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Pre-surgical Psychological and Neuroendocrine Predictors of Psychiatric Morbidity Following Major Vascular Surgery: A Prospective Longitudinal Study

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Abstract

Objective—Major life stressors, including major surgeries, are often followed by psychiatric symptoms and disorders. Prior retrospective work found abdominal-aortic aneurysm (AAA) repair is followed by increased psychiatric morbidity, which may adversely influence physical and functional recovery. Identifying risk factors prior to surgery, such as dysregulation in stress response systems, might be useful to improving preventative intervention.

Methods—Two hundred and sixteen patients receiving open AAA or aortofemoral bypass (AFB) surgeries, endovascular AAA repair (EVAR), or nonsurgical AAA treatment were recruited from two vascular surgery services. Psychiatric symptoms and salivary cortisol measures (waking, 4 pm, and 11 pm, before and after low-dose dexamethasone) were obtained at intake and 3 and 9 month followups.

Results—Following open surgeries, 18% of patients had new psychiatric disorders, compared to 4% of patients receiving EVAR or nonsurgical treatment (odds ratio = 6.0, 95% CI 1.6 - 22.1, $p=.007$). Having a history of major depression predicted onset of new disorders in surgical patients. Pre-surgical cortisol levels were associated with both baseline ($r=.23$, $p<.05$) and 9 month ($r=.32$, $p<.01$) psychiatric symptoms (cortisol $B=1.0$, $SE=0.48$, $p<.05$ in repeated measures mixed model).

Conclusion—Open AAA repair surgery is prospectively linked to development of psychiatric morbidity, and history of depression elevates risk. Cortisol measures prior to surgery are associated with current and future psychological functioning, suggesting potential neurobiological mechanisms that may contribute to vulnerability. These results can help identify surgical patients at risk, and point to potential targets for risk reduction interventions.

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Keywords

HPA axis; cortisol; surgery; dexamethasone suppression test; stress; stress-related psychopathology; PTSD

INTRODUCTION

Psychiatric disorders (e.g., depression and posttraumatic stress disorder (PTSD)) can develop following stressful life events, including medical illnesses. Medical conditions requiring intensive care, such as myocardial infarctions and major surgeries, produce particularly high rates of psychiatric morbidity in several forms, including depression, anxiety, and posttraumatic stress disorder (PTSD). Elevated depressive symptoms are seen in as many as 65% of patients following myocardial infarction, with up to 20% developing Major Depressive Disorder (1). Depression following cardiac artery bypass graft (CABG), and the relationship between depression and post-surgery cardiac outcomes, has been examined in a number of studies (2-4) with rates of depression following major surgery documented at 20 – 30%.

Elevated rates of PTSD have also been reported following surgical procedures (5-8). PTSD symptoms are also common in acute cardiac syndromes (ACS)(9) – a PTSD rate of 12% was reported in a large meta-analysis of ACS (10, 11). Cardiac events represent extreme stressors both psychologically and physiologically, posing sudden grave threats to life and function, but cardiac and vascular surgeries, even when undertaken electively, are also associated with substantial rates of psychiatric morbidity. PTSD rates following bypass surgery or heart transplant can be as high as 20% (12-14), likely because even scheduled surgery of this type carries significant morbidity, threat of mortality, physiological trauma, and exposure to intensive care units (ICU), where fear of dying, helplessness and loss of control are common. We have shown retrospectively that elective abdominal vascular surgery is associated with substantially elevated levels of post-operative depression, anxiety, and PTSD(15). Anxiety disorders such as generalized anxiety disorder (GAD) and panic disorder (PD) also appear to play a role in recovery from surgery. The relationship of pre-operative anxiety as a predictor of post-surgical cardiac outcomes has been examined (4, 16), although less work has specifically demonstrated increased anxiety disorder symptoms following surgery.

Psychiatric symptoms associated with medical illness contribute to medical morbidity (17, 18) and mortality (13), undermining outcomes and adding substantially to costs of care. PTSD symptoms following MI double the risk of death or a second heart attack (10). Even when physical recovery occurs, depression, posttraumatic stress, and anxiety symptoms(5, 9, 13, 15) impair functional outcomes and raise costs(19, 20). Identifying risks and developing preventive interventions could improve overall outcomes and reduce associated cost burdens.

Since stress-related disorders develop in some but not all exposed individuals, vulnerability factors must exist. Identifying biological and psychosocial factors that mark risk and contribute to pathophysiology (21-23) could improve outcomes by identifying those in need

of psychiatric monitoring and facilitating development of early or preventative interventions that specifically target mechanisms of vulnerability. To identify predictors of risk and mechanisms of vulnerability, prospective studies that include both biological and psychosocial factors are needed. Abdominal vascular surgeries provide a useful model since they lead to substantial psychiatric morbidity(15) and their scheduled nature is more amenable to pre-surgical data collection than is possible with acute cardiac events.

A number of psychosocial risk factors for stress-related psychiatric morbidity following surgeries have been identified (15, 24-26). However, they have not been translated into clinical use and are unable to reveal neurobiological mechanisms of vulnerability as potential intervention targets. The hypothalamic-pituitary adrenal (HPA) axis is worth examining since (1) its adult functioning is shaped, in animals and humans, by early life stressors(27-29); (2) these early life stressors also contribute to risk for adult psychopathology (30, 31); (3) HPA axis changes mediate psychopathology relevant behavioral changes in the animal early stress models (32-35); and (4) the HPA axis is dysregulated in patients with depression and PTSD (36-40). Early stress exposure, interacting with genetic factors, creates lasting HPA axis dysregulation in humans that parallel those seen in the animal models, and which is often best seen in adulthood in the context of challenge studies (41, 42). The HPA axis abnormalities seen in psychiatric disorders may thus reflect pre-morbid vulnerability factors – created by early gene-environment interactions, setting the stage for development of psychiatric symptoms in response to subsequent major stressors, such as medical illness and surgery, perhaps most evident as people face the challenge of surgery, and perhaps both predicting risk and mechanistically contributing to vulnerability.

