecting the blood after the interview, allowing physical rest time for the patient before the blood draw. In order to minimize unintended platelet activation, tourniquet pressure was kept to a minimum during the 19-gauge butterfly stick and the initial 3 mL of blood was discarded. Samples were then collected in 3.2% sodium citrate tubes that were gently inverted 3–5 times and kept in upright position till processing. Tests for the measurement of platelet reactivity were initiated within 2 h of blood collection.

Platelet reactivity

Two different techniques were employed for the measurement of platelet reactivity: optical aggregometry and flow cytometry. In both methodologies, platelets were activated using three agonists: (i) adenosine diphosphate (ADP 5 μM), (ii) 5HT:E (L) (serotonin 4 μM with epinephrine 4 μM), and (iii) 5HT:E (H) (serotonin 10 μM with epinephrine 4 μM). As serotonin alone is a weak agonist of platelets, a fixed concentration of epinephrine was added to both of its doses to amplify its stimulatory effect.

- Platelet aggregation studies were conducted in platelet-rich plasma using optical aggregometry as previously described.[54] The aggregometer (Model 570VS) and reagents for platelet aggregation were purchased from Chrono-log, Havertown, PA, USA.

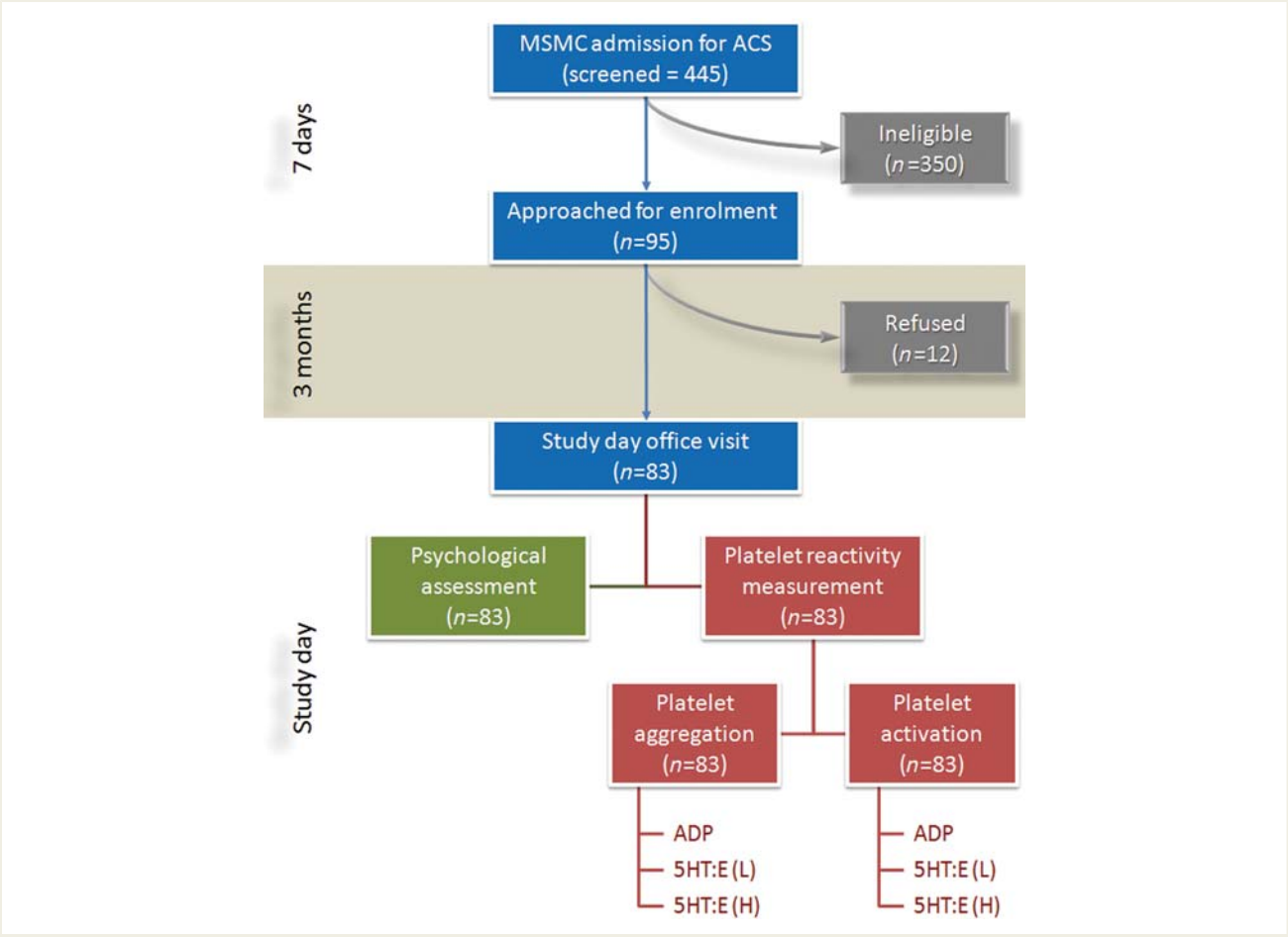

Figure 1 Flow chart of the study design. MSMC, Mount Sinai Medical Center; ACS, acute coronary syndrome.

- Platelet surface receptor activation studies were carried out in whole blood by measuring fibrinogen binding to the glycoprotein IIb/IIIa receptor complex on platelet surface, following activation with ADP and 5HT:E.[54] Blood sample was split into 200 μL aliquots, and incubated with the agonists for 10 min, followed by 30 min of direct immunofluorescence staining. Phycoerythrin-conjugated CD42b antibody (Immunotech, Fullerton, CA, USA) was used to label all platelets and the activated sub-population was identified using the anti-human fibrinogen antibody conjugated with fluorescein isothiocyanate (WAK-Chemie Medical GmbH, Steinbach, Germany). Samples were fixed with 2% paraformaldehyde and analysed in BD FACSCalibur™ using CellQuest Pro software (BD Biosciences, San Jose, CA, USA) without delay.

