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## Stressing Out About the Heart: A Narrative Review of the Role of Psychological Stress in Acute Cardiovascular Events

Paul Musey Jr, MD<sup>1</sup>, Katharina Schultebrucks, PhD<sup>2</sup>, Bernard P. Chang, MD PhD<sup>2</sup>

<sup>1</sup>Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN

<sup>2</sup>Department of Emergency Medicine, Columbia University Medical Center, New York, NY

### Abstract

**Objectives:** Survivors of acute cardiovascular disease events, such as acute coronary syndrome and stroke may experience significant psychological distress during and following the acute event. Long term adverse effects may follow, including the development of posttraumatic stress disorder (PTSD) and increased overall all-cause mortality and recurrent cardiac events. The goal of this concepts paper is to describe and summarize the rates of adverse psychological outcomes, such as PTSD, following cardiovascular emergencies, to review how these psychological factors are associated with increased risk of future events and long-term health, and to provide a theoretical framework for future work.

**Methods:** A panel of 2 board certified emergency physicians, 1 with a doctorate in experimental psychology, along with 1 PhD clinical psychologist with expertise in psychoneuroendrinology were co-authors involved in the paper. Each author used various search strategies (e.g. PubMed, Psycinfo, Cochrane, and Google Scholar) for primary research, and review articles related to their section. The references were reviewed and evaluated for relevancy and included based on review by the lead authors

**Results:** A meta-analysis of 24 studies (N >2300) found the prevalence of ACS-induced posttraumatic stress disorder (PTSD) at nearly 12%, while a meta-analysis of 9 studies (N=1138) found 25% of survivors of transient ischemic attack (TIA) and stroke report PTSD symptoms. Presences of PTSD doubles 3-year risk of CVD/mortality risk in ACS survivors. Cardiac patients treated during periods of ED overcrowding, hallways care, and perceived poor clinician-patient communication appear at greater risk for subsequent PTSD.

**Conclusion:** Psychological stress is often present in patients undergoing evaluation for acute CVD events. Understanding such associations provides a foundation to appreciate potential contribution of psychological variables on near and long-term cardiovascular recovery, while also stimulating future areas of research and discovery.

### Introduction:

Cardiovascular diseases (CVD) including coronary heart disease, heart failure and stroke remain the leading cause for morbidity and mortality worldwide, leading to millions of hospitalizations and accounting for approximately one third of deaths in the US.<sup>1,2</sup> Emergency clinicians serve on the frontline of acute CVD management and care, evaluating more than 7.5 million patients with chest pain in 2016 alone.<sup>3</sup> While most acute care

resources and efforts appropriately focus on the detection and stabilization of acute CVD events, like acute coronary syndrome (ACS), the psychological experience of patients during medical events may also play an important role in the assessment and recovery of these patients. An emerging body of literature has found that for some patients, the psychological stress experience during CVD events may be durable and may even be associated with the development of adverse long-term anxiety symptoms, such as posttraumatic stress disorder (PTSD).<sup>4</sup> While these psychological outcomes are important in and of themselves, they have also been associated with cardiovascular recovery and increased risk for the development of new and recurrent CVD events.<sup>4-6</sup> The interplay of psychological stress with personality and emotion is multidimensional and complex.<sup>7</sup> Further, the psychological experience of acute illness may impact CVD patients on multiple levels, from autonomic stress to secondary cardiovascular behavior (e.g. medication adherence, ED recidivism and rehospitalization).<sup>7-10</sup> The goal of this concepts paper is to describe and summarize, for emergency clinicians, the rates of adverse psychological outcomes, such as PTSD, following cardiovascular emergencies, and to review how these psychological factors are associated with increased risk of future events and long-term health. In doing so, we seek to introduce a theoretical framework for understanding the relationship between psychological variables and acute cardiovascular disease, while also establishing future areas of research.

## Methods

A panel of 2 board certified emergency physicians, 1 with a doctorate in experimental psychology, along with 1 PhD clinical psychologist with expertise in psychoneuroendocrinology, were co-authors involved in the paper. Each author used various search strategies (e.g PubMed, Psycinfo, Cochrane, and Google Scholar) for primary research, and review articles related to their section. The references were reviewed and evaluated for relevancy and included based on review by the lead authors. This was a non-systematic research synthesis and narrative review to evaluate the evidence regarding the contribution of psychological variables to acute CVD events and sequelae.