The human work on psychiatric disorders has not yet identified which, if any, of their associated HPA axis abnormalities are pre-existing (and influence vulnerability) and which are the result of recent stress or active illness. Prospective studies of at risk populations, which can be studied both before and after the stressful event, are needed. The potential link to a predictable, precipitating event, like surgery, creates the opportunity for a prospective study to identify risk factors or vulnerability markers that will predict the development of these disorders in patients “at risk”. We have previously demonstrated that open aortic surgeries (AAA repair and aorto-femoral bypass surgeries) are major stressors associated with substantial psychiatric risk, when compared to patients treated nonsurgically (15); but underlying illness severity usually differs between those receiving surgery and those being treated conservatively. Abdominal aortic aneurysms can also be repaired, however, using an endovascular surgical technique (endovascular aneurysm repair, EVAR). EVAR is much less physiologically stressful, because it does not involve full opening of the abdomen, but produces good cardiovascular outcomes in comparably ill patients. EVAR thus creates the opportunity for a comparison group with similar illness severity and exposure to a discrete surgical procedure, but less physical stress and pain. We therefore undertook a prospective follow-up to our retrospective study of *de novo* psychiatric symptom risk in patients undergoing open abdominal aortic surgeries, compared to patients receiving EVAR, and to control patients with smaller AAA treated non-surgically.

METHODS

Participants

All procedures were approved by UM and VA IRBs, and all enrolled participants provided informed consent. Participants were recruited from patients with abdominal aortic aneurysm (AAA) or aortoiliac occlusive disease (AIOD) treated in surgical clinics at the University of Michigan (UM) and the Ann Arbor VA Healthcare Systems. Inclusion criteria were 52 to 81 years old, with AAA or AIOD and residing within a 150 mile radius of the research site. Exclusion criteria included concurrent treatment that interferes with HPA axis or noradrenergic measures (e.g., oral steroid preparations, narcotics, antidepressants, benzodiazepines, neuroleptics, barbiturates or other anti-seizure medications); current alcohol or drug abuse or dependence; clinically significant abnormalities on routine laboratory screening (blood count, glucose, liver and renal function, electrolytes, thyroid functions); and a history of traumatic brain injury or any documented, organic CNS pathology. Medical charts for approximately 2050 patients seen in the vascular surgery service at AAVA (between 2002 – 2006) and at UMMC (2002 – 2009) were reviewed for study eligibility; 303 patients screened met study criteria (see Figure S1, Supplemental Digital Content 1, for details of screening and recruitment), and 239 were enrolled. Reasons for not enrolling included patients declining due to perceived study burden (N=22), physician declined (N=18), or no reason recorded or not approached (N=24). Psychiatric measures and vascular disease severity are not available from patients who did not enroll. Twenty-three patients consented but did not provide pre-surgery data (due to patient death or major medical complication, change in medication, declined due to perceived burden or stress, did not properly collect specimens or lost to follow-up, see Figure S1). The remaining enrolled patients (N=216) received treatment as usual by clinic physicians, which included conservative (non-operative) medication management or one of three surgeries – open aorto-femoral bypass (AFB), open AAA repair, and endovascular AAA repair (EVAR).

Psychosocial Assessment and Measures

At an intake “baseline” session, and at 3 mo and 9 mo follow-ups, patients completed self-report psychosocial measures (Beck depression inventory (BDI), RAND corporation short form 36 (SF-36)) and a structured psychiatric diagnostic interview conducted by a trained social worker, which also assessed changes in medication prescriptions (including adding psychiatric medications) and utilization of psychotherapy services. Psychiatric diagnoses (DSM-IV criteria) were made only from diagnostic interviews by a trained clinical social worker. Major depressive disorder (MDD) was diagnosed using the SCID-IV mood disorders module, which included current and lifetime history of major depressive episodes, depression NOS, dysthymia, and bipolar disorder. Generalized anxiety disorder (GAD), panic disorder (PD), and social anxiety disorder were diagnosed using World Health Organization Composite International Diagnostic Interview (CIDI) modules. PTSD was diagnosed using the Clinician Administered PTSD Scale (CAPS), which also provides a continuous measure of symptom severity. The CAPS was modified, such that at baseline lifetime trauma exposures were assessed as usual, but symptoms in the intrusive, avoidant and hyperarousal scales were assessed whether or not patients endorsed trauma. At follow-up visits, patients were queried for interim traumas, but lifetime traumas were not re-

assessed. For surgical patients who had surgery, the surgery experience was used as index for intrusive symptoms, and symptoms were assessed whether or not trauma was endorsed. Patients were defined as *de novo* psychiatric “cases” if they met DSM-IV diagnostic criteria for any of these disorders at either the 3 mo or 9 mo time points.

