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BRIEF REPORT

Alexithymia and Cardiac Outcome in Patients at First Acute Coronary Syndrome

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Abstract

Background This cohort study was aimed to verify whether subjects at their first acute coronary syndrome (ACS) were more alexithymic than healthy controls (HC) and whether alexithymia can predispose patients with coronary artery disease to new major adverse cardiac events (MACE) during a 24-month follow-up period.

Methods The sample included 100 HC with no history of depression or ACS and 304 never depressed patients with a first-ever ACS. A total of 266 patients completed the 2-year follow-up.

Results Patients and HC reported similar Toronto Alexithymia Scale (TAS-20) scores. During the follow-up, 69 (22.69%) patients developed incident depression and 57 (18.75%) developed a new MACE. In a proportional hazard model, developing a first-ever depressive episode, but not alexithymia (hazard ratio = 1.008, 95% confidence interval = 0.984–1.033; $p = 0.500$), was associated with almost 3 times the risk of a recurrent cardiac event.

Conclusion Incident depression, but not TAS-20 scores, represented risk factor for MACE.

Keywords Coronary artery disease · Alexithymia · Incident depression · Major cardiac adverse event

Introduction

Alexithymia is a multidimensional construct characterized by (1) difficulty identifying feelings (DIF), (2) difficulty communicating and describing feelings (DDF), and (3) external-oriented thinking (EOT) [1]. The Toronto Alexithymia Scale 20 items (TAS-20) is the most widely used and studied self-report measure [2, 3].

Alexithymia, reflecting a disordered affect regulation, is thought to increase vulnerability to several medical disorders; however, epidemiological evidence regarding alexithymia as a prognostic risk factor for health problems, including coronary artery disease (CAD), remains lacking [4].

In patients with acute coronary syndrome (ACS), previous studies observed that alexithymia is significantly related with anxiety and depression [5, 6] and might be a consequence of an acute myocardial infarction [7]. These findings suggest that TAS-20 could also measure negative affects associated with a general distress syndrome, which is induced by a life-threatening condition rather than alexithymia itself [6].

It is still debated whether alexithymia is simply a consequence of an acute coronary disease or can predispose to new major adverse cardiac events (MACE).

This study has the dual aim of evaluating whether (1) never depressed subjects at their first acute coronary syndrome have a disorder of affect regulation compared to healthy controls (consequence hypothesis) and (2) alexithymic levels, representing a stable personality trait, predicted MACE during a 24-month period of follow-up (predisposition hypothesis).

Since it is possible that TAS-20 is associated with different measures of negative affects [8], we hypothesize that the relationship between alexithymia and cardiac disease, whether present, would be mediated by depressive symptoms.

Methods

The study sample was selected among patients, who were consecutively admitted to a Coronary Intensive Care Unit of Parma for a first-ever ACS from January 2009 to March 2012.

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Healthy subjects were recruited among the university employers and their relatives, between July 2016 and July 2017, trying to match the clinical sample on key characteristics (age and gender).

Participants older than 18 years, speaking Italian, reporting a Mini Mental State Examination score higher than 25 and with no history of CAD were included in the study, whereas those with either previous or current depressive episodes were excluded.

At baseline, all the subjects completed (1) a schedule for the collection of the socio-demographic information; (2) the Primary Care Evaluation of Mental Disorder (PRIME-MD) [9], followed by an interview by a trained psychiatrist to diagnose current or previous depressive episodes; (3) the Hospital Anxiety and Depression Scale (HADS) [10] to assess severity of anxious (HADS-A, anxiety score) and depressive (HADS-D, depression score) symptoms; and (4) the TAS-20. Patients were evaluated within 3 days after the ACS [11]. Patients were assigned a Global Registry of Acute Coronary Events (GRACE) score which assesses mortality risk after acute coronary events, considering age, history of myocardial infarction, past or current congestive heart failure (CHF), heart rate, systolic blood pressure, serum creatinine, elevated cardiac enzymes, ST segment depression on ECG at admission, and in-hospital percutaneous intervention [12].

