Gender as a Determinant of Responses to a Self-Screening Questionnaire on Anxiety and Depression by Patients With Coronary Artery Disease

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Abstract

Background—Because patients with coronary artery disease (CAD) could benefit from interventions to decrease psychological distress, it is important to identify these individuals. Both salivary cortisol level and the Hospital Anxiety and Depression Scale (HADS) are recognized measures of stress/anxiety and depression.

Objectives—This study was designed to determine whether there is an association between anxiety and depression, as measured by the HADS, and salivary cortisol levels among patients with CAD, and whether this association is affected by gender.

Methods—All adult residents of Alberta, Canada, undergoing their first cardiac catheterization for CAD (≥ 50% occlusion of ≥ 2 coronary arteries) were eligible for participation in this study. A 14-question survey (the HADS) and 3 saliva-collection devices (a 1-day supply) were sent to the participants' home within 1 week of their initial cardiac catheterization. Participants were asked to take saliva samples for determination of cortisol levels on waking and at 30 and 60 minutes after waking, and then return the completed questionnaire and saliva samples using a prepaid express mailing envelope.

Results—Seventy-one adults (52 men and 19 women) participated in the study. Mean (SD) ages were 68.4 (4.6) years for men and 69.1 (4.4) years for women. Among the women, significant negative correlations were found between the HADS anxiety score and the wake-up and 30-minute cortisol levels (higher HADS scores were associated with lower cortisol levels) (all, $P < 0.05$). Also among women, negative correlations were found between the HADS depression score and the salivary cortisol values, but the differences were not statistically significant. Conversely, among the men, nonsignificant positive correlations were found between the HADS anxiety scores and the salivary cortisol levels (higher HADS scores were associated with higher cortisol levels),

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and statistically significant positive correlations were observed between the HADS depression scores and all 3 salivary cortisol values (all, $P < 0.05$).

Conclusions—Our findings suggest that the HADS is an appropriate screening instrument for anxiety and depression in patients with CAD. In particular, the scale appears to be sensitive for measuring anxiety in women and depression in men. When the HADS is used clinically as a screening tool, it should be examined through a “gender-based lens.”

Keywords

gender differences; anxiety; depression; coronary artery disease

INTRODUCTION

Any type of cardiac event (eg, acute myocardial infarction, unstable angina) is clearly a stressful experience. Postevent stress symptoms are common, but most fade over several weeks.^{1–3} However, ~20% of people who experience such events have more severe or lasting anxiety or depression.⁴ A large body of literature reveals associations between depression and risk for cardiac events, as well as links between depression and increased morbidity and mortality after such events have occurred.^{5–7} Recent data suggest that clinically significant anxiety can also affect outcomes including health-related quality of life in populations with cardiac disease.^{5–10} Thus, there would be considerable clinical advantages to identifying clinical subpopulations at high risk for anxiety and/or depression who could benefit from interventions to decrease psychological distress. Proactively focusing on individuals with coronary artery disease (CAD) could serve to both decrease the risk of further cardiac events and improve outcomes for this population. Identification of key stress-related indicators appropriate for the CAD population, who have higher levels of psychological distress and are at greater risk for cardiac events than are people without CAD, requires integration of both psychological and physiologic parameters. In addition, our recent research findings^{7,11} suggest that identification strategies must acknowledge the importance of gender¹ as a determinant of cardiac outcomes.

In terms of psychological distress, the Hospital Anxiety and Depression Scale (HADS) identifies patients with symptoms of clinically significant anxiety and depression, and comorbid chronic diseases. The HADS is widely used in hospital settings, and a review identified 747 studies that had used this scale.¹² The sensitivity and specificity of the HADS are similar to those of other screening measures of anxiety and depression.¹³ Of note, the HADS has been used extensively and effectively among patients with CAD.¹⁴

Herrmann¹⁵ reported that the HADS has been used successfully in cross-sectional studies for screening purposes, comparisons of mean levels between patient groups, prevalence of anxiety and depression in patient groups, and correlations with parameters of somatic disease, personality, and/or quality of life. Of the 200 published studies reviewed by Herrmann, 10 specifically addressed differences in HADS scores based on gender. Herrmann reported that although women scored higher than men on the HADS anxiety subscale, no significant gender-based differences were observed on the HADS depression subscale. This increased anxiety in women has also been reported in the psychiatric

literature related to stress and mental health, in which women have been found to have more comorbid anxiety and depressive disorders than men.¹⁶