## Results

### 1. The psychological stress experienced by some patients undergoing a CVD event may lead to the development of sustained adverse psychological outcomes

Past work has found that psychological contributors, such as anxiety and depression, may be associated with acute presentations of non-psychiatric somatic complaints such as chest pain.<sup>11,12</sup> However, distinct from this psychosomatic literature, the anxiety and stress experienced by individuals undergoing an acute evaluation of a CVD event may lead to the development of longer term psychological morbidity, including posttraumatic stress disorder (PTSD).<sup>13-15</sup> According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), PTSD is psychiatric condition which can develop after an individual experiences or witnesses a traumatic event. Triggers may include physical or sexual assault, natural disaster, combat and other forms of threatened death. The resulting symptoms cause a significant amount of distress and impair the individual's ability to function. In addition to symptoms lasting more than 1 month, there are four criteria that are required: 1) Intrusive

thoughts of the traumatic event through flashbacks or dreams; 2) Avoidance – individuals will avoid situations, people and places that bring on reminders of the traumatic event; 3) Negative cognitions and mood – distorted beliefs regarding blame or shame around the event; and 4) Arousal – sleep disturbance, hypervigilance and aggressive or self-destructive behavior.<sup>16</sup> In a meta-analysis of 24 studies (N >2300) the prevalence of ACS-induced PTSD worldwide was nearly 12%.<sup>4</sup> Additionally, evidence suggests that the subjective psychological experience of having a “perceived” life threatening event may play an important role, regardless of whether there was an actual CVD diagnosis. In a cohort of 1000 ED patients, there was essentially no difference in the rate of 1-month positive PTSD screens in the two-thirds of patients who ruled out for acute ACS (19%) versus those who ruled in (17%).<sup>17</sup> Interestingly, in a study of 143 patients with either non-ST elevation myocardial infarction or unstable angina, patients who were managed medically had higher rates of ACS-induced PTSD than those who underwent catheterization regardless of whether they were revascularized.<sup>6</sup> The presence of sustained psychological outcomes exists along the spectrum of CVD, including transient ischemic attack (TIA) and stroke survivors, where approximately 25% are found to have developed significant PTSD symptoms within one year of the event according to a meta-analysis of more than 1100 patients.<sup>18</sup> Unfortunately these PTSD symptoms are long-lasting and not only associated with worse overall health status including poor quality of life but also adverse effects on overall cardiovascular well-being.<sup>19,20</sup> Along with PTSD, anxiety and depression post-CVD event are also prevalent at a rate of approximately 15%<sup>21,22</sup> and associated with a high risk for poor outcomes “at 1 year on all dimensions of the 36-item short form quality-of-life measure and on specific measures of everyday activity and reports of chest pain, use of primary care resources, and secondary prevention lifestyle changes”.<sup>23</sup> One meta-analysis of approximately 25,000 patients placed the pooled proportion of depression at 25% (CI 16–33%) in the one to five year period after stroke.<sup>24</sup>

This development of PTSD and other psychological sequelae after CVD evaluation or events may be due to a number of a diverse range of pre-existing trait, state, neurophysiological and environmental factors. Given the subjective experience of fear, cognitive factors, including a sense of loss of control may help drive the development of PTSD.<sup>25</sup> Unsurprisingly, patients who perceived more threat (e.g. a sense of danger, risk of serious medical harm due to their symptoms) during their ED evaluation, had higher threat recall and were more vulnerable to developing posttraumatic psychological problems.<sup>26</sup> Additionally, factors of the ED environment itself may also contribute to the development of adverse psychological outcomes during acute medical events. ED crowding has been associated with multiple adverse patient outcomes, ranging from delays in antibiotic administration to decreased patient satisfaction.<sup>27,28</sup> ED crowding has been shown to affect the development of psychological distress medically ill patients. In a study of 912 patients undergoing ACS evaluation, as objective measures of ED crowding increased, patients with prior depression reported the perceptions of the ED being more stressful and of receiving poorer care.<sup>29</sup> Other work by Edmondson et al. found that increased tertiles of ED crowding (as operationalized by EDWIN scores)<sup>30</sup>, were associated with increased 1 month PTSD symptoms at followup.<sup>31</sup>