Statistical analysis

The data were analysed using SPSS (version 16) and SYSTAT (version 10) statistical software. Data are summarized as means ± standard deviations (unless specified otherwise) or percentages for frequency data. Statistical significance was set at the nominal $P < 0.05$ level and no adjustments were made for multiple comparisons. Standard univariate plots (e.g. stem and leaf, boxplots) and bivariate plots (e.g. residual-predictor, quantile–quantile) were used to assess distributional and other assumptions of the analyses. We did not find any clear departures from these assumptions in these data.

Simple correlations were used to summarize the basic relation of anxiety and depression symptom severity with platelet aggregation, and multiple regression was used to evaluate the partial relation of these two factors to platelet aggregation measures, adjusting for the covariates and each other. Covariates were selected judiciously based on consistent significant correlations between the covariates and the independent or dependent variables. For the categorical analyses, anxiety and depression were dummy coded using the standard cutoffs described previously, as 0 = below the cutoff and 1 = at or above the cutoff. The covariates were centred around their sample mean as were the BDI and HADS-A scores for the continuous analysis. The predicted aggregation measures were adjusted at the means of the covariates. The sample size for this study is relatively small, but with this sample size we had power of 0.80 to detect moderate simple correlations and for the regression analysis we had power of 0.80 to detect a large population partial correlation.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Demographic characteristics of the total study population and its grouping according to depression and anxiety status are presented