In terms of investigating physiologic measures of anxiety and depression that may help characterize a high-risk group within the CAD population, 2 major stress response systems should be considered. Activation of the sympathetic-adrenal-medullary (SAM) axis results in the release of epinephrine into the systemic circulation. Epinephrine is a powerful vasoconstrictor and positive chronotrope that increases both heart rate and blood pressure. However, interpretation of SAM-axis parameters is complicated by the broad impact of medications typically used for the treatment of CAD.⁶

Activation of the hypothalamic-pituitary-adrenal (HPA) axis occurs in response to both internal stressors (eg, infection, hunger) and external stressors (eg, physical threat, emotional distress), and results in the release of corticosteroids (in humans, this is mainly in the form of cortisol) from the adrenal cortex. Circulating cortisol is also a vasoconstrictor and increases heart rate, albeit to a lesser degree than epinephrine. However, cortisol has multiple other effects on immune and metabolic functions. Both of these stress systems are activated in response to a perceived threat or stimuli and deactivated when the threat is removed.

Studies in cardiac populations have identified a number of neurohormonal sequelae^{17–21} ensuing from acute stress and the resulting effects on cardiovascular function in depressed individuals.²² These include exaggerated HPA-axis responses to stress, higher levels of norepinephrine and its metabolites in blood and urine, and reduced heart variability (beat-to-beat fluctuations in heart rate). Reduced heart variability has been validated as a measure of autonomic regulation of the heart and is associated with poor cardiovascular outcomes.^{23,24} It has been proposed that the loss of cardiac parasympathetic control leaves the heart vulnerable to unopposed stimulation by the sympathetic nervous system under stressful conditions and predisposes depressed individuals to lethal arrhythmias.¹⁹ A major limitation to measuring SAM parameters (plasma norepinephrine levels and heart variability) is that measurements typically require a visit to a health care center for blood sampling and/or electrocardiographic monitoring.

In contrast, saliva has been shown to be a noninvasive, valid, and reliable medium for quantitatively assessing cortisol levels.²⁵ Salivary cortisol represents only unbound cortisol; hence, interpretation of results of saliva sampling is not complicated by potential changes in corticosteroid-binding globulin (CBG), as is the case with plasma sampling.²⁶ For example, women have higher levels of CBG than do men,²⁶ and evidence suggests that depressed women have decreased levels of CBG compared with normal (nondepressed) women and depressed men.²⁷ Only unbound cortisol is active; therefore, changes in CBG levels may affect the degree of impact that increased levels of cortisol may exert on body systems. Another advantage of saliva sampling is that it can be accomplished in a more natural setting (eg, an individual's own home), and serial collections can be easily incorporated into daily routines.

Because both salivary cortisol and the HADS are recognized measures of stress response and stress-related symptoms, the aim of this study was to determine the association between salivary cortisol levels and HADS anxiety and depression scores among patients catheterized for CAD in Alberta, Canada. Furthermore, we wished to examine whether there were gender differences in the associations between salivary cortisol levels and HADS scores.¹

METHODS

This HADS cortisol analysis was an exploratory substudy of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH). APPROACH is a provincewide inception cohort of all adult Alberta residents undergoing cardiac catheterization for ischemic heart disease. The APPROACH project was initiated to study provincial outcomes of care and to facilitate quality assurance/quality improvement for patients with CAD in Alberta.²⁸ The APPROACH database contains detailed clinical and treatment information for adult patients with known or suspected CAD. The data provide a unique opportunity to study outcomes in an unselected patient population.

Eligible subjects included all residents of Alberta, Canada, 18 years of age who were undergoing their first cardiac catheterization for CAD (50% occlusion of 2 coronary arteries; Duke Coronary Index, 3–13²⁸) and registered in the APPROACH database. Patients were excluded if they did not consent to become part of the APPROACH follow-up cohort. The outcome data were collected by means of a self-reported questionnaire mailed to patients within 1 week of their initial cardiac catheterization. Consent to follow-up was acquired at the time of catheterization, and ethics committees at each of the participating hospitals approved the study. For the purposes of this study, APPROACH follow-up surveys included an envelope that contained 3 saliva-collection devices* (1-day supply), a record sheet, instructions for collecting the saliva samples, and the HADS questionnaire. Participants were provided with a prepaid express mailing envelope that could be dropped into any mailbox to return the samples and questionnaire. Participants also were given a contact number to schedule a pickup if they were unable to leave their home to mail the envelope.

