Prevalence of Depression in Patients With Chest Pain and Non-Obstructive Coronary Artery Disease

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Many studies have demonstrated the prevalence of depression in patients with coronary artery disease (CAD), but few have examined this relation in those with chest pain who do not have obstructive CAD on angiography. The aim of this study was to compare the prevalence of depression amongst patients with chest pain in the presence or absence of obstructive CAD and a healthy control group without chest pain. This prospectively designed, observational cohort study used 2 independent data sets: (1) The Queen Elizabeth Hospital Coronary Angiogram Database (n = 1,144), consisting of 819 patients with obstructive CAD and 325 patients with nonobstructive CAD (NoCAD), all of whom had chest pain and (2) the North West Adelaide Health Study (NWAHS; n = 3,168), a population-based biomedical cohort, from which patients with chest pain were excluded. The presence of depression was determined by a previously validated method using the Short Form 36. The prevalence of depression differed among the 3 groups, with 63% in those with NoCAD, 53% in those with CAD, and only 24% in the healthy NWAHS cohort. Analysis of the angiography cohort revealed age, gender, antidepressant medication, previous myocardial infarction, previous airway disease, Short Form 36 physical summary score, Seattle Angina Questionnaire physical limitation score, and NoCAD on angiography to be independent predictors of depression. In conclusion, these findings highlight the importance of screening for depression in patients with NoCAD. **(Am J Cardiol 2013;112:656−659)**

Depression is reported to occur in 10% to 40% of patients with coronary artery disease (CAD)[1,2] and is an independent predictor of mortality in those who experience acute myocardial infarctions (AMIs).[3,4] Coronary angiography is the benchmark investigation for the evaluation of CAD and enables the distinction between patients who have obstructive CAD and those who do not have significant CAD, that is, nonobstructive CAD (NoCAD). Patients with NoCAD constitute a puzzling cohort for clinicians, because symptoms are often indistinguishable from those with obstructive CAD,[5] yet the causes of the chest pain may be diverse, including cardiac (coronary spasm and microvascular dysfunction) and noncardiac (esophageal reflux, musculoskeletal, and psychiatric) disorders.[5−7] Although many studies have focused on the prevalence of depression in patients with obstructive CAD, few have investigated its prevalence in those with NoCAD, despite psychiatric conditions' potentially contributing to the associated chest pain. In the present study, we examined the relation between depression and the presence or absence of obstructive CAD by (1) comparing the prevalence of depression in patients with chest pain and obstructive CAD or NoCAD, using a healthy control cohort as a reference population and (2) determining if the presence or absence of obstructive CAD is an independent predictor of depression.

Method

This prospectively designed cohort study used 2 independent data sets to evaluate 3 study groups: (1) a healthy control group derived from the North West Adelaide Health Study (NWAHS) and (2) patients with chest pain with or without obstructive CAD on angiography obtained from The Queen Elizabeth Hospital (TQEH) Coronary Angiogram Database. The 2 data sets recruited patients from the same geographic region, the northwestern districts of Adelaide.

Details of the design used in the NWAHS have been previously reported.[8,9] In brief, the NWAHS is a population-based biomedical cohort study investigating the prevalence of chronic conditions and health-related risk factors. Households within the northwestern districts of Adelaide with telephone numbers in the electronic directory were randomly selected and invited to participate in the study. Analysis of bias in the study showed no differences in self-reported general health status and social demographics compared with the general population.[10] Those recruited underwent telephone interviews to ascertain their health problems and completed health status questionnaires.[8,9] The original NWAHS consisted of 4,060 participants. For this study, those with histories of chest pain or cardiac disorders or who had missing cardiovascular data were excluded from the analysis, thereby resulting in a "healthy cohort" of 3,168 participants (mean age 52 ± 15 years, 54% women).

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The coronary angiography cohort included patients who underwent angiography for the evaluation of chest pain at TQEH from 2003 to 2007. This hospital provided cardiac catheterization facilities for the northwestern districts of Adelaide. The database was established to determine the clinical characteristics, health status, and subsequent outcomes of patients who underwent coronary angiography for the evaluation of chest pain. On the basis of the subsequent coronary angiographic findings, patients were grouped into those with obstructive CAD (i.e., coronary artery stenosis $\geq$50%) and those with NoCAD (i.e., normal coronary angiographic results or minor lesions [<50%]). Of the 1,268 patients recruited to TQEH Coronary Angiogram Database, 124 had alternative cardiac causes of their chest pain (e.g., severe aortic stenosis) and were excluded from the analysis. Of the remaining 1,144 patients, 819 had obstructive CAD (mean age 62 $\pm$ 11 years, 26% women), and 325 had NoCAD (mean age 57 $\pm$ 12 years, 57% women).