After inclusion in the study, patients only were reevaluated with the PRIME-MD confirmed by a psychiatric interview at 1, 2, 4, 6, 12, and 24 months. A patient was defined as non-depressed if he or she did not satisfy the criteria for major or minor depression at any evaluation during the follow-up period. Information regarding the incidence of recurrent major adverse cardiovascular event (MACE) was collected by the Coronary Intensive Care Unit Information Technology registry and matched by phone calls to the participants in case the cardiac event was treated outside of the catchment area. MACE included recurrence of ACS, non-elective revascularization, acute hospitalization because of post-ischemic heart failure, or any death unless an unequivocal non-cardiac cause could be established. Of 397 patients assessed as eligible for inclusion in the study, 93 (23.42%) refused to complete all the baseline evaluation or withdrew.

Table 1 Socio-demographic and clinical features of patients with first acute coronary syndrome (ACS) and healthy controls (HC)

	ACS $n = 304$	HC $n = 100$	χ^2/t	p
Gender (male)	245 (80.6)	68 (68.0)	6.837	0.009
Age years (mean ± sd)	61.43 ± 10.975	58.28 ± 4.204	4.148	< 0.001
Education years (mean ± sd)	10.13 ± 3.747	11.16 ± 3.725	− 2.392	0.018
GRACE score	174.553	–		
Marital status			8.164	0.043
Never married	36 (11.8)	4 (4.0)		
Married	223 (73.4)	79 (79.0)		
Separated/divorced	24 (7.9)	13 (13.0)		
Widowed	21 (6.9)	4 (4.0)		
Family status			7.548	0.006
Living alone	52 (17.1)	6 (6.0)		
Living with someone	252 (82.9)	94 (94.0)		
Working status			25.884	< 0.001
Not working	8 (2.6)	6 (6.0)		
House-wife	16 (5.3)	6 (6.0)		
Working	130 (42.8)	67 (67.0)		
Retired	150 (49.3)	21 (21.0)		
HADS				
Anxiety (mean ± sd)	9.125 ± 5.126	6.11 ± 3.225	6.908	< 0.001
Depression (mean ± sd)	7.111 ± 4.216	5.62 ± 3.422	3.560	< 0.001
TAS-20				
DIF (mean ± sd)	15.069 ± 5.734	14.970 ± 6.131	0.142	0.887
DDF (mean ± sd)	13.023 ± 4.232	13.040 ± 4.244	0.035	0.972
EOT (mean ± sd)	21.223 ± 4.303	21.060 ± 5.212	0.284	0.777
Total (mean ± sd)	49.32 ± 11.129	49.07 ± 12.182	0.179	0.858

Figures represent number (%) unless stated otherwise

HADS Hospital Anxiety Depression Scale, *TAS-20* Toronto Alexithymia Scale 20 items, *DIF* difficult identifying feelings, *DDF* difficult describing feelings, *EOT* externally oriented thinking

Statistical Analysis

Patients and healthy controls were compared on alexithymia scores at TAS-20 with a *t* test and then with an analysis of covariance (ANCOVA) to exclude the effect of depression (HADS-D scores), anxiety (HADS-A scores), and other confounding variables such as age, gender, education, marital and occupational status. To overcome the number of covariates, we performed a *t* test between the healthy subjects ($n = 100$) and a sub-sample of patients ($n = 100$) matched for age ($p = 0.743$), sex ($p = 1$), and HADS total score ($p = 0.306$).

The rate of patients classified as with or without a recurrent MACE over the course of the follow-up were calculated. As it has been done previously in the same dataset [11], in the patients' group, two proportional hazard model (Cox regression) were used to evaluate which socio-demographic and clinical variables predicted the development of a MACE during the follow-up period. In the first model, we entered age, gender, years of education, widowhood, and working status, which might affect the adherence to treatment. In the second model, beyond those variables in the previous one, we added the GRACE score, which is a validated predictor of outcome, and whether the subjects developed a first-ever incident depressive episode (coded as 0 = no; 1 = yes). Lastly, in two alternative models, we entered in the first one the TAS-20 total score at baseline (model 3a) and in the other the TAS-20 subscales' scores, namely DIF, DDF, and EOT scores (model 3b).

The TAS-20 scores were also compared in patient groups of completers vs non-completers and in MACE vs non-MACE patients with analyses of variance (ANOVAs).