Salivary Cortisol and Dexamethasone Suppression Test

Patients collected saliva specimens at home over two days immediately following each assessment interview (at intake / pre-surgery, at 3 mo and at 9 mo follow-ups) for measurement of circadian free cortisol levels and a dexamethasone suppression test (DST). For surgical patients, the saliva collection and DST were always performed two days before surgery. Participants received salivettes and collection instructions from the social worker at interview, collecting three samples (8 am, 4 pm, and 11 pm) on Day 1, taking dexamethasone (DEX, 0.25mg) at 11:05 pm, and collecting three additional samples on Day 2 (same times). Specimens were kept on ice and were retrieved the following day. Cortisol was assayed using Diagnostic Products Corporation Coat-a Count cortisol assay, an [125 I] competition radioimmunoassay assay with intra-assay variability less than 5%.

Statistical analyses

Primary outcome variables included psychiatric diagnoses (DSM-IV criteria for *de novo* mood and/or anxiety disorders), and continuous psychiatric symptom severity measures based on clinician rated (CAPS) and self-report instruments (BDI, SF-36). Initial analyses tested whether open surgery or EVAR was associated with increased rates of psychiatric morbidity by comparing relative risk for *de novo* psychiatric diagnoses (odds ratio) in surgically and conservatively treated patients without psychiatric disorders at intake. Pre-surgical predictors of post-operative psychiatric morbidity were sought using regression analyses of diagnostic outcomes (logistic) and psychiatric symptoms (linear). Potential risk factors were tested separately in logistic regression models. Predictor variables included demographics (age, gender, marital status), history of previous depression, current smoking status, surgery characteristics (duration of surgery, blood loss, post-surgery complications, duration of ICU stay), and pre-surgical HPA measures (baseline cortisol, calculated as area under the curve (AUC) on Day 1, and DEX suppression (DST%), calculated as percent decrease in 8 am cortisol from Day 1 to Day 2). Psychiatric symptoms (CAPS, BDI, SF36) across the follow-up were tested in repeated measures ANCOVA (with history of depression as covariate), and in regression models at 3 and 9 months adjusting for intake symptom levels.

Effects of pre-surgical cortisol AUC on psychological symptoms in the group of patients receiving surgeries was tested in repeated measures mixed models, with time (i.e., intake and 3 and 9 mo follow-ups) as the repeated measure. Pre-surgical cortisol AUC, patient age, history of major depression, and current smoking were modeled as fixed effects in models fit with a compound symmetric variance-covariance structure, using maximum likelihood estimation. Cortisol measures were natural logarithm (ln) transformed and psychiatric symptoms measures (CAPS, BDI) were square-root transformed to reduce positive skew (transformed data showed skew <0.5 or >-0.5). Missing measures in the psychiatric symptom data (e.g. missed follow-ups or self-report measures) were analysed using missing

values patterns analysis, and then filled in using multivariate imputation methods (fully conditional specification, a chained equation Markov Chain Monte Carlo (MCMC) algorithm in IBM SPSS version 22.0 software). We assumed missingness occurred at random, dependent upon observed but not unobserved variables. Patterns of missingness were analyzed in SPSS with expectation-maximization (EM) and Little's test of MCAR, and imputed values were constrained to valid values. Analysis results are reported for original data and for pooled results from 10 imputations.

RESULTS

Surgery and *de novo* psychiatric morbidity

Of the total sample of 216 patients enrolled, 42 patients (19.4%) were lost to follow-up (i.e. an intake assessment was obtained, but no 3 month or 9 month follow-up was obtained). (see Figure 1). The proportions of patients lost to follow-up (16.3% in the open surgery group, 17.2% in the EVAR group, and 23.6% in the non-surgical group) did not differ between groups ($\chi^2 = 1.68$ $p = 0.43$). Reasons for discontinuation included patient death ($N=11$), CVA or other major medical complication ($N=6$), declining due to burden of specimen collection ($N=7$), and lost to follow-up / unknown ($N=18$). Those completing at least one follow-up did not differ from those who did not in age, psychiatric symptoms (CAPS and BDI), somatic and physical health perception (SF36 PH and MH subscales), rates of history of major depression, and current smoking status. Psychiatric disorder rates at intake did not differ among patients receiving open surgeries, EVAR, or conservative treatment ($\chi^2=0.39$, $p=.82$). Patients assessed with psychiatric diagnoses at intake were excluded from further analyses, leaving 152 patients without psychiatric disorder at intake and with 3 month and/or 9 month FU data for predictor analyses. Table 1 shows demographics, current smoking status, and cortisol measures at intake for the 152 followed patients receiving conservative (non-surgical) care ($N=59$), EVAR ($N=22$), and open surgeries (open AAA repair or AFB, $N=71$). Our sample was predominantly male (only 11% female) due to a 5-fold higher rate of AAA in males than females of the same age(43) and recruitment of half of our sample from a VA surgery service in which patients are almost exclusively male. At intake, the open surgery group had a slightly higher score on CAPS avoidance, and the endovascular group had a higher CAPS hyperarousal score and a lower rate of current smoking; there were no other differences at intake in demographics and psychiatric symptoms, and no differences in cortisol measures.