Variables recorded in the NWAHS and TQEH Coronary Angiogram Database included (1) demographics (age, gender, the Socio-Economic Indexes for Areas Index of Relative Socioeconomic Disadvantage (IRSD)),[11] (2) cardiac-associated risk factors (smoking status, hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, number of risk factors, acute or stable chest pain pattern at angiography presentation, previous AMI, angina pectoris, heart failure, stroke or transient ischemic attack, airway disease, and musculoskeletal disease), (3) depression-associated risk factors (antidepressant medication), and (4) psychometric data obtained from the Short Form 36 (SF-36) mental and physical summary scores and Seattle Angina Questionnaire domains. The IRSD quintiles are produced by the Australian Bureau of Statistics[11] to measure socioeconomic status by postal code. IRSD scores are grouped into quintiles (highest, high, middle, low, and lowest) for analysis, where the highest quintile represents postal codes with the highest IRSD scores (most advantaged areas) and the lowest quintile represents postcodes with the lowest IRSD scores (most disadvantaged areas).[11] Of relevance, most TQEH Coronary Angiogram Database patients completed questionnaires before the coronary angiographic study, so that patients and clinicians were unaware of the diagnosis of obstructive CAD or NoCAD.

The diagnosis of depression for this study was based on a previously validated method using the SF-36 mental summary score.[12] The SF-36 was scored using the method of Tucker et al,[13] which allows for the correlation between physical and mental health in producing factor score weights for the component summary scores. Using a threshold mental summary score value of $\leq$45, this method has 93% sensitivity and 64% specificity for the diagnosis of depression.[12] On the basis of this method, patients were classified as depressed or not depressed at the time of study recruitment.

Statistical analyses were performed using SPSS version 17 (SPSS, Inc., Chicago, Illinois). In the univariate analyses, ambiguous responses to categorical variables (e.g. "not sure," "not asked," "not stated") were recoded as missing values. Patients with missing SF-36 mental summary scores were excluded from analyses. Descriptive statistics for the study cohorts are expressed as mean $\pm$ SD for continuous data and as percentages for categorical data. Baseline characteristics were compared using Student's *t* tests and chi-square tests for the respective data. The primary end point (prevalence of depression) was compared among the 3 study groups using binary logistic regression. On the basis of the available data from the angiography database and the prespecified depression definition (SF-36 mental summary score $\leq$45), the study had 76% power to detect an odds ratio (OR) of 1.44 for the prevalence of depression at the

Table 1
Baseline characteristics of NWAHS healthy controls and chest pain patients

Characteristic	Healthy Controls (n = 3,168)	Obstructive CAD	
		Yes (n = 819)	No (n = 325)
Age (yrs)*,†	52 ± 15	62 ± 11	57 ± 12
Women*,†	1,714 (54%)	215 (26%)	185 (57%)
Hypertension*,†	622 (22%)	533 (66%)	182 (58%)
Hypercholesterolemia*,†	1,600 (56%)	589 (75%)	184 (60%)
Diabetes mellitus*,†	217 (8%)	263 (33%)	58 (18%)
Number of risk factors*,†			
0	1,096 (35%)	58 (7%)	54 (16%)
1	1,308 (41%)	219 (27%)	113 (35%)
2	644 (20%)	315 (38%)	110 (34%)
3	110 (3.5%)	198 (24%)	43 (13%)
4	10 (0.5%)	29 (4%)	5 (2%)
Family history of CAD*,†	1,554 (54%)	418 (55%)	189 (62%)
Smoking status*,†			
Ex-smoker	1,052 (37%)	340 (43%)	102 (32%)
Current smoker	527 (18%)	174 (22%)	58 (18%)
Angiographic presentation*			
Stable chest pain pattern	—	505 (62)	253 (78%)
Previous AMI*	—	250 (31%)	20 (6%)
Previous angina pectoris	—	360 (44%)	134 (41%)
Previous airway disease	—	139 (18%)	69 (22%)
Previous heart failure*	—	18 (2%)	0 (0%)
Previous musculoskeletal disease	—	107 (14%)	57 (18%)
Previous stroke/transient ischemic attack	—	46 (6%)	25 (8%)
Antidepressant medication	—	91 (11%)	47 (15%)
Health/psychological indexes			
SAQ angina frequency	—	63 ± 28	65 ± 24
SAQ angina stability	—	41 ± 33	44 ± 31
SAQ physical limitation	—	58 ± 24	60 ± 25
SAQ quality of life	—	43 ± 22	44 ± 22
SF-36 physical summary score*,†	49 ± 10	36 ± 10	38 ± 11
SF-36 mental summary score*,†	51 ± 10	43 ± 11	41 ± 11
Depression*,†	697 (24%)	394 (53%)	186 (63%)