Adding to the complexity of these environmental factors is the element of social interactions in the ED. In 763 ED patients evaluated for ACS, significantly higher 1-month PTSD symptoms were found in the 12% of patients who perceived a high likelihood that a “nearby” patient would die.<sup>32</sup> Additionally, in a cohort of 484 ED patients, negative social support in the ED (needing to comfort their social support person and/or their social support person making them anxious) was associated with developing posttraumatic stress symptoms after evaluation in the ED.<sup>33</sup> Moreover, simply bringing close others (spouse/partner or child) to the ED during these evaluations is associated with increase recall of threat during the ED evaluation and ultimately correlated with subsequent PTSD symptoms.<sup>34</sup>

Whatever the ultimate mechanism may be, the fact that PTSD and these other psychological comorbidities are so prominent after CVD evaluation or event is notable because PTSD is often associated with an external traumatic stimulus (motor vehicle accident, combat, assault etc.). The enduring somatic threat model (EST) proposed by Edmonson suggests that the evaluation and experience of life-threatening medical events i.e. myocardial infarction or stroke leads to the development of PTSD-like symptoms which is unique and goes beyond what is traditionally accepted as an adjustment disorder.<sup>6,35</sup> In the appraisal of this EST model, interestingly, for patients undergoing ACS evaluation, threat perception levels were not significantly different between patients who were ultimately diagnosed with ACS versus those without ACS.<sup>36</sup> Additionally those with higher peritraumatic ED cardiac threat had higher ongoing cardiac threat levels at 1 month follow-up evaluations which were associated with ACS-induced PTSD.<sup>37</sup> In this model, younger patients appear to be more vulnerable to the effects of threat perception and developing posttraumatic stress symptoms after ACS evaluation.<sup>38</sup> These findings are especially important as they suggest that the adverse psychological outcomes associated with ACS induced PTSD may be associated with not only psychological, but also cardiovascular outcomes, such as major adverse cardiovascular events (MACE).

## **2. Psychological outcomes such as PTSD following acute CVD are associated with adverse CVD outcomes in survivors.**

The negative effects of psychological stress such as PTSD experienced by some CVD survivors may not be limited to behavioral outcomes, but may also have adverse effects on broader health outcomes such as recurrent CVD risk and mortality.<sup>4,7,22,39</sup> Past work has found that pre-existing psychiatric disease is associated with increased odds of death post-ED discharge compared with those who do not have any known psychiatric comorbidity; notably, these deaths were largely medical in nature, with ACS being the most common cause.<sup>5</sup> In a prospective cohort study (N >220,000), psychological distress displayed a dose-response association with increased risk of ACS (30% and 18% in men and women respectively) as well as stroke (24% and 44% respectively in men and women) even when controlling for traditional sociodemographic covariates.<sup>40</sup> In the case of patients developing PTSD symptoms following CVD evaluation, recent evidence has found a significant increase in cardiovascular mortality and recurrent events, even after adjusting for depression and other covariates.<sup>41</sup> In a meta-analysis of 3 studies and n=609 patients found that ACS survivors who developed PTSD following ACS had a doubling of ACS recurrence or

mortality in the subsequent 1 to 3 years (risk ratio: 2.20; 95% CI 1.69, 2.37) relative to patients with no PTSD symptoms”.<sup>4</sup> Intrusive symptoms (nightmares, flashbacks and intrusive thoughts or images) have been associated with an adjusted hazard ratio of greater than 3 for the combined outcome of MACE and all-cause mortality even when controlling for clinical characteristics in addition to age, gender, and depression.<sup>42</sup> Similarly, among a cohort of more than 800 patients followed after their ACS presentation, patients who screened positive for major depressive disorder or generalized anxiety disorder were at greater risk for MACE in the 2 years following their event compared to those who did not screen positive.<sup>43</sup> This is consistent with Shibeshi et al., who also showed that the hazard ratio of high anxiety with relation to MACE was 1.97.<sup>44</sup> Likewise, PTSD is associated with increased stroke risk with a hazard ratio of 3.47 for ischemic stroke.<sup>45</sup>

