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The interaction between anxiety and depressive symptoms on brachial artery reactivity in cardiac patients

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ABSTRACT

The association between anxiety, depression, and endothelial function (EF) was assessed in a sample of 295 cardiac outpatients ($n = 222$ men; mean age = 59). Patients were administered the Beck Depression Inventory-II and the State-Trait Anxiety Inventory, trait scale. EF was assessed through forearm hyperemic reactivity, a nuclear medicine variation of the flow-mediated dilatation technique, which calculates the rate of uptake ratio (RUR) between hyperaemic and non-hyperaemic arms. Neither effect of anxiety ($F = 1.40$, $p = .24$) nor depression ($F = 2.66$, $p = .10$) was found in a model predicting EF, however there was an interaction ($F = 4.11$, $p = .04$). Higher anxiety and lower depressive symptoms were associated with superior RUR compared to lower anxiety and lower depressive symptoms. Anxiety had no influence on RUR in those patients with higher depressive symptoms, who generally displayed the lowest levels of RUR, i.e., poor function. It is speculative whether this potential protective role of anxiety may be guided by behavioral or physiological mechanisms.

1. Introduction

Psychological variables, including affective states such as depressed mood and anxiety are risk factors for the development of cardiovascular disease (CVD) (Kubzansky, Kawachi, Weiss, & Sparrow, 1998; Lesperance, Frasure-Smith, Juneau, & Theroux, 2000; Suls & Bunde, 2005). Findings from meta-analyses suggest that the presence of increased depressive symptoms are associated with a doubling of risk for developing CVD and risk for CVD mortality compared to individuals with low levels of depressive symptoms (Barth, Schumacher, & Herrmann-Lingen, 2004; Rugulies, 2002). Associations between anxiety and CVD have also been examined in a recent meta-analysis, showing elevated anxiety symptoms to be associated with a greater risk of developing CVD (HR: 1.26, 95% CI: 1.15–1.38) and cardiac death (HR: 1.48, 95% CI: 1.14–1.92) (Roest, Martens, de Jonge, & Denollet, 2010).

Unfortunately, the bio-behavioral mechanisms underlying these relationships remain unclear, though processes such as hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, sympathomedullary hyperactivity, and proinflammatory cytokine activation have been implicated (Gonzalez & Selwyn, 2003; Joynt, Whellan, & O'Connor, 2003; Musselman, Evans, & Nemeroff, 1998). One hypothesized mechanism for the relationship between depression and CVD has been via endothelial dysfunction (Lavoie, Pelletier, Arsenault, Dupuis, & Bacon, 2010).

The endothelium is a dynamic layer of cells lining the vascular walls that regulates many homeostatic processes (Vita & Keaney, 2002). These include the production of vasodilators (e.g., nitric oxide) and vasoconstrictors (Gonzalez & Selwyn, 2003), and the

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regulation of blood fluidity and inflammation. Endothelial dysfunction is strongly and independently associated with increased risk of CVD development, (Lerman & Zeiher, 2005; Quyyumi, 2003; Schachinger, Britten, & Zeiher, 2000), as it is considered to reflect a composite of many factors affecting cardiovascular health (e.g., dyslipidemia, hypertension, smoking, diabetes, and inflammation) (Bonetti, Lerman, & Lerman, 2003; Lekakis et al., 2011).

We have previously shown the presence of major depressive disorder in cardiac outpatients to be associated with poorer forearm hyperemic reactivity, a proxy measure for endothelial function (Lavoie et al., 2010). Separate studies have demonstrated impaired endothelial function to be associated with depressive symptoms in CVD patients (Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005) and major depressive disorder in healthy individuals with no CVD risk factors (Rajagopalan et al., 2001). This inverse association between depressive symptoms and flow mediated dilation, another proxy measure of endothelial function, has been supported by a recent meta-analysis which identified a combined effect size correlation coefficient of $r = .19$ ($p = .001$) (Cooper et al., 2011). As an example of potential mechanisms linking depression to endothelial dysfunction, a previous study showed that major depressive disorder was associated with decreased nitric oxide synthase activity (Chrapko et al., 2004). Nitric oxide synthase is a precursor required to catalyze L-arginine into nitric oxide, which is a messenger molecule released by the endothelium that regulates vasodilation (Lowenstein, Dinerman, & Snyder, 1994).

Anxiety and depression are highly comorbid, as evidenced by high concurrence in both psychiatric and cardiac samples (Frasure-Smith & Lespérance, 2008), and high correlations between questionnaire measures (Endler, Denisoff, & Rutherford, 1998; Stulz & Crits-Christoph, 2010). In contrast to the depression literature, there is a limited amount of data looking at the potential associations between endothelial function and anxiety. However, it would appear that there is a negative correlation between trait anxiety and brachial artery flow-mediated dilation (Narita, Murata, Hamada, Takahashi, Kosaka, & Yoshida, 2007). Despite the well-documented comorbidity of anxiety and depressive symptoms, to our knowledge only one study has examined an interaction between anxiety and depression on endothelial function. This study observed less vasodilation in postmenopausal women with elevated anxiety and depression (Harris, Matthews, Sutton-Tyrrell, & Kuller, 2003).