Figure 1 shows patient flow through the study, including patients excluded due to having a psychiatric diagnosis at intake or lost to follow-up, and psychiatric status over the 9 month follow-up period. Open surgeries (AFB and open AAA repair) were followed by *de novo* psychiatric diagnoses within 9 months in 13 of 71 patients (18.3%) (4 major depressive disorder (MDD), 4 depression NOS, 1 posttraumatic stress disorder (PTSD), 2 generalized anxiety disorder (GAD), 2 panic disorder). One of 22 patients (4.5%) receiving EVAR had a new diagnosis (MDD), and 2 of 59 patients (3.3%) treated conservatively did so (1 depression NOS, 1 anxiety NOS). Four patients, all in the open surgery group, received new prescriptions for psychiatric medications (lorazepam, fluoxetine, es-citalopram, and clonazepam); two of these were also diagnosed with *de novo* psychiatric disorder by the

study, but two did not meet diagnostic criteria at the time of the interview. No patients in the study reported utilization of psychotherapy services during the study

Logistic regression analyses were used to examine demographic and surgical factors for risk for development of *de novo* psychiatric disorder over the study follow up period (Table 2). Age, gender, and marital status were not associated with increased risk. Having an open surgery (open AAA repair and AFB), was associated with an increased psychiatric risk compared to non-surgical treatment. In contrast, EVAR was not associated with increased risk compared to non-surgical treatment. Characteristics of surgeries (in surgical patients), including duration of surgery, volume of blood loss, having a complication that required return to OR, or the number of additional days in the surgical intensive care unit, were not associated with increased risk. Lifetime history of major depression was associated with increased risk in the entire cohort and among surgery patients.

Open surgical patients who later developed a mood or anxiety disorder had higher pre-surgical (intake) CAPS and BDI scores than those who did not (CAPS scores $t=2.31$, $p=.031$, BDI scores $t=2.71$, $p=.018$), whereas perceived mental and physical health (SF-36) were lower ($t=2.59$ $p=.023$; $t=3.02$, $p=.004$, respectively). Although perceptions of physical health at intake were lower in patients who developed psychiatric morbidity, objective measures of cardiovascular health did not differ between surgery patients who did and did not develop psychiatric diagnoses (systolic blood pressure (BP), 140 mm vs 128 mm, $t=1.39$ $p=.17$, diastolic BP 73 mm vs 74 mm, $t=0.99$, $p=.92$, AAA diameter (5.54 cm vs. 5.47 cm, $t=0.184$, $p=.85$).

The time-course of changes in CAPS, BDI, and SF36 MH scores across the study is shown in Figure 2 (Table S1, Supplemental Digital Content 1, shows the corresponding means and SD and N of each measure). Symptom levels were generally fairly stable across time, with relatively little differences between groups, except for CAPS scores, which rose and then fell in the group with open procedures. Initial models excluded patients with any missing data points; multivariate imputation was then used to fill in missing data to allow testing of models including all patients ($N=152$). Analyses of missing data with Little's MCAR test found $X^2(119)=130.2$, $p=.228$.

To test effects of having open surgery on psychiatric symptoms at 3 month and 9 month follow-ups, regression models were run with surgical group represented by dummy coding and controlling for initial values of CAPS, history of MDE, age, and smoking status (see results in Table 3). As expected, intake CAPS levels predicted CAPS at 3 month and 9 month follow-ups using the original data and with multivariate imputation. Having an open surgery and having history of MDE predicted were both associated with significantly increased CAPS at 3 months but not at 9 months. Similar analyses of BDI and SF-36 mental health scale scores (time courses in Figure 2B and 2C), with and without multivariate imputation, found no significant effect of surgery group or any variable at 3 or 9 months other than intake levels (data not shown).

HPA axis activity, psychiatric diagnoses, and psychiatric symptom levels

There were no significant changes in any HPA measure from intake to follow-up and no differences between surgical and non-surgical patients (RM-ANOVA for morning cortisol, main effect of time $F[2,220]=0.70$, $p=.49$; time-by-treatment interaction $F[2,220]=.01$, $p=.98$; similar results seen for cortisol circadian AUC, DST and diurnal decline; see Supplemental Figure S2, Supplemental Digital Content 1, for circadian cortisol over two days in patients who received conservative treatment, EVAR, or open surgery). Cortisol AUC at intake was correlated with cortisol AUC at 3 month followup, and evening and post-dexamethasone morning cortisol at 9 month followup (Supplemental Table S2, Supplemental Digital Content 1). HPA indices did not differ in patients who did or did not develop *de novo* psychiatric diagnoses at follow-up. Intake indices of HPA axis function (Day 1 AUC, Day 1 morning cortisol, post-DEX morning cortisol, DST %) did not significantly predict categorical development of a *de novo* psychiatric diagnosis in logistical regression models.

Although HPA intake indices did not predict categorical psychiatric diagnoses, there were significant relationships between HPA axis function and continuous measures of mental health symptoms and functioning. Given the small number of patients receiving EVAR, all surgical patients (open and EVAR) were combined in the cortisol analyses. HPA axis measures were significantly correlated with CAPS scores at intake and 9 month follow-up, (Table 4). Intake Day 1 AUC and 8 am cortisol were significantly correlated with total CAPS score also measured at intake and they both predicted CAPS score at 9 month follow-up. These relationships were entirely due to surgical patients, i.e. higher cortisol predicted higher CAPS in surgical patients but not in the non-surgical group. Among the combined group of surgical patients, Day 1 cortisol AUC also correlated with BDI at intake and 9 month FU, and DEX suppression was associated with SF-36 mental health (MH) and physical health (PH) subscales at intake and 9 month FU (Table S3, Supplemental Digital Content 1).

Table 5 shows Type III tests of fixed effects and parameter estimate of separate repeated measures mixed model analyses using available data from patients experiencing a surgical procedure, with CAPS, BDI, and SF-36 MH scores over the three time points as dependent variables. The 9 month outcome was used as the reference while modeling cortisol AUC at intake, age, history of depression, and current smoking as predictors. Cortisol AUC at intake was a significant predictor of CAPS, BDI, and SF-36 MH scores, with higher cortisol levels at intake associated with significantly higher levels of psychiatric symptoms at 9 months. There were no significant differences in the association of cortisol with symptoms across time points, cortisol AUC $\times$ time interaction was not significant (non-significant parameter estimates for each time point not shown). Current smoking (at the time of the surgery) was also associated with higher levels of CAPS scores. Results of the same mixed models using imputed data are shown in Supplemental Table S4, Supplemental Digital Content 1; imputed data produced similar results.