Table 1 Baseline characteristics of the study population

	Total ($n = 83$)	Non-depressed, non-anxious ($n = 17$)	Depressed only ($n = 32$)	Depressed and anxious ($n = 32$)	*P*-value	Anxious only ($n = 2$)
Age (years)	61.9 ± 11.1	61.9 ± 13.8	65.0 ± 9.8	59.7 ± 10.4	0.15	50.0 ± 1.4
Males (%)	41 (49.4)	12 (70.6)	13 (40.6)	14 (43.8)	0.11	2 (100.0)
Body mass index (kg/m^2)	29.7 ± 5.7	26.8 ± 5.2	30.7 ± 7.5	30.7 ± 4.9	0.08	27.9 ± 1.8
Diabetes (%)	38 (45.8)	7 (43.8)	15 (46.9)	16 (50.0)	0.92	0 (0.0)
Current smoker (%)	22 (26.5)	3 (17.6)	10 (31.3)	8 (25.0)	0.58	1 (50.0)
Hypertension (%)	70 (84.3)	15 (88.2)	28 (87.5)	27 (84.4)	0.91	0 (0.0)
Hypercholesterolaemia (%)	61 (73.5)	11 (64.7)	21 (67.7)	28 (87.5)	0.11	1 (50.0)
Previous MI (%)	20 (24.7)	1 (5.9)	10 (31.2)	9 (28.1)	0.12	0 (0.0)
Systolic BP (mmHg)	129.3 ± 20.2	124.9 ± 19.6	134.9 ± 20.8	127.4 ± 20.0	0.21	114.5 ± 13.4
Diastolic BP (mmHg)	74.4 ± 11.4	76.2 ± 7.8	71.8 ± 10.8	75.3 ± 13.5	0.35	77.5 ± 3.5
Total cholesterol (mg/dL)	155.3 ± 45.4	157.9 ± 43.5	145.5 ± 41.1	163.7 ± 51.1	0.97	165.5 ± 0.7
LDL (mg/dL)	87.4 ± 37.1	95.5 ± 39.6	82.0 ± 33.5	89.4 ± 40.5	0.48	74.5 ± 13.4
HDL (mg/dL)	45.6 ± 12.5	42.4 ± 8.7	48.2 ± 13.7	44.8 ± 11.2	0.12	52.5 ± 36.1
Triglycerides (mg/dL)	113.1 ± 80.8	116.5 ± 96.7	83.6 ± 42.1	134.5 ± 92.1	0.58	192.0 ± 107.5
Beta-blockers (%)	60 (72.3)	11 (64.7)	25 (78.1)	23 (71.9)	0.60	1 (50.0)
Lipid-lowering meds. (%)	69 (83.1)	15 (88.2)	24 (75.0)	28 (87.5)	0.33	2 (100.0)
ACE-inhibitors (%)	35 (42.2)	6 (35.3)	15 (46.9)	14 (45.2)	0.72	0 (0.0)
ARBs (%)	16 (19.8)	2 (11.8)	5 (15.6)	9 (28.1)	0.30	0 (0.0)
Ca-channel blockers (%)	23 (27.7)	3 (17.6)	11 (34.4)	9 (28.1)	0.47	0 (0.0)

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; Ca, calcium; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.

in *Table 1*. Only two patients qualified for the category of anxious only and their data, although included in analyses, are not presented except in *Table 1*. The reporting has been structured following the STROBE statement guidelines.[55]

There were no statistically significant differences, based on one-way ANOVAs or 2 × 3 contingency table analyses between the groups except in their BDI and HADS-A scores, which was expected. Overall, a moderate correlation was observed between scores on these indices of depression and anxiety symptom severity ($r^2 = 0.51$, $P < 0.001$).

Figures 2 and *3* (top panels) present the mean platelet reactivity of patients after adjusting for age and body mass index (BMI). For the two anxiety only patients, the means (± standard errors) of platelet aggregation (ADP—17.1 ± 10.1%, 5HT:E (L)—43.4 ± 10.3%, and 5HT:E (H)—49.0 ± 10.6%) and platelet surface receptor activation (ADP—13.3 ± 13.4%, 5HT:E (L)—23.5 ± 12.7%, and 5HT:E (H)—25.5% ± 12.5%) are not included in the figures.