Results

Alexithymia in Patients and Healthy Controls at Baseline

Study population included 304 patients (245 men; 80.6%), with a mean age of 61.43 years and 100 healthy controls (68 men; 68.0%) with a mean age of 58.28 years. Their socio-demographic characteristics are in Table 1. Patients were significantly more anxious and depressed than healthy controls

Table 2 Baseline socio-demographic and clinical features of the completers ($n = 266$) with or without recurrent MACE during the 2-year follow-up period

	Non-MACE $n = 209$	MACE $n = 57$	χ^2/t	p
Gender (male)	169 (80.9)	48 (84.2)	0.334	0.563
Age years (mean ± sd)	60.78 ± 11.148	65.32 ± 9.089	− 2.825	0.005
Education years (mean ± sd)	10.05 ± 3.635	9.56 ± 3.923	0.889	0.375
Grace score (mean ± sd)	177.086 ± 42.077	173.421 ± 39.471	0.590	0.555
Marital status			4.839	0.184
Never married	27 (12.9)	3 (5.3)		
Married	150 (71.8)	47 (82.5)		
Separated/divorced	18 (8.6)	2 (3.5)		
Widowed	14 (6.7)	5 (8.8)		
Family status			0.030	0.863
Living alone	35 (16.7)	9 (15.8)		
Living with someone	174 (83.3)	48 (84.2)		
Working status			3.504	0.320
Not working	5 (2.4)	0 (0)		
House-wife	8 (3.8)	4 (7.0)		
Working	90 (43.1)	20 (35.1)		
Retired	106 (50.7)	33 (57.9)		
HADS-D (mean ± sd)	6.588 ± 4.159	7.298 ± 4.066	− 1.147	0.252
HADS-A (mean ± sd)	8.674 ± 5.268	9.491 ± 4.939	− 1.051	0.294
TAS-20				
DIF (mean ± sd)	15.091 ± 5.791	14.772 ± 5.676	0.370	0.712
DDF (mean ± sd)	13.048 ± 4.269	12.667 ± 3.879	0.609	0.543
EOT (mean ± sd)	20.982 ± 4.458	21.982 ± 4.134	− 1.526	0.128
Total (mean ± sd)	49.12 ± 11.394	49.42 ± 11.269	− 0.177	0.859

Figures represent number (%) unless stated otherwise

HADS Hospital Anxiety Depression Scale, *TAS-20* Toronto Alexithymia Scale 20 items, *DIF* difficult identifying feelings, *DDF* difficult describing feelings, *EOT* externally oriented thinking

whereas the two groups had similar scores at TAS-20 (Table 1). After controlling for age, gender, years of education, marital and occupational status, HADS-A, and HADS-D scores, the TAS-20 scores between patients and healthy controls were still not significantly different (TAS-20 total score $F = 0.734$ *df* 1403; $p = 0.392$; DIF score $F = 0.468$; *df* 1403; $p = 0.494$; DDF score $F = 0.260$; *df* 1403; $p = 0.61$; EOT score $F = 0.589$; *df* 1403; $p = 0.443$). Similarly, in our subsample analysis, TAS-20 scores did not differ between groups (TAS-20 total score: $t = -0.856$, 95%CI = −4.693, 1853, $p = 0.393$; DIF: $t = -0.398$, 95%CI = −1.963, 1.303, $p = 0.691$; DDF: $t = -0.796$, 95%CI = −1.739, 0.739, $p = 0.427$; EOT: $t = -0.895$, 95% = −1.891, 0.711, $p = 0.372$).

Alexithymia as a Predictor of MACE over the Follow-Up

Out of 304 subjects who completed the baseline evaluation, 38 refused to complete further psychiatric evaluations, resulting in a sample of 266 patients for this second part of the analyses (Table 2). Completer and non-completer socio-demographic features are presented in Table 3. Among the completers, 15 passed away. Sixty-nine (22.69%) patients developed an incident depressive episode (major depression was diagnosed in 43 patients and minor depression in 26) and 57 (18.75%) subjects developed a MACE (Table 2). Using Cox regression, incident depression but not baseline TAS-20 scores represented a risk factor for MACE (Table 4). Even when covariates were not included, TAS scores were not predictive in two alternative models (TAS-20 total score: HR = 1.007; 95%CI = 0.984, 1.031; $p = 0.530$; DIF score: HR = 1.009; 95%CI = 0.945, 1.077; $p = .0799$; DDF score: HR = 1.012; 95%CI = 0.926, 1.104; $p = 0.797$; EOT score: HR = 1.002; 95%CI = 0.933, 1.076; $p = 0.958$). When considering non-completers as censored, results were substantially overlapping with incident depression being the best predictor [11].