DISCUSSION

Exposure to open AAA or AFB surgical procedures was associated with increased risk for developing a new psychiatric (mood or anxiety) disorder, relative to the risk incurred after non-surgical AAA treatment. This elevation in risk following open surgeries is comparable to that seen in our previous, retrospective study(15), substantiating those results in a prospective design that objectively assessed psychiatric symptoms pre-operatively, avoiding the confound of retrospective bias. Elevated risk for open procedures relative to endovascular repair suggests that the greater physiological stress, pain, and healing time associated with open surgeries may contribute to psychiatric risk. However, there may still be contributions from illness or patient differences that shape intervention choice, since random assignment to treatment type was not possible. Though precise causation cannot be determined, it does appear, prospectively as well as retrospectively, that a substantial minority of vascular surgery patients (~20%) may develop post-surgical psychiatric morbidity, despite the fact that these operations have good medical outcomes (<5% 30 day and ~15% 2 year mortality rates(44)). Data from other sources suggest that this incidence of psychiatric morbidity adds substantially to the costs of the procedures, not only financially, but also in medical morbidity and mortality(12-15)

Identifying predictors of psychiatric risk can help to identify vulnerable patients and perhaps reduce costs by facilitating selectively increased monitoring and application of preventive interventions. In absence of overt psychopathology, the immediate level of mood and anxiety symptoms (e.g. scores on CAPS, BDI, and SF-36 mental health scales) predicted developing *de novo* psychiatric morbidity. Lifetime history of major depressive episode (MDE), even in the absence of current depressive symptoms, also predicted post-surgical psychiatric morbidity, consistent with a diathesis / stress model of psychopathology. This suggests that in addition to screens of current psychiatric symptom levels using standard hospital instruments (e.g. BDI or PHQ9), assessing lifetime depression history may be a relatively easy to obtain and valuable indicator of post-surgical psychiatric risk, though confirmation in larger-scale, epidemiological studies is needed.

HPA axis measures were associated with baseline psychiatric symptoms and predicted symptom levels at 9 month follow-up in patients receiving surgeries, suggesting that HPA activity in the days before a major life stressor is associated with risk for development of stress-related psychopathology over the following months. Pre-surgical cortisol levels did not predict development of specific *de novo* categorical psychiatric diagnoses during the post-operative follow-up period, but they were associated with symptom levels 9 months later (CAPS, BDI, SF36 scores). The small number of DSM diagnoses, including low rates of full-criteria PTSD, makes conclusions about disorder predictors tentative, but the data suggest that “baseline” HPA axis function can predict risk for development of anxiety and depression symptoms even in the absence of diagnosable disorders. This result is consistent with accumulating evidence that HPA axis dysregulation that has long been thought to reflect disorder-based abnormalities may not in fact be disorder specific or be primarily linked to presence of psychiatric disorders themselves. For example, elevated morning salivary cortisol levels have been found in multiple classes of current psychopathology (major depression, GAD, panic disorder), as well as remitted depression(45, 46). Studies of

acute HPA axis reactivity have suggested that a history of early life stress, but not current depression or PTSD, accounted for elevated responses in both women and men(41, 42, 47). A study of female Vietnam veteran nurses suggested that the low basal cortisol levels and DST hyper-suppression seen in other PTSD studies may actually reflect factors other than simply having PTSD(48). Alterations in the HPA axis may reflect previous environmental exposures, genetic factors, and general psychiatric vulnerability rather than being a “biomarker” of a specific psychiatric syndrome. Our data are consistent with this interpretation in that HPA axis activity measured in anticipation of a major life challenge predicted psychiatric symptom levels 9 months later.

The links that we found between HPA axis activity and psychiatric symptoms were all positive (higher cortisol levels linked to higher symptoms), were seen only in surgical patients, and were consistent longitudinally (baseline cortisol predicting baseline and 9 month symptoms, but less so cross-sectionally (cortisol measured at 3 or 9 months were not linked to concurrent symptoms). The positive associations may be in some contradiction to reports that low levels of cortisol at time of surgery (cortisol stress responses to the surgery) may be associated with greater PTSD risk and that hydrocortisone administered during surgery could be a preventive intervention(6). Our methodology, however, differs in critical ways. We report cortisol levels measured in anticipation of surgery and not during it, and these are linked to development of symptoms, not full criteria diagnoses. Anticipatory reactivity of the system may well be under different regulatory control than its reactivity to the physical stress of surgery itself. In the context of the moderate psychological challenge posed by impending surgery, higher levels of cortisol reactivity might reflect greater psychological vulnerability and contribute to symptom development.

It is intriguing that multiple cortisol measures taken at intake, in those anticipating surgery, were linked to psychological symptoms measured at the same time and 9 months later, but not with symptoms at 3 months (Table 3), and that symptoms at 3 and 9 months were not linked to cortisol measures taken at the same time. Furthermore, pre-surgical cortisol remained a significant predictor of future symptoms when controlling for history of MDE and smoking status. That these relationships were only seen for those who were anticipating surgery within a few days of the intake measurements suggests that “intake” measures perhaps captured some aspect of HPA reactivity to anticipated threat, and this carries information with longitudinal predictive power. This is reminiscent of earlier data from our laboratory, in which cortisol secretion during a 24 hour hospital stay predicted functioning 18 months later in patients with panic disorder(49). It suggests that HPA reactivity to moderate challenge may reflect a trait vulnerability that predicts future functioning or symptom expression. Such trait vulnerability could be created by genetic or gene-by-environment interaction factors (34, 41) that are expressed in HPA axis reactivity to challenge and symptom development in the context of prolonged stress.