The anxiety only groups (with and without depression) demonstrated a consistent association with higher reactivity to serotonin, in all measures of platelet function. In aggregation studies, the depressed and anxious group had significantly higher 5HT:E-mediated platelet reactivity than the depressed only and the non-depressed and non-anxious groups, whereas the latter two groups were not significantly different from each other (*Figure 2*). Platelet aggregation in response to ADP was higher in the depressed groups (with and without anxiety) vs. the non-depressed, but this was not statistically significant.

Findings in the flow cytometric assessment of platelet activation were similar (*Figure 3*), but only the results with high-dose 5HT:E achieved statistical significance.

Depression and anxiety symptom severity as predictors of platelet reactivity

Anxiety symptom severity, represented by continuous HADS-A scores, exhibited consistent correlations with serotonin-mediated platelet reactivity in both aggregation and flow cytometry studies. These correlations were significant with 5-HT:E-mediated aggregations at both low dose ($r = 0.25$, $P = 0.023$) and high dose ($r = 0.28$, $P = 0.011$). In flow cytometry studies, these correlations were just as strong with platelet surface receptor activation in response to 5HT:E ($r = 0.33$, $P = 0.003$ with low dose and $r = 0.28$, $P = 0.012$ with high dose). Depression symptom severity displayed a weaker and inconsistent relationship to platelet reactivity measures, with some degree of correlation noted in 5HT:E-mediated aggregation that only reached statistical significance with the high dose ($r = 0.20$, $P = 0.079$ and $r = 0.26$, $P = 0.02$). Neither depression nor anxiety symptom severity showed any associations with ADP-mediated platelet reactivity.

To better define the relationship of depression and anxiety symptom severity with platelet reactivity, a multivariate model was tested, controlling for age and BMI. With both BDI and HADS-A score in the equation, anxiety symptom severity remained a significant predictor of 5HT-mediated platelet reactivity, whereas depression symptom severity did not (*Tables 2* and *3*,