Discussion

The present study was aimed to evaluate whether (1) never depressed subjects at their first acute coronary syndrome were

Table 3 Baseline socio-demographic and clinical features of completer and non-completer patients with first acute coronary syndrome (ACS)

	Completers $n = 266$	Non-completers $n = 38$	χ^2/t	p
Gender (male)	217 (81.6)	28 (73.7)	1.325	0.250
Age years (mean ± sd)	61.75 ± 10.885	59.16 ± 11.483	1.311	0.196
Education years (mean ± sd)	9.95 ± 3.697	11.42 ± 3.895	− 2.195	0.033
Grace score (mean ± sd)	176.301 ± 41.487	162.316 ± 40.804	1.972	0.054
Marital status			1.267	0.737
Never married	30 (11.3)	6 (15.8)		
Married	197 (74.1)	26 (68.4)		
Separated/divorced	20 (7.5)	4 (10.5)		
Widowed	19 (7.1)	2 (5.3)		
Family status			0.477	0.490
Living alone	44 (16.5)	8 (21.1)		
Living with someone	222 (83.5)	30 (78.9)		
Working status			11.507	0.009
Not working	5 (1.9)	3 (7.9)		
House-wife	12 (4.5)	4 (10.5)		
Working	110 (41.4)	20 (52.6)		
Retired	139 (52.3)	11 (28.9)		
HADS-D (mean ± sd)	6.741 ± 4.142	9.710 ± 3.841	− 4.414	< 0.001
HADS-A (mean ± sd)	8.849 ± 3.841	11.053 ± 5.201	− 2.967	0.004
TAS-20				
DIF (mean ± sd)	15.022 ± 5.757	15.395 ± 5.640	− 0.380	0.703
DDF (mean ± sd)	12.966 ± 4.184	13.421 ± 4.595	− 0.577	0.567
EOT (mean ± sd)	21.195 ± 4.402	21.421 ± 3.576	− 0.353	0.726
Total (mean ± sd)	49.18 ± 11.347	50.24 ± 9.542	− 0.620	0.538

Figures represent number (%) unless stated otherwise

HADS Hospital Anxiety Depression Scale, *TAS-20* Toronto Alexithymia Scale 20 items, *DIF* difficult identifying feelings, *DDF* difficult describing feelings, *EOT* externally oriented thinking

Table 4 Baseline predictors of major adverse cardiac events during the 24 months of follow-up in 266 patients at their first ACS

		B	Wald	Exp(B)	95%CI	*p*
Block 1	Age (years)	0.020	1.185	1.021	0.984–1.058	0.276
	Gender (female)	0.368	0.693	1.445	0.607–3.438	0.405
	Education (years)	0.049	1.254	1.050	0.964–1.145	0.263
	Widowhood	0.079	0.019	1.082	0.352–3.330	0.891
	Occupation	0.236	0.488	1.226	0.653–2.457	0.485
Block 2	Age (years)	0.013	0.481	1.013	0.977–1.050	0.488
	Gender (female)	0.021	0.002	1.021	0.407–2.560	0.946
	Education (years)	0.038	0.686	1.038	0.950–1.136	0.407
	Widowhood	0.317	0.279	1.373	0.423–4.454	0.597
	Occupation	0.205	0.376	1.228	0.637–2.364	0.540
	GRACE score	− 0.001	0.077	0.999	0.991–1.007	0.781
	Incident depression	− 0.816	5.219	0.442	0.220–0.891	0.022
Block 3a	Age (years)	0.011	0.324	1.011	0.975–1.048	0.569
	Gender (female)	0.011	0.001	1.011	0.405–2.523	0.981
	Education (years)	0.040	0.751	1.040	0.951–1.138	0.386
	Widowhood	0.297	0.250	1.345	0.421–4.302	0.617
	Occupation	0.165	0.235	1.179	0.606–2.294	0.628
	GRACE score	− 0.001	0.074	0.999	0.991–1.007	0.785
	Incident depression	− 0.828	5.338	0.437	0.217–0.882	0.021
	TAS-20 total score	0.008	0.445	1.008	0.984–1.033	0.500
Block 3b	Age (years)	0.012	0.429	1.012	0.976–1.050	0.512
	Gender (female)	0.049	0.010	1.050	0.406–2.717	0.920
	Education (years)	0.030	0.372	1.031	0.935–1.135	0.542
	Widowhood	0.390	0.399	1.476	0.441–4.945	0.527
	Occupation	0.203	0.334	1.225	0.615–2.441	0.563
	GRACE score	− 0.002	0.171	0.998	0.990–1.007	0.680
	Incident depression	− 0.884	5.620	0.413	0.199–0.858	0.018
	TAS-20					
	DIF	0.018	0.228	1.018	0.946–1.096	0.633
	DDF	0.022	0.208	1.022	0.930–1.124	0.648
	EOT	− 0.019	0.220	0.981	0.906–1.062	0.639