Laboratory Measures

Daily cortisol levels are known to peak ~30 minutes after awakening.²⁹ Evidence suggests that the awakening cortisol response is sensitive to psychosocial variables.³⁰ Thus, participants were instructed to collect saliva samples immediately on awakening, 30 minutes after waking, and 60 minutes after waking (to record the expected decline from the 30-minute peak). Participants were provided with a kit containing 3 well-marked (waking, 30-min, and 60-min) saliva-collection devices. The instructions given were: *Take the cotton roll from the tube, put it in your mouth, swirl it around, and chew on it for ONE MINUTE (ie, for a full 60 seconds). It is important that the cotton roll gets very wet. Then spit it back into the tube and put the cap back on. Be sure to keep all samples refrigerated until they are mailed.*

*Trademark: Salivette® (Sarstedt Inc., Montreal, Quebec, Canada).

Salivary cortisol is stable for at least 7 days under refrigeration,³¹ and the prepaid envelopes for overnight delivery ensured that mailed samples would not be left at room temperature for extended periods. On receipt, the saliva samples were centrifuged and stored at -80°C . Assays were conducted at the Women's Health Research Unit Laboratory at the Faculty of Nursing, University of Alberta (Edmonton, Alberta, Canada). Levels of salivary cortisol were determined by a commercially available, ultrasensitive ELISA (Salivary Cortisol Kit; Salimetrics, LLC, State College, Pennsylvania). The quoted range of detection for the assay was 0.003 to 3.0 mg/dL.

Demographic, Psychosocial, and Behavioral Measures

Demographic, clinical, and procedural variables were collected at catheterization through the APPROACH registry. The APPROACH follow-up survey included the HADS, 2 health-related quality-of-life measures (the Seattle Angina Questionnaire³² and the EuroQol-5D³¹), the Medical Outcomes Study Social Support Questionnaire,³³ and questions regarding ethnicity, marital status, education, and employment status.

The HADS consists of 14 questions (7 related to anxiety and 7 related to depression). Patients are asked to respond to the amount of time they have experienced symptoms related to anxiety and depression over the past month. Patients can choose 1 response from the 4 given for each symptom. For example, in response to the question "I feel tense or 'wound up'," patients could choose from the following answers: most of the time (score, 3); a lot of the time (2); from time to time, occasionally (1); or not at all (0). Summary anxiety and depression scores are created by summing the scores from the individual questions on each scale. The maximum score for each scale is 21. Categories have been established for the total score of each scale, with 0 to 7 considered "normal," 8 to 10 considered "borderline abnormal," and 11 to 21 considered "abnormal."¹⁵

Statistical Analysis

Data were analyzed cross-sectionally (mean values of all variables). Exploratory analyses were performed on cortisol levels to determine the adequacy of the assumption of normality. Cortisol values were highly skewed; therefore, for the purpose of modeling, cortisol levels were transformed using a natural log transformation. The mean cortisol levels were computed using the mean log-transformed values at each time point, as well as the overall mean log-transformed values for all 3 time points, by participant. HADS scores were calculated, and both summary and categorical scores were created for the anxiety and depression scales. Bivariate analyses were performed to determine the association between the HADS anxiety score, HADS depression score, and log-transformed mean cortisol value for each time point, as well as the overall mean value. Correlations were rerun, stratifying the bivariate analysis by gender. To examine the gender differences in the mean HADS anxiety score, HADS depression score, and log-transformed mean cortisol value for each time point, *t* tests were used. Finally, ANOVA was used to model mean log-transformed cortisol levels as a function of the anxiety and depression scores stratified by gender. No sample size calculation was performed. Statistical significance was set at $P < 0.05$.

RESULTS

Seventy-one respondents (52 men [73%] and 19 women [27%]) returned their saliva samples and questionnaires (response rate, 79%). Mean (SD) ages were 68.4 (4.6) years for men and 69.1 (4.4) years for women. Of the 71 respondents, 84% had a history of hypertension and 79% had a history of hyperlipidemia. Other reported comorbidities included diabetes mellitus (24%), congestive heart failure (14%), cerebrovascular disease (8%), pulmonary disease (7%), peripheral vascular disease (6%), and renal disease (3%). The APPROACH data registry indicated cardiac catheterization as the inception point. As a result, we were not able to determine the duration of CAD for patients in the registry.