This study sought to better understand the relationships between anxiety symptoms, depressive symptoms and endothelial function by assessing the interaction of anxiety and depressive symptoms on brachial artery reactivity, in a sample of cardiac patients referred for myocardial perfusion imaging. Based on previous findings highlighting the severity of comorbid anxiety and depressive disorders, it was hypothesized that a multiplicative interaction effect will be observed. Patients displaying elevated levels of depressive and anxiety symptoms would have worse reactivity, thus indicating the greatest amount of endothelial dysfunction, than those displaying either elevated anxiety or depressive symptoms independently. Of note, this study represents a reanalysis of a previously published data set. Lavoie et al. (2010) identified a main effect of mood disorder, in that patients with major depressive disorder demonstrated lower forearm hyperemic reactivity than patients without depression. In this previous study, a dichotomous diagnosis of mood disorder was utilized, as per the PRIME-MD (Spitzer, Kroenke, Williams, 1999) criteria. In contrast, this current project analyzed depressive symptoms continuously, rather than dichotomously, allowing us to not neglect subclinical levels of depressive symptoms. Additionally, through the analysis of anxiety symptoms in this current study, we were able to test for the presence of an interaction effect.

2. Materials and methods

2.1. Participants

The current study represents a sub-analysis of the Cross-sectional Mechanisms and Longitudinal Outcomes of Silent Myocardial Ischemia (MOSMI) study, which was designed to assess the relationship between blood pressure and silent myocardial ischemia (Gordon et al., 2012; Pelletier et al., 2011). A total of 906 outpatients referred for a single photon emission computed tomography (SPECT) perfusion exercise stress test in the outpatient nuclear medicine service of the Montreal Heart Institute between May 2005 and December 2006 were recruited. Approximately one-third ($n = 328$) were recruited for the forearm hyperemic reactivity (FHR) test. Due to limited camera availability, these patients were recruited consecutively from the total sample until three available testing slots per day were filled. Patients were included if they were at least 18 years of age, and spoke either English or French. Patients were excluded from the MOSMI study if they suffered from a pain disorder other than angina; used a prescription or non-prescription analgesic on the day of exercise testing; used a non-steroidal anti-inflammatory agent (NSAID), coxibs, or anti-neoplastic agent within the last 7 days; were pregnant; had a severe or comorbid condition and were not expected to survive for 12 months (e.g., cancer); had a history of drug or alcohol abuse; or had a mental condition (determined via self-report and chart review of prescribed medications) rendering the participant unable to understand the nature, scope, and possible consequences of the study. Patients were excluded from the FHR test if they reported having exercised in the last 24 h, smoked within 6 h, or eaten within 4 h, prior to the test. The human ethics committee of the Montreal Heart Institute approved the protocol, and all patients provided written, informed consent prior to participation. This subsample has been utilized in two previous studies assessing the association of mood and anxiety disorders with endothelial function (Lavoie et al., 2007, 2010). The complimentary nature of the current study with this previous research is elaborated in our discussion.

2.2. Procedure

Patients presenting for exercise stress testing at the Nuclear Medicine Service of the Montreal Heart Institute were invited to participate. On the first day of the SPECT perfusion imaging testing, patients began with a standard treadmill exercise stress test (modified Bruce protocol) followed by standard SPECT imaging (Anagnostopoulos et al., 2004). Patients were administered a battery of self-report questionnaires assessing sociodemographic and medical history information which were provided to them after they had completed the exercise stress test. On the following day, patients who had accepted to enter the FHR sub-study had their fasting blood drawn and resting blood pressure taken (using a manual sphygmomanometer) (Tycos-767 series, Welch Allyn, Skaneateles Falls, NY) by an experienced nuclear medicine technician. Patients then completed the FHR test, followed by the rest scan according to the SPECT protocol. The FHR test was conducted between 7 and 9 am. Patients were asked to maintain all usual medications, but asked to refrain from taking β blockers due to the SPECT test.

2.2.1. Brachial artery reactivity

Reactivity was assessed using a nuclear medicine variation of the well-established flow-mediated dilation protocol (Corretti et al., 2002), a technique developed in our laboratory (Dupuis et al., 2004). Participants were seated with both arms extended over a large field of view gamma-camera (Seintronix, London, UK) facing upward, hands prone. A blood pressure cuff (Adult First Responders, B&A Instruments, New York, NY) was placed over the right upper-arm, and inflated to 50 mm Hg above systolic blood pressure for 5 min, creating a hyperemic challenge. Thirty seconds after sudden cuff release, a tracer in the form of technetium-99m-tetrofosmin was injected as a bolus (15.5 MBq/kg) via a small catheter positioned in the bend of the left arm, with the injection trajectory masked using a lead lining between the arm and the tubing. Dynamic imaging of the forearms was taken and sustained for 10 min, using 128×128 matrices at a sampling rate of one frame per second. Comparing activity-time curves over identical regions of interest in the hyperemic right arm and the non-hyperemic control left arm using custom software (SyGeSa, Montreal, Canada) allowed for the derivation of a relative-uptake-ratio (RUR), a unit-less index of maximum rise in activity. A higher ratio reflects greater endothelial reactivity and better endothelial function. This technique has been shown to predict the presence of CAD using a cutoff RUR of 3.55 with a sensitivity of .70 and a specificity of .60 (Arsenault, Bacon, Kavoie, & Meloche, 2005; Dupuis et al., 2004). This technique has shown to have excellent measurement properties, including high test–retest reliability ($r = .89$) (Bacon, Meloche, Lavoie, & Arsenault, 2012) and very good inter- and intra-rater reliability ($r = .98$) (Veldhuijzen van Zanten et al., 2006), and is comparable to other similar techniques (Karacalioglu et al., 2006). The longitudinal predictive nature of the technique is less well established, and is being addressed currently in a number of ongoing studies (Bacon et al., 2011).

2.2.2. Depressive symptoms assessment

The Beck Depression Inventory-II (BDI) is a self-report measure of 21 multiple-response items, each which relate to a depressive symptom (Beck, Steer, Ball, & Ranieri, 1996). Each response is rated on a scale of 0 to 3, allowing for total scores