While multiple pre-surgical cortisol measures were associated with both pre-surgical and 9 month symptoms, none correlated with symptoms at 3 months post-surgery, which was also the time point with the greatest level of symptoms overall. Additionally, 3 month symptoms were not associated with 3 month cortisol levels. At 3 month follow-up, variance in post-operative physical recovery rates (e.g., wound healing, pain, physical capabilities) was likely

quite high and was perhaps the predominant shaper of psychological symptoms at this time point, but with more complete physical recovery at 9 months, HPA-related traits were again apparent. Post-surgical cortisol levels were not different among patients who developed *de novo* diagnoses, nor where they correlated with post-surgical symptoms, so the evidence does not suggest that HPA activity is being shaped by diagnoses or symptoms.

Our study has a number of limitations. It was a naturalistic, longitudinal study that followed consecutive vascular surgery patients who had come for surgeries from a 150 mile radius. It was not possible to utilize random assignment, as the decision to perform surgery was based upon medical need (e.g. aortic diameter or aorto-iliac blockage), so patients who received surgeries were likely seen as more “at risk.” On the other hand, the study design excluded patients with co-morbid psychiatric, neurological, substance use, and some metabolic disorders, and thus our sample is expected to have relatively higher levels of mental and physical health at intake than the general population of patients with advanced vascular disease. While efforts were made to approach every eligible patient being scheduled for aortic surgeries by the participating services, there was an approximately 20% refusal rate for the study among eligible patients. Potentially unmeasured characteristics of patients declining participation could introduce some selection bias that could limit generalizability. Selective attrition could also introduce potential biases. A substantial portion of loss was due to medical complication or death (5% of enrolled patients, 11 of 216) and study burden (3%, 7 of 216). However, a substantial portion was also due to patients moving or unexplained reasons (another 8%, 18 out of 216). Psychiatric morbidity could have played a role in those dropping out due to “unexplained reasons”, and could perhaps have even contributed to complications and death(3, 4). If so, this would mean that rates of psychiatric morbidity may be even higher than those reported, but this could also have distorted our predictor results. Similar consequences could have been produced by patients who received new prescription of psychiatric medications during the study, ameliorating symptoms and disorders that might have otherwise been seen, but the number of such subjects was quite low. Generalizability may also be limited in some analyses that were complicated by higher rates of missing data (e.g. self-report measures like the BDI and SF-36 were returned by mail and have missing data points in ~10% of subjects). Also, as reported in other studies of elderly persons(50), our patients appeared to minimize psychological symptoms, especially in self-report, and some analyses may be vulnerable to a floor effect. Given this, we focused analyses primarily on CAPS, which is a clinical interview and which provided more range than the self-report measures. We also did not control for multiple testing (i.e. of CAPS, BDI, and SF-36), which increased the potential for statistical type I error. However, after a Bonferoni adjustment for 3 tests, the effect of open surgery on CAPS at 3 months follow-up would remain significant (adjusted $p < .05$) in the linear regression model (Table 3), and the effects of intake cortisol AUC on CAPS and BDI scores in patients receiving open surgeries would also remain significant (adjusted $p < .05$) in the mixed model analyses (Table 5). In addition, our longitudinal dataset overall had relatively small numbers of *de novo* categorical diagnoses, and the number of patients in the EVAR group in particular was small, limiting power for logistic regression and between-group analyses. It is also possible that additional factors which we did not measure directly, including diet and sleep patterns, could have

influenced pre-surgical cortisol levels and contributed to the predictor effects seen for cortisol measures.

Despite these caveats, the data suggest that in addition to current levels of symptoms, prior history of depression may be an important predictor of risk for development of psychiatric symptoms following vascular surgery, perhaps indicating a need for enhanced psychiatric monitoring in patients with these risk factors, and a search for preventive psychosocial and/or psychopharmacological interventions. The data also provide further evidence that HPA axis function prior to a major stressful life event may predict long-term psychological outcomes. Higher cortisol levels across the circadian curve, and relatively lower negative feedback inhibition (higher post-DEX morning cortisol levels) immediately before a major surgery appear to predict poorer psychological recovery (greater psychological symptoms) at 9 month follow-up. Further study of the pathways that link HPA axis activity to psychological and functional outcomes may reveal additional targets for preventive intervention. Such work could enhance outcomes and reduce costs, in so far as poor psychological recovery may be linked to greater cost and overall worse mental and somatic health outcomes (51).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAA	abdominal aortic aneurysm
AFB	aortofemoral bypass
AIOD	aorta-iliac obstructive disorder
AUC	area under the curve
BDI	Beck Depression Inventory
CAPS	clinician administered PTSD scale
DEX	dexamethasone
DST	dexamethasone suppression test
EVAR	endovascular aortic repair
GAD	generalized anxiety disorder
HPA axis	hypothalamic pituitary adrenal axis
MDD	major depressive disorder
OR	odds ratio

PTSD	posttraumatic stress disorder
RM-ANOVA	repeated-measures ANOVA

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Figure 1. Recruitment and flow of patients through the study

Consecutive patients with peripheral vascular disease (AAA and AOID) were recruited in vascular surgery services at VA and UM hospitals. Those who met criteria for current psychiatric diagnosis were excluded from further analyses. Patients were administered repeat psychiatric diagnostic assessments at 3 months and 9 months follow-ups.