Data are expressed as mean ± SD or number (percentage). Values may not add up to the total, because of missing cases.

SAQ = Seattle Angina Questionnaire.

* p <0.05, obstructive CAD versus NoCAD.

† p <0.05 among healthy controls, obstructive CAD, and NoCAD.

Table 2
Multivariate predictors of depression in patients with chest pain

Predictor	OR (95% CI)	p Value
NoCAD	1.44 (1.03−2.03)	0.03
Age	0.97 (0.96−0.99)	<0.001
Female gender	1.69 (1.23−2.32)	<0.001
Antidepressant medication	2.58 (1.57−4.25)	<0.001
Previous acute myocardial infarct	1.64 (1.17−2.30)	0.004
Previous airway disease	1.48 (1.01−2.17)	0.045
SF-36 physical summary score	1.03 (1.01−1.05)	0.009
Seattle Angina Questionnaire physical limitation score	0.97 (0.96−0.98)	<0.001

0.05 significance level for NoCAD compared with obstructive CAD.

To determine if the presence or absence of CAD on angiography was an independent determinant of depression, a multivariate binary logistic regression model was developed. Comparisons between the angiographic groups for potential univariate predictors of depression were undertaken as described earlier. A significance level of $p \leq 0.25$ in the univariate analyses was used as a criterion for entry into the multivariate analysis. The categorical form of SF-36 mental summary score was used as the dependent variable (i.e., depressed or not depressed), to determine the ORs (exp [β]) and 95% confidence intervals (CIs) of predictor variables. Missing and "not sure," "not asked," or "not stated" responses (≥10 cases) for the categorical covariates were combined into a valid category to include the maximum number of records possible in the analysis and to mitigate bias. The identified variables from the univariate analyses were entered into the regression model and the best predictors selected using the backward elimination of nonsignificant terms. Covariates were removed from the regression model 1 by 1 according to the significance criterion specified ($p = 0.05$) using the log likelihood test. The best fit model of non-nested alternatives was determined using the Akaike information criterion. The significance level for predictors of depression in the final model was defined as $p < 0.05$.

Results

The clinical and psychometric characteristics of the healthy NWAHS patients compared with those with chest pain (obstructive and NoCAD) are summarized in Table 1. Compared with the healthy controls, the chest pain (angiography) population was older with more cardiovascular risk factors and had a poorer quality of life. Unadjusted analyses demonstrated a significant difference in the prevalence of depression among the 3 groups. Compared with the NWAHS healthy control cohort, the OR was higher for the obstructive CAD (OR 3.483, 95% CI 2.947 to 4.117, $p < 0.001$) and NoCAD (OR 5.359, 95% CI 4.166 to 6.895, $p < 0.001$) patients. Furthermore, depression was more prevalent in those with NoCAD (OR 1.539, 95% CI 1.166 to 2.030, $p = 0.002$) relative to those with obstructive CAD.

Univariate analyses of the TQEH angiography cohort revealed the following as significant potential predictors of depression: age (continuous and categorical), gender, hypertension, hypercholesterolemia, diabetes mellitus, number of risk factors, smoking status, family history of CAD, antidepressant medication, angiographic presentation, previous AMI, airway disease, heart failure, musculoskeletal disease, stroke or transient ischemic attack, SF-36 physical summary score, and Seattle Angina Questionnaire physical limitation and angina stability scores. Multivariate analyses using the Akaike information criterion to determine the model of best fit among non-nested alternatives (continuous vs categorical age predictors) identified 8 factors as significant independent predictors of depression in chest pain patients, including the presence of NoCAD (Table 2).