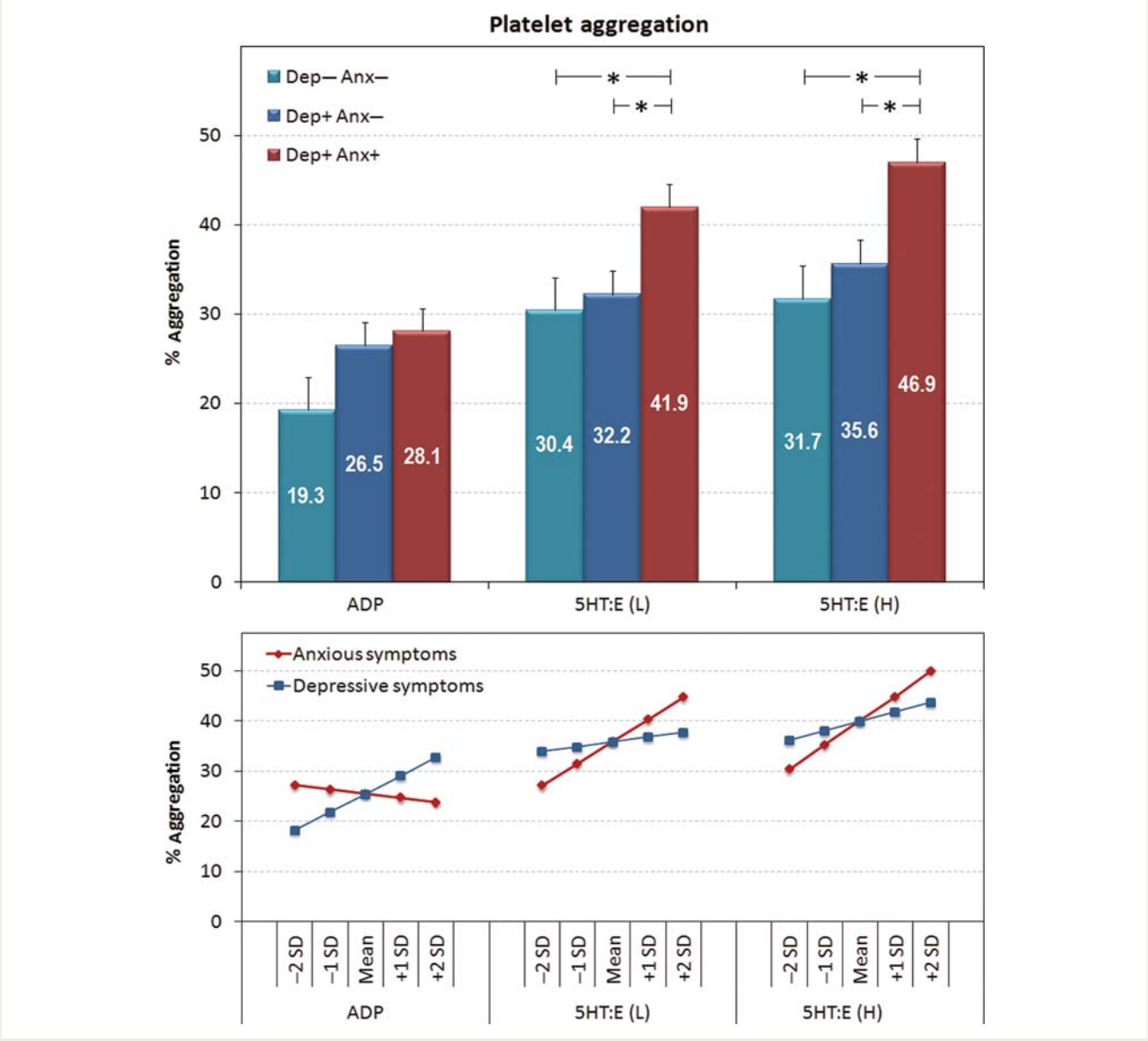

Figure 2 Top panel shows platelet aggregation result (estimated means ± standard error) in stable CAD patients grouped into *non-depressed and non-anxious* (Dep− Anx−), *depressed only* (Dep+ Anx−), and *depressed and anxious* (Dep+ Anx+). Bottom panel presents linear relations of depressive and anxious symptoms (BDI and HADS-A scores expressed in standard deviations from their means) to aggregation after controlling for age, BMI, and each other. *$P < 0.05$.

bottom panels of *Figures 2* and *3*). Thus, depression symptom severity, which had exhibited significant correlation with high-dose 5HT:E platelet aggregation in the unadjusted analysis, was no longer associated with any of the platelet reactivity measures. Findings with ADP-mediated platelet reactivity did not change from the unadjusted analysis.

To ensure that the differences in platelet reactivity to 5HT:E were in fact serotonin-mediated and not the result of epinephrine, same concentration of epinephrine (4 μM) was tested separately as a sole platelet aggregation agonist. No differences in epinephrine-mediated platelet reactivity between any of the groups were observed (data not shown).

Discussion

Despite the associations of psychological factors with recurrent cardiac events, and emerging evidence that in addition to such factors as hostility and depression, anxiety may have independent 'cardiotoxic' effects, few studies have examined the roles of depression and anxiety in such associations concurrently. Furthermore, a complete understanding of the mechanisms that may link these emotional factors with cardiac events has been lacking.[13] Depression has been associated with an increase in platelet reactivity in ACS patients, and serotonin, one of many platelet activators, has been hypothesized to be one of the links connecting