Note: Results of the two Cox regressions with the first (3a) considering the TAS-20 total score only in the third and last block, and the second (3b) including all the TAS-20 subscales. Widowhood coded as 0 = no, 1 = yes; occupation coded as 0 = unemployed-retired; 1 = employed. Incident depression coded as 0 = no, 1 = minor or major depression

DIF difficulty identifying feelings, *DDF* difficulty describing feelings, *EOT* externally oriented feelings

more alexithymic than healthy controls and (2) alexithymic levels predicted major adverse cardiac events (MACE) during a 24-month period of follow-up, controlling for the effect of incident depression.

When comparing never depressed subjects few days after their first ACS and healthy controls, we found similar TAS-20 scores. This finding does not confirm the results of previous studies, which found high levels of alexithymia or high rates of alexithymic subjects (ca. 21–32%) in patients with CAD [13–16].

This discrepancy could have at least two different explanations. First, even though some authors suggested that alexithymia could be a risk factor for CAD, all previous studies enrolled patients with past episodes of coronary disease and most of them found a positive association between TAS-20 scores and previous MI or angina episodes. In contrast, the present study enrolled patients at their first ACS, and then, the TAS-20 scores could not be influenced by the effect of recurrent episodes of CAD. Further, the present finding is in line with the results of a recent prospective study, which did not find any association between alexithymia and cardiovascular events in a large non-clinical sample [17].

Second, it is well known that depressive episodes are associated with high levels of alexithymia. All previous studies did not evaluate the effect of depressive disorders on TAS-20 scores. In contrast, an exclusion criterion of the present study

was the presence of current and previous depressive episodes at baseline. Moreover, the severity of anxious and depressive symptoms, which could represent a distress reaction to the first ACS, was considered when the difference of TAS-20 scores between patients and HC was evaluated.

Our results seem therefore to suggest that alexithymia is neither a consequence of nor a risk factor for a first ACS.

When verifying whether alexithymic levels represented a risk factor for MACE, TAS-20 scores (total and DIF, DDF, and EOT subscale scores) did not predict new cardiac events. Our data suggest that alexithymia is not involved in the development of MACE, while incident depression exerted a negative effect on ACS outcome.

A possibility is that alexithymia increases the risk of MACE acting as a risk factor for the onset of incident depression. In the same sample, we previously demonstrated [18] that this was not the case.

Altogether, the present data suggest that alexithymia is not involved in the development neither of a first ACS nor of MACE.

The present study has some limitations.

First, the evaluation of alexithymia with the TAS-20 can be limited by the fact that alexithymia cannot be validly assessed by a self-report instrument because people with alexithymia, by definition, should not be able to report their psychological state. Therefore, the findings of the present study need to be confirmed using observer ratings (e.g., Toronto Structured Interview for Alexithymia).

Second, alexithymia was evaluated few days after the first ACS. Then, to conclude that alexithymia does not represent a personality trait increasing the risk of CAD, it should be evaluated before the first clinical manifestation of CAD.

Third, even though previous and current depressive episodes were excluded using the PRIME-MD, a screening instrument developed for psychiatric morbidity in primary care, all the subjects were interviewed by a trained psychiatrist, who verified the appropriateness of the answers.

Fourth, the sample includes mostly male patients, thus limiting this study's applicability to female gender.

In conclusion, in the present study, never depressed patients at their first ACS reported the same level of alexithymia observed in healthy controls and alexithymia did not represent a risk factor for the development of MACE in the following 2 years. These findings suggest that alexithymia and cardiovascular events were not associated in a clinical population. This casts some doubt on whether alexithymia could be a meaningful target in the prevention of MACE.

Compliance with Ethical Standards

All procedures performed in this study, involving human participants, were in accordance with the ethical standards of the institutional research committee (Comitato Etico dell'Area Vasta Emilia Nord, segreteria di Parma, at the time of the study protocol approval, in 2009, Comitato Etico di Parma) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed written consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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