Figure 2. Time course of psychiatric symptoms among vascular surgery patients who received open surgery (AFB or open AAA repair), EVAR, or non-surgical treatment

Panel A. shows means of CAPS scores (PTSD symptoms) across the 3 time points in the 9 month follow-up period, Panel B. shows means of BDI scores (depression symptoms), and panel C. shows SF-36 Mental Health subscale.

Table 1

Demographics and Intake cortisol measures

	No surgery N=59		EVAR N=22		Open Surgery N=71		X2	p
	N	%	N	%	N	%		
gender (female)	9	15%	3	13%	5	7%		.31
marital status (married)	51	85%	17	77%	56	79%		.46
Previous MDE history	9	15%	4	18%	7	7%		.16
smoker current	21	35%	1	5%	16	23%		.015

	Mean	Std. Dev	Mean	Std. Dev	Mean	Std. Dev	P
Age	69.8	6.2	70.9	5.3	69.5	7.2	.34
Saliva cortisol 8 am - Day 1 (pre-DEX)	0.54	0.43	0.59	0.62	0.48	0.33	.51
Saliva cortisol 8 am - Day 2 (post-DEX)	0.26	0.42	0.19	0.09	0.24	0.25	.50
DEX suppression (% DST)	58.8%	33.8	60.3%	30.1	55.5%	32.3	.79

Between group differences in categorical measures were tested using chi-squared test, those in continuous variables using ANOVA. Age is in years, cortisol measures are ug/ml.

Table 2
Risk factors associated with development of *de novo* psychiatric diagnoses within the 9 month follow-up period

Risk Factors among all patients (N=152)									
	B	S.E.	Wald	df	Odds Ratio	Lower	Upper	Sig.	95% C.I.
Age	-0.01	0.04	0.09	1	0.99	0.91	1.07	0.76	
Gender (reference - male)	0.17	0.80	0.04	1	1.18	0.24	5.71	0.84	
Marital status (reference - married)	0.80			2				0.67	
Divorced	-0.63	1.08	0.34	1	0.53	0.06	4.41	0.56	
Widowed	0.42	0.70	0.35	1	1.52	0.38	5.97	0.55	
Treatment (reference - nonsurgical)	7.01			2				0.032	
EVAR	0.32	1.25	0.07	1	1.38	0.12	16.03	0.80	
Open Surgery (AAA or AFB)	1.85	0.78	5.63	1	6.39	1.38	29.57	0.026	
History of major depression	1.39	0.61	5.24	1	4.03	1.22	13.27	0.024	
Current smoking status	0.68	0.55	1.49	1	1.97	0.66	5.84	0.22	
CAPS score at intake	0.13	.05	8.88	1	1.15	1.05	1.26	0.003	
BDI score at intake	0.17	.07	5.27	1	1.18	1.03	1.37	0.23	
AUC Cortisol (Day 1) at intake	0.63	.39	2.58	1	1.88	0.87	4.02	0.11	
DEX suppression (DST%)	-0.21	0.92	0.05	1	0.81	0.13	4.99	0.82	

Risk Factors among Patients undergoing surgeries only (AAA, AFB, EVAR, N=93)									
	B	S.E.	Wald	df	Odds Ratio	Lower	Upper	Sig.	95% C.I.
Duration of surgery (minutes)	0.001	0.001	0.487	1	1.00	0.99	1.00	0.49	
Duration of cross clamp (minutes)	0.007	0.009	0.514	1	1.01	0.99	1.03	0.47	
Blood loss during surgery (ml)	<.001	<.001	0.429	1	1.00	1.00	1.00	0.51	
Complication requiring return to OR	-0.080	1.121	0.005	1	0.92	0.10	8.31	0.94	
Additional days in SICU (days)	0.155	0.111	1.931	1	1.17	0.94	1.45	0.164	
CAPS score at intake	0.222	0.087	6.532	1	1.25	1.05	1.48	0.011	
History of major depression	1.792	0.751	5.699	1	6.00	1.38	26.12	0.022	

Risk Factors among Patients undergoing surgeries only (AAA, AFB, EVAR, N=93)									
95% C.I.									
	B	S.E.	Wald	df	Odds Ratio	Lower	Upper	Sig.	
Current smoking status	1.132	0.640	3.130	1	3.10	0.88	10.87	0.081	
AUC Cortisol (Day 1) at intake	0.44	0.46	0.82	1	1.55	0.60	3.99	0.36	
DEX suppression (DST%)	−0.81	1.07	0.68	1	0.44	0.05	3.61	0.45	

Effects of having open surgery on psychiatric symptoms (CAPS level) at 3 months and 9 months (linear regression model)

Table 3

A. CAPS score at 3 month follow-up as dependent variable									
	Original data (N=135)				Imputed data (N=152)				p
	B	SE	Beta	T	p	B	SE	T	
Open surgery	.741	.286	.222	2.591	.011	.752	.298	2.523	.012
EVAR	.502	.447	.098	1.124	.263	.548	.425	1.288	.198
Age	.036	.022	.138	1.671	.097	.022	.022	.995	.320
History of MDE	.958	.394	.196	2.429	.017	.891	.411	2.167	.031
Current Smoking	.421	.314	.112	1.338	.183	.472	.329	1.433	.152
CAPS at intake	.404	.100	.325	4.056	<.001	.416	.102	4.083	<.001