The mean differences between the sexes in salivary cortisol levels and HADS scores are presented in Table I. Although the mean HADS anxiety score was significantly higher in women than in men ($P = 0.03$), the differences in salivary cortisol levels and HADS depression scores between the 2 groups were not statistically significant. The normal and log-transformed salivary cortisol values on waking are shown in the figure; the log-transformed data approached normal distribution. The correlations between the HADS scores and the salivary cortisol values are presented in Table II.

Although no statistically significant correlations were observed when analyzing the entire sample, analysis by gender presented entirely different results. Among the women, significant negative correlations were found between the HADS anxiety score and the waking and 30-minute cortisol levels (higher HADS scores were associated with lower cortisol levels) (all, $P < 0.05$). Also among women, negative correlations were found between the HADS depression score and the salivary cortisol values, but the differences were not statistically significant. Conversely, among the men, nonsignificant positive correlations were found between the HADS anxiety scores and the salivary cortisol levels (higher HADS scores were associated with higher cortisol levels), and statistically significant positive correlations were found between the HADS depression scores and all 3 salivary cortisol values (all, $P < 0.05$).

DISCUSSION

No associations were observed between either the HADS anxiety scale or the HADS depression scale and salivary cortisol levels for the overall sample. However, statistically significant, gender-specific associations were identified (all, $P < 0.05$). Whereas the women in the sample had negative correlations between the HADS anxiety and depression scores and salivary cortisol levels, the men had positive correlations.

Although comparisons between measures of psychological distress typically remain within 1 framework, ours is the first study (to our knowledge) in the cardiovascular literature that compared a commonly used psychological measure with physiologic measures of anxiety and depression. For example, in a review of the HADS by Bjelland et al,¹² which “confirmed the assumption that HADS is a questionnaire that performs well in screening for the separate dimensions of anxiety and depression,” the evaluation of its performance was limited to comparisons with other psychological tools. An electronic search identified only 1

study that investigated the association between HADS scores and salivary cortisol levels in patients with recurrent aphthous stomatitis.³⁴ Although the group of symptomatic patients who were not responding to treatment had significantly higher HADS scores and salivary cortisol levels than did the asymptomatic patients, anxiety scores and salivary cortisol levels were not well correlated.³⁴ The authors interpreted this lack of correlation by suggesting that the HADS measures more “trait” anxiety, and the transient increase in salivary cortisol levels in the symptomatic group was more a reflection of stress than of anxiety.

Anxiety can be considered either a psychological response to a given situation (state anxiety) or a persistent behavioral characteristic (trait anxiety). Thus, the state of feeling anxious can exist along a continuum, from a transient (state anxiety) to a stable personality characteristic (trait anxiety) to a generalized anxiety disorder (GAD) with specific diagnostic criteria and functional impairment.³⁵ Although GAD by definition has a duration of at least 6 months, no consistent definition of time frames for state versus trait anxiety is available.

The HADS relates to patients’ symptoms over the previous month. This temporal issue is important in chronic diseases such as CAD, because chronic symptoms can lead to persistent feelings of anxiety. Thus, high scores on the anxiety scale would not necessarily reflect trait anxiety, but rather the impact of cardiac symptoms experienced on a day-to-day basis. It may be more clinically relevant to consider HADS anxiety scores as an indicator of generalized psychological distress. It is important to note that we are not inferring that the HADS is superior to other anxiety and depression scales used in this and other clinical populations, such as the Hamilton Depression Rating Scale, the Beck Depression Inventory, and the Centre for Epidemiological Studies Depression Scale. The choice is often related to convention in the particular field of study and the desire to compare results across studies using similar tools.

Cortisol levels are known to increase and remain elevated in the face of acute stressors.³⁶ Studies in chronically stressed populations and those who have experienced overwhelming stress reported lower-than-normal levels.^{37,38} Our data suggest that, for the women, the HADS anxiety scale reflected a more chronic state of anxiety (statistically significant negative correlation [$P < 0.05$]; as the HADS anxiety score increased, the salivary cortisol level decreased) compared with the men. In contrast, cortisol hypersecretion is regarded as a marker of major depressive disorder (MDD) that remits with clinical improvement.³⁹ The statistically significant positive correlation between the HADS depression scale and the salivary cortisol levels in men ($P < 0.05$) would suggest that the HADS depression scale is more sensitive in measuring symptoms of depression that are associated with disturbances in HPA-axis activity. It will be important to further explore why this finding was limited to men. Although hypercortisolemia is an often-cited marker for MDD, it is only observed in ~50% of patients with MDD.³⁹