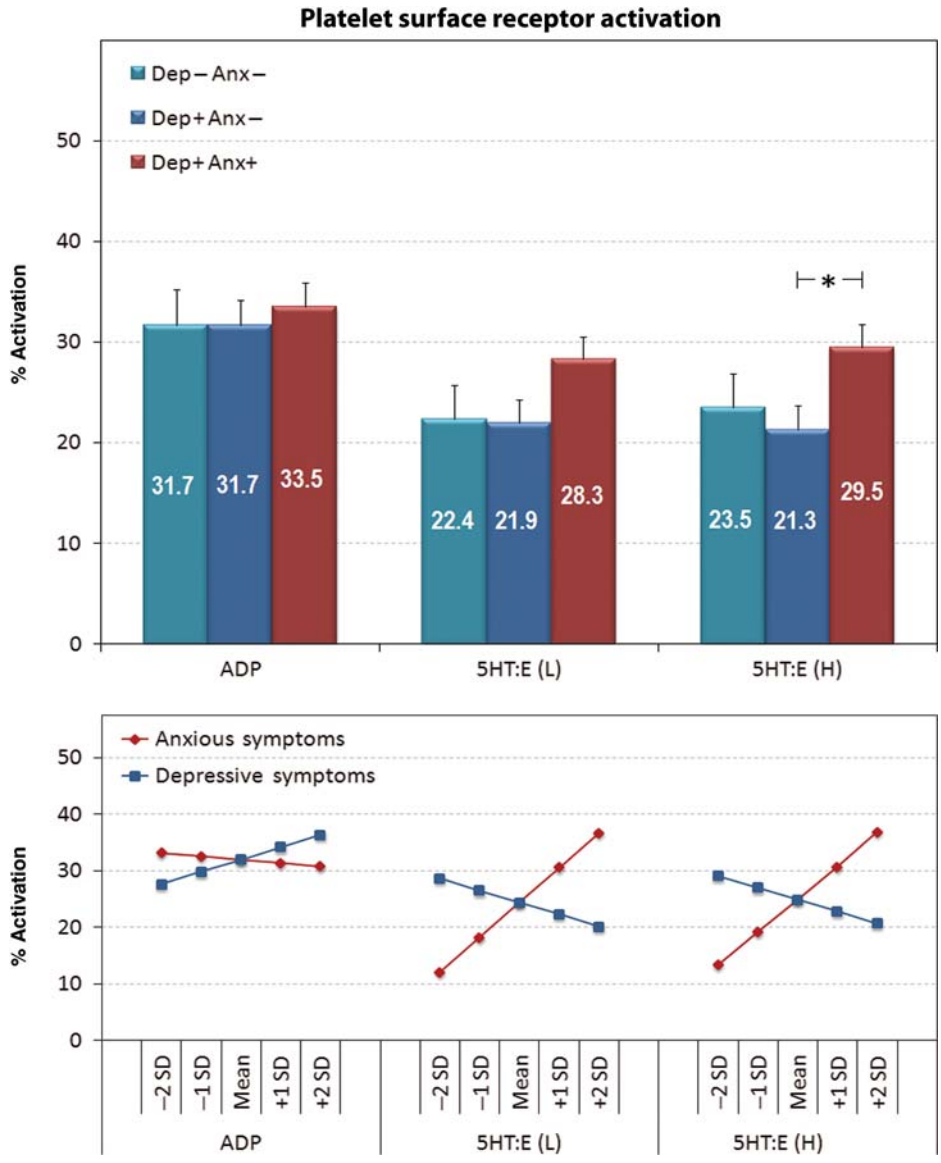

Figure 3 Top panel presents flow cytometric measurement of platelet surface receptor activation (estimated means ± standard error) in stable CAD patients grouped into *non-depressed and non-anxious* (Dep− Anx−), *depressed only* (Dep+ Anx−), and *depressed and anxious* (Dep+ Anx+). Bottom panel presents linear relations of depressive and anxious symptoms (BDI and HADS-A scores expressed in standard deviations from their means) to platelet surface receptor activation after controlling for age, BMI, and each other. *$P < 0.05$.