B. CAPS score at 9 month follow-up as dependent variable									
	Original data (N=122)				Imputed data (N=152)				p
	B	SE	Beta	T	p	B	SE	T	
Open surgery	-.400	.289	-.128	-1.383	.169	-.394	.277	-1.419	.156
EVAR	-.112	.452	-.023	-.247	.805	-.072	.418	-.173	.863
Age	.035	.022	.144	1.583	.116	.025	.022	1.142	.255
History of MDE	.504	.371	.120	1.358	.177	.493	.384	1.285	.200
Current Smoking	.051	.334	.014	.153	.878	.112	.306	.365	.715
CAPS at intake	.390	.098	.341	3.962	<.001	.378	.095	3.972	<.001

Model F[6, 129] = 5.61, $p < .001$, adjusted $R^2 = .172$.

Model F[6, 116] = 4.16, $p = .001$, adjusted $R^2 = .136$.

Table 4
Association of intake salivary cortisol with psychiatric symptoms (CAPS score) at intake and 3 and 9 month follow-ups

	CAPS at Intake				CAPS at 3 mo FU				CAPS at 9 mo FU			
	All N=137	Surgery N=80	Non- surgical N=57		All N=104	Surgery N=58	Non- surgical N=45		All N=103	Surgery N=57	Non- surgical N=46	
AUC day 1	0.163 [*]	0.227 [*]	0.069		0.081	0.120	0.108		0.266 [*]	0.320 ^{**}	0.210	
8 am	0.156 [*]	0.249 [*]	-0.034		0.145	0.160	0.144		0.220 [*]	0.267 [*]	0.153	
4 pm	0.167 [*]	0.255 [*]	-0.008		-0.051	0.091	-0.191		0.230 [*]	0.256 [*]	0.105	
11 .pm	0.012	0.046	-0.030		-0.053	0.051	-0.120		0.165 ^a	0.183 [*]	0.136	
AUC day 2 (post DEX)	0.021	0.185	-0.154		-0.159 ^a	-0.104	-0.261 ^a		0.158 ^a	0.235 ^a	-0.002	
8 am	0.134 ^a	0.304 ^{**}	-0.164		-0.084	-0.030	-0.153		0.197 [*]	0.245 ^a	-0.027	
4 pm	-0.114	0.093	-0.179		-0.174 ^a	-0.118	-0.240		0.106	0.112	-0.021	
11 .pm	-0.054	.111	-0.106		-0.183 ^a	-0.185	-0.239		0.037	-0.059	0.093	
DST %	-0.134	-0.215 [*]	0.013		0.142	0.109	0.227 ^a		-0.145	-0.205	-0.105	

Shown are parameter estimates from unadjusted linear regression analyses.

* p < .05,

** p < .01,

^a p < .10.

Table 5
Repeated Measures Mixed Models analyses in patients receiving surgeries – with CAPS, BDI, and SF-36 MH as dependent variables (original data)

Type III Tests of Fixed Effects.													
CAPS scores					BDI scores				SF36 mental Health				
Num.	Denom	df	F	p	Num.	df	F	p	Num.	Denom	df	p	
Intercept		1	75.24	0.94	0.335	1	71.38	0.41	0.524	1	72.24	10.96	0.001
Time (Followup)		2	129.78	2.32	0.102	2	116.88	0.20	0.822	2	113.42	1.00	0.372
Age		1	75.45	2.77	0.1	1	71.81	0.03	0.872	1	72.34	0.14	0.712
Cortisol AUC at intake		1	71.20	8.46	0.005	1	72.12	6.08	0.016	1	77.05	4.14	0.045
History of MDE		1	81.53	3.09	0.082	1	72.47	0.92	0.34	1	74.09	0.62	0.433
Current smoking		1	71.68	5.43	0.023	1	71.04	3.50	0.066	1	70.95	1.72	0.193
Time * Cortisol AUC Intake		2	128.32	0.01	0.991	2	116.86	1.29	0.279	2	117.11	1.25	0.29

Parameter Estimates of Fixed Effects.															
CAPS scores					BDI Scores				SF36 Mental Health						
B	SE	df	t	p	B	SE	df	t	p	B	SE	p			
Intercept (9 mo FU)	-1.86	1.50	76.32	-1.24	0.217	0.77	1.16	72.2	0.66	0.509	77.12	22.36	73.6	3.45	0.001
[Time=1] (intake)	0.59	0.32	129.2	1.84	0.069	-0.09	0.18	116.9	-0.53	0.595	-4.16	4.51	113.6	-0.92	0.358
[Time=2] (3 mo FU)	0.66	0.34	132.7	1.95	0.054	0.00	0.18	116.3	0.02	0.981	-6.22	4.50	110.5	-1.38	0.17
Age	0.03	0.02	75.4	1.66	0.1	0.00	0.02	71.81	0.16	0.872	-0.11	0.31	72.3	-0.37	0.712
Cortisol AUC intake	1.04	0.48	168.9	2.17	0.032	0.84	0.32	121.6	2.59	0.011	-14.94	6.68	140.2	-2.24	0.027
History of MDE	1.05	0.60	81.5	1.76	0.082	0.43	0.45	72.5	0.96	0.34	-6.92	8.78	74.1	-0.79	0.433
Current smoking	0.85	0.36	71.6	2.33	0.023	0.53	0.29	71.04	1.87	0.066	-7.18	5.47	70.9	-1.31	0.193