Earlier studies of the HPA axis and depression did not adequately address gender differences. In a 1997 review of the international experiences with the HADS, Herrmann¹⁵ noted that when gender differences were addressed (10 of the 200 studies reviewed), women consistently scored higher than men on the HADS anxiety scale, whereas no significant gender differences were found “in most studies” using the HADS depression scale. This is

not surprising in light of the results of our study, whereby the correlations between the HADS anxiety and depression scores and salivary cortisol levels go in opposite directions for men and women. This suggests that the HADS may be measuring different constructs or different subtypes of anxiety and/or depression based on gender that are not detected when simply comparing mean HADS scores. Alternatively, the differences may be due to different physiologic reactions in men and women, which are in turn reflected in the salivary cortisol levels.

Results of our study indicate that the patterns of salivary cortisol (waking, 30-min, and 60-min levels) were similar for men and women; both sexes experienced decreases in 30- and 60-minute cortisol levels. However, as a result of the small sample size, we were unable to further stratify the analysis by anxiety or depression categories and, therefore, were unable to suggest differences (or lack thereof) in the physiologic reactions between men and women. Moreover, because of the limited size of this exploratory study, we were unable to do extensive analyses of the potential intervening variables that may have influenced our findings. Interestingly, although statistically significant differences in the mean total social support scores were found between men and women in this study, the correlations between the HADS anxiety and depression scores and salivary cortisol levels did not change significantly when we controlled for social support.

CONCLUSIONS

Our findings suggest that the HADS is an appropriate screening instrument for anxiety and depression in patients with CAD. In particular, the scale appears to be sensitive for measuring anxiety in women and depression in men. Our data suggest that gender-based analyses be conducted when the HADS is used for population studies. Furthermore, when the HADS is used as a screening tool, it should be examined through a “gender-based lens.” In either case, failing to do so may result in misleading conclusions that will miss opportunities to intervene early in clinically treatable circumstances and to improve the outcomes of both men and women with CAD. The increased recognition of significant gender differences in the types of stressors experienced, the responses to stressors, and the implications for health outcomes and service delivery has led to calls for more gender sensitivity and specificity in research endeavors as well as clinical practice guidelines. Further validation that commonly used psychological tools can identify clinically relevant gender differences is an important first step.

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Figure.

(A) Normal and (B) log-transformed salivary cortisol levels, measured on awakening.

Mean gender-based differences in salivary cortisol levels and Hospital Anxiety and Depression Scale (HADS) scores.*

Table 1

Measure	Men, Mean (SD) (n = 52)	Women, Mean (SD) (n = 19)	P	Minimum	Maximum
Salivary cortisol, µg/dL					
On waking	0.57 (0.36)	0.52 (0.31)	0.60	0.15	1.82
30 Minutes after waking	0.48 (0.30)	0.44 (0.26)	0.58	0.28	1.47
60 Minutes after waking	0.42 (0.32)	0.36 (0.28)	0.45	0.07	1.82
HADS					
Anxiety score	3.36 (3.19)	5.39 (3.59)	0.03	0	12.00
Depression score	2.51 (2.46)	3.89 (3.28)	0.07	0	12.00

* Maximum score for each scale is 21, with scores of 0 to 7 considered “normal,” 8 to 10 considered “borderline abnormal,” and 11 to 21 considered “abnormal.”¹⁵

Table II

Correlation coefficients of Hospital Anxiety and Depression Scale (HADS) scores, by cortisol level.

HADS	Salivary Cortisol Measured								
	On Waking			30 Minutes After Waking			60 Minutes After Waking		
	Men (n = 52)	Women (n = 19)	All (N = 71)	Men (n = 52)	Women (n = 19)	All (N = 71)	Men (n = 52)	Women (n = 19)	All (N = 71)
Anxiety score	0.21	-0.49 [*]	-0.01	0.22	-0.46 [*]	0	0.24	-0.28	0.06
Depression score	0.35 [*]	-0.37	0.01	0.37 [†]	-0.33	0.12	0.34 [*]	-0.28	0.10

^{*} $P < 0.05$.

[†] $P < 0.01$.