the two variables. Anxiety has similarly been associated with platelet function and activity during laboratory stress probes among individuals characterized by chronic life stress.[40]

Our aim was to investigate the associations of both depression and of anxiety with platelet function among patients several months after ACS when they were presumed to be stable. We also sought to assess the independent predictive value of these factors on platelet function in the same model. We found that patients categorized with depression demonstrated greater platelet reactivity to both ADP and serotonin, though this relationship did not reach statistical significance. In contrast, patients characterized with anxiety, according to this same criterion, demonstrated significantly greater platelet reactivity. A multivariate model that included these two factors as continuous measures of symptom severity revealed that only anxiety was associated with higher platelet reactivity, in both aggregation and flow cytometric measures of platelet function, and furthermore, that this hyper-reactivity was mediated via serotonin. The lack of any significant differences in the ADP-mediated platelet reactivity could be due to clopidogrel treatment, which specifically inhibits the P2Y12 receptor responsible for ADP-mediated platelet reactivity. Aspirin and clopidogrel combination therapy has also been reported to affect serotonin-induced platelet aggregation at 15 min, but not 6 min, of test run.[56] However, as our run times for aggregation studies were 6 min and all patients were on daily aspirin (81 mg) and clopidogrel (75 mg) therapy for 3 months prior to platelet function testing, it is unlikely to be a factor of any significance.

Table 2 Relation of depression and anxiety symptom severity to platelet aggregation

	Unstandardized coefficients		Standardized coefficients	t	*P*-value
	Beta	Std. error	Beta		
ADP-mediated					
Constant	25.48	1.56		16.30	0.00
Depressive symptoms	0.48	0.25	0.25	1.95	0.06
Anxious symptoms	−0.19	0.43	−0.06	−0.45	0.65
Age	0.22	0.15	0.17	1.50	0.14
BMI	−0.44	0.28	−0.17	−1.58	0.12
5HT:E (low dose)-mediated					
Constant	35.90	1.59		22.63	0.00
Depressive symptoms	0.13	0.25	0.07	0.54	0.59
Anxious symptoms	0.99	0.43	0.29	2.28	**0.03**
Age	0.27	0.15	0.20	1.87	0.07
BMI	−0.61	0.26	−0.25	−2.35	**0.02**
5HT:E (high dose)-mediated					
Constant	39.59	1.64		24.13	0.00
Depressive symptoms	0.25	0.26	0.12	0.98	0.33
Anxious symptoms	1.12	0.45	0.30	2.49	**0.02**
Age	0.40	0.15	0.28	2.64	**0.01**
BMI	−0.62	0.27	−0.24	−2.30	**0.02**

ADP, adenosine diphosphate; BMI, body mass index; 5HT:E, serotonin + epinephrine. Bold values indicate $P < 0.05$.

Table 3 Relation of depression and anxiety symptom severity to platelet receptor activation

	Unstandardized coefficients		Standardized coefficients	t	*P*-value
	Beta	Std. error	Beta		
ADP-mediated					
Constant	31.99	1.52		21.03	0.00
Depressive symptoms	−0.08	0.24	−0.04	−0.33	0.75
Anxious symptoms	0.49	0.41	0.16	1.20	0.24
Age	0.25	0.14	0.21	1.81	0.08
BMI	−0.37	0.28	−0.15	−1.32	0.19
5HT:E (low dose)-mediated					
Constant	24.40	1.32		18.44	0.00
Depressive symptoms	−0.28	0.21	−0.16	−1.32	0.19
Anxious symptoms	1.37	0.36	0.48	3.83	**<0.01**
Age	0.35	0.12	0.31	2.88	**<0.01**
BMI	−0.09	0.22	−0.04	−0.38	0.71
5HT:E (high dose)-mediated					
Constant	24.81	1.38		17.94	0.00
Depressive symptoms	−0.28	0.22	−0.16	−1.28	0.21
Anxious symptoms	1.30	0.37	0.44	3.47	**<0.01**
Age	0.42	0.13	0.35	3.31	**<0.01**
BMI	−0.06	0.23	−0.03	−0.25	0.81

ADP, adenosine diphosphate; BMI, body mass index; 5HT:E, serotonin + epinephrine. Bold values indicate $P < 0.05$.