Discussion

The major finding of this study is that depression is more prevalent in patients with chest pain with NoCAD than either those with obstructive CAD or healthy controls. Moreover, NoCAD is an independent predictor of depression in patients who undergo coronary angiography for the evaluation of chest pain. These observations have important implications in the pathogenesis and treatment of patients with chest pain referred for coronary angiography.

We used SF-36 mental summary scores to identify depressed patients in healthy control and chest pain cohorts. The method has been previously validated in similar cohorts using a well-established depression scale (the Center for Epidemiologic Studies Depression Scale),[12] and the findings of the present study provide further face validity for this method. First, consistent with previous studies of depression, there was a 2-fold greater probability of depression in patients with obstructive CAD compared with healthy controls.[14] Second, the use of antidepressants was a strong predictor of the SF-36 score−derived depression category (Table 2), suggesting that it was comparable with clinician-diagnosed and clinician-treated depression. Third, other well-characterized predictors of depression, including previous AMI,[3] airway disease,[15] and impaired physical activity,[16] were independent predictors. Given the consistencies in the study findings with the established research on depression, the novel methodologic approach is verified, so that attention to the unique findings of this study can be addressed.

Patients with NoCAD constitute a heterogeneous clinical group, with multiple causes for the chest pain prompting angiography. One study reported that 25% had psychiatric disorders, 25% microvascular angina, 25% esophageal disorders, and the remaining a variety of other medical conditions responsible for the chest pain prompting angiography referral.[17] However, this is an oversimplification, because these disorders may coexist or be difficult to delineate. Cardiac syndrome X, for example, is characterized by normal angiographic findings despite positive results on exercise stress testing and has been associated with a high prevalence of depression.[18−20] These findings can be explained by 3 plausible alternative mechanisms. First, the exercise test finding is a "false-positive," and the source of the chest pain is depression or some other noncardiac disorder (e.g., esophageal reflux). Second, the patient has a coronary microvascular disorder resulting in myocardial ischemia producing chest pain and positive stress test

results, with depression ensuing from the suboptimal therapies available for this disabling disorder. Third, depression and coronary microvascular disorders have a common pathophysiologic or genetic pathway, so that the disorders coexist.[21] It may therefore be difficult to identify the primary cause for the chest pain in patients with NoCAD, although the presence of causative or contributory disorders such as depression can be quantified. However, whether treatment of the depressive illness improves the presenting chest pain symptoms can be more readily addressed.

In a landmark study, Cannon et al[22] recruited 60 consecutive patients with NoCAD and subjected them to systematic assessment, reporting that 22% had abnormal exercise test results, 41% had abnormal esophageal motility testing, and 63% had $\geq$1 psychiatric disorder. Furthermore, using a randomized, double-blind, placebo-controlled study design, they demonstrated that imipramine therapy reduced chest pain episodes by 52 $\pm$ 25%. Because the prevalence of depression and other psychiatric disorders were matched between the treatment groups, the treatment effect was attributed to the pain sensitivity−altering properties of imipramine, although an antidepressant effect cannot be excluded.

The present study highlights the importance of screening for depression in patients who undergo coronary angiography for the evaluation of chest pain. This is particularly pertinent considering (1) the high prevalence of depression in this population, especially in comparison with other published studies that have undertaken screening studies after AMI, general cardiac admissions,[23] and cardiac outpatients[1] and (2) the availability of potential therapies to alleviate chest pain[22] and improve quality of life.[24−26] In conclusion, depression is prevalent in patients who undergo coronary angiography for the evaluation of chest pain, and those with NoCAD should be particularly targeted for assessment.

Disclosures

The authors have no conflicts of interest to disclose.

1. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA* 2003;290:215−221.
2. Sheps DS, Shepard D. Depression, anxiety and cardiovascular system: the cardiologist's perspective. *J Clin Psychol* 2001;62(suppl):12−16.
3. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. *JAMA* 1993;270: 1819−1825.
4. Wheeler A, Beltrame J, Tucker G, Air T, Ling L-H, Schrader G. Depression and 5-year mortality in patients with acute myocardial infarction: analysis of the IDACC database. *Aust N Z J Psychiatry* 2012;46:669−675.
5. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA* 2005;293:477−484.
6. Watson GS. Noncardiac chest pain: a rational approach to a common complaint. *JAAPA* 2006;19:20−25.
7. Brims FJH, Davies HE, Lee YCG. Respiratory chest pain: diagnosis and treatment. *Med Clin N Am* 2010;94:217−232.
8. Grant JF, Chittleborough CR, Taylor AW, Dal Grande E, Wilson DH, Phillips PJ, Adams RJ, Julianne C, Price K, Gill T, Ruffin RE; The North West Adelaide Health Study Team. The North West Adelaide Health Study: detailed methods and baseline segmentation of a cohort for selected chronic diseases. *Epidemiol Perspect Innov* 2006;3:1−14.
9. Grant JF, Taylor AW, Ruffin RE, Wilson DH, Phillips PJ, Adams RJT, Price K, The North West Adelaide Health Study Team. Cohort profile: the North West Adelaide Health Study (NWAHS). *Int J Epidemiol* 2009;38:1479−1486.
10. Taylor AW, Dal Grande E, Gill T, Chittleborough CR, Wilson DH, Adams RJ, Grant JF, Phillips P, Ruffin RE; The North West Adelaide Health Study Team. Do people with risky behaviours participants in biochemical cohort studies? *BMC Public Health* 2006;6:11.
11. Australian Bureau of Statistics. An Introduction to Socio-Economic Indexes for Areas (SEIFA) 2006. Canberra, Australia: Australian Bureau of Statistics, 2008.
12. Tavella R, Air T, Tucker G, Adams R, Beltrame JF, Schrader G. Using the Short Form-36 mental summary score as an indicator of depressive symptoms in patients with coronary heart disease. *Qual Life Res* 2010;19:1105−1113.
13. Tucker G, Adams R, Wilson D. New Australian Population scoring coefficients for the old version of the SF-36 & SF-12 health status questionnaires. *Qual Life Res* 2010;19:1069−1076.
14. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, and correlates and association of health resource utilisation, lost productivity and functional disability. *Gen Hosp Psychiat* 2007;29:409−416.
15. Lacasse Y, Rousseau L, Maltais F. Prevalence of depressive symptoms and depression in patients with severe oxygen-dependent chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2001;21:80−86.
16. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003;160:1147−1156.
17. Beitman BD, Mukerji V, Lamberti JW, Schmid L, DeRosear L, Kushner M, Flaker G, Basha I. Panic disorder in patients with chest pain and angiographically normal coronary arteries. *Am J Cardiol* 1989;63:1399−1403.
18. Ketterer MW, Brymer J, Rhoads K, Kraft P, Kenyon L, Foley B, Lovallo WR, Voight CJ. Emotional distress among males with "syndrome X." *J Behav Med* 1996;19:455−466.
19. Asbury EA, Creed F, Collins P. Distinct psychosocial differences between women with coronary heart disease and cardiac syndrome X. *Eur Heart J* 2004;25:1695−1701.
20. Piegza M, Pudlo R, Badura-Brzoza K, Hese RT. Cardiac syndrome X from a psychosomatic point of view. *Arch Psych Psych* 2009;2:23−27.
21. Vaccarino V, Votaw J, Faber T, Veledar E, Murrah NV, Jones LR, Zhao J, Su S, Goldberg J, Raggi JP, Quyyumi AA, Sheps DS, Bremner JD. Major depression and coronary flow reserve detected by positron emission tomography. *Arch Intern Med* 2009;169:1668−1676.
22. Cannon RO III, Quyyumi AA, Mincemoyer R, Stine AM, Gracely RH, Smith WB, Geraci MF, Black BC, Uhde TW, Waclawiw MA, Maher K, Benjamin SB. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994;330:1411−1417.
23. Wade V, Cheok F, Schrader G, Hordacre A-L, Marker J. Depression after cardiac hospitalization. The Identifying Depression as a Comorbid Condition (IDACC) study. *Aust Fam Physician* 2005;34:985−989.
24. Skevington SM, Wright A. Changes in the quality of life of patients receiving antidepressant medication in primary care: validation of the WHOQOL-100. *Br J Psychiatry* 2001;178:261−267.
25. Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, Keller MB. A randomized, placebo-controlled trail of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. *J Psychiatr Res* 2009;43:205−214.
26. Reed C, Monz BU, Perahia DGS, Gandhi P, Bauer M, Dantchev N, Demyttenaere K, Garcia-Cebria A, Grassi L, Quail D, Tylee A, Montejo AL. Quality of life outcomes among patients with depression after 6 months of starting treatment: results from FINDER. *J Affect Disord* 2009;113:296−302.