Our findings suggest that although depression is associated with general platelet hyper-reactivity, anxiety may be a more dominant factor driving this increase, mediated via serotonin. This biological mechanism may account for the increased risk of recurrent events observed in cardiac patients with clinically meaningful levels of anxiety. The association of anxiety with platelet reactivity could also provide a plausible explanation for some of the inconsistencies in published reports linking emotional distress with increased CVD risk.[57] A varying proportion of patients with anxiety may be enrolled in some of these studies, rendering anxiety an unmeasured confound.

Our present study supports the findings reported in recent clinical studies. For example, Strik *et al.*[32] reported both anxiety and depression to be predictors of cardiac death or recurrent events in post-AMI patients, whereas Frasure-Smith and Lesperance[34] found both depression and anxiety to be predictive of cardiac events in stable post-ACS patients. However, in both studies, multivariate analysis including both depression and anxiety showed only anxiety to be an independent predictor of recurrent events. In yet another study, average exposure to anxiety over time in stable CAD patients was independently associated with an increased risk of non-fatal myocardial infarction or mortality; this study, however, did not examine the contributions of depression.[58]

It is important to note that a number of pathways have been suggested to link psychological factors, including depression and anxiety, to CAD-related outcomes. Among these are dysregulation in autonomic function, characterized by increased sympathetic and decreased parasympathetic control[59] and inflammatory processes.[60,61] Furthermore, the influence of autonomic pathways in the regulation of inflammatory processes, as suggested by Tracey,[62] has been observed in depressed patients with CHD.[63] Of interest, the latter study also found indices of coagulability elevated in relation to autonomic factors in this population; whether this occurs when anxiety is present is not yet known.

Current guidelines suggest screening cardiac patients for depression as its presence signals a worse cardiovascular prognosis.[23] Much less attention has been focused on anxiety. Our findings suggest that we should also be alert to symptoms of anxiety in these patients. Their timely identification could lead to the initiation of appropriate intervention to mitigate the risk for adverse cardiovascular outcomes associated with this factor. Interventions to accomplish this could include both more intensive antiplatelet therapy to directly address the mechanisms revealed in the current study, and behavioural interventions including exercise training that has also been shown to reduce depression and improve event free-survival in CAD patients,[25,64] and stress management, which has been shown to reduce overall psychosocial risk while improving both event-free survival and emotional stress provoked myocardial ischaemia.[65] However, it remains unknown if decreasing anxiety would remediate platelet function, or improve CAD outcomes.

Study limitations

The overall study sample was small and thus, the number of patients who qualified as anxious but not depressed in this study was low. This, however, represents the real world occurrence of anxiety, which is rarely encountered in the absence of depression. Importantly, this limitation applies only to the categorical analyses and is overridden by the stronger findings of the multivariate analysis, where symptoms of anxiety are shown to have a highly significant, linear relationship with platelet reactivity, independently of depression symptoms. Also of note, the relationship between anxiety and platelet function was found to be mediated by serotonin but not epinephrine. Although serotonergic pathways have been implicated in anxiety disorders,[66] sympathetic activation is also a hallmark of this clinical classification.[67] This finding may in part be a function of the co-morbid status of most patients with classified with anxiety in the current study. Further research with larger samples should address this issue.

Conclusions

The presence of anxiety symptoms is associated with higher platelet reactivity in stable CAD patients. This increase in platelet function is serotonin mediated and is independent of the effects of depression. Anxiety may therefore be a better predictor of platelet reactivity in CAD patients than depression.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

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