Comparable to PTSD, anxiety has been associated with a 71% higher risk for stroke and a 41% increased risk of cardiovascular mortality in a meta-analysis of 28 studies (N >222,000).<sup>46</sup> With regard to depression, in a cohort of 3600 patients who survived stroke, depression was associated with a mortality hazard ratio of 1.41.<sup>47</sup> Further, in a recent meta-analysis including seven studies looking at post stroke depression in patients early after the CVD event (N >119,000), depression was associated with a short-term mortality relative risk of 1.50.<sup>48</sup> Similar findings were found in a 2019 meta-analysis of 15 prospective cohort studies (N >250,000) showing a post-stroke depression related all-cause mortality hazard ratio of 1.59.<sup>49</sup> These results mirror the all-cause mortality hazard ratio of 1.9 at 2 years seen in a meta-analysis of over 30 studies of post-ACS depression.<sup>50</sup>

### **3. Psychological outcomes in patients evaluated for CVD may also impact healthcare utilization and recidivism (e.g. rehospitalization) in CVD survivors.**

Psychological variables amongst patients evaluated for potential CVD may also impact other healthcare measures such as ED recidivism and healthcare utilization. In a cohort of 167 patients presenting to the ED with “low-risk” chest pain, 47% screened positive for abnormally high anxiety symptoms and these patients displayed a relative risk for 2 or more return ED visits of 9.1.<sup>12</sup> Similarly, in a longitudinal analysis of 196 seeking evaluation for chest pain, anxiety and interoceptive fear at evaluation was associated with increased healthcare utilization.<sup>51</sup> Furthermore, acute stress disorder symptoms or “early PTSD” in a sample of 974 patients evaluated for ACS was associated with 30-day ED and hospital (all-cause) readmissions with an adjusted odds ratio of 1.24.<sup>7</sup>

Likely contributing to the recidivism, morbidity and mortality outlined above, CVD related PTSD may be associated with medication nonadherence.<sup>52</sup> Kronish et al. showed that in a cohort of 535 post stroke patients, 18% screened positive for PTSD and had a relative risk of medication non-adherence of 2.7 compared to patients without PTSD.<sup>53</sup> This non-adherence may be due in part to stroke survivors’ concerns and worry regarding their medications including long-term effects.<sup>8</sup> One theory is that the medications themselves serve as a “traumatic reminder” as shown in a cohort of 424 patients evaluated in the ED for suspected ACS, higher PTSD scores were correlated with an increased likelihood of missing doses of cardiovascular medications in order to avoid reminders of the interaction, anxiety and

thoughts of future risk.<sup>54</sup> This is significant as medication non-adherence has been shown to be associated with worse adverse events and even mortality in MI survivors.<sup>55</sup>

#### **4. An opportunity to develop a multidisciplinary approach to understand biopsychosocial systems in the management of CVD.**

Similar to established evidence suggesting the presence of nosocomial risks hospitalization, ranging from multidrug resistant infections to delirium in the hospital setting, there may be nosocomial psychological effects associated with the ED and acute CVD events, ranging from increased anxiety during hospitalization, to dysregulations in sleep/wake cycles, and nutrition habits, leading to increased affective symptoms such as depression.<sup>56</sup> The concept of a nosocomial associated psychological stress model may help frame our understanding of psychological stress during life threatening conditions, such as ACS.<sup>57</sup> With this in mind, the specialty of Emergency Medicine is uniquely positioned to lead a scientifically rigorous multidisciplinary effort to understand the biopsychosocial processes underpinning these psychological and CVD outcomes after acute care evaluation. We propose the following research agenda items as areas of focus as we continue to study these phenomena in the ED: 1) Accurate characterization and definitions; 2) Acute care specific bedside assessment tools; 3) Accurate outcome assessments; 4) Quantifying the contribution of environmental factors; and 5) ED interventions to mitigate adverse outcomes.

Psychological stress, peritraumatic ED threat, PTSD, and enduring somatic threat are just a few of the terms and phrases used to characterize these complex interactions and outcomes during and after CVD evaluation. Definitions and characterizations of these terms need to be harmonized between the stakeholder specialties (EM, cardiology, neurology, psychiatry, psychology, etc.). This in turn, will reduce heterogeneity and directly affect the selection of bedside assessments to be used at the time of patient inclusion for risk stratification. There have been multiple bedside screening tools for mood disorders used previously in the outpatient setting including the Hospital Anxiety and Depression Scale (HADS)<sup>58,59</sup>, the Generalized Anxiety Disorder 7-item scale (GAD-7)<sup>60,61</sup>, Patient Health Questionnaire 9-item (PHQ-9)<sup>62</sup> scale for depression or the 4-item screener for anxiety and depression (PHQ-4).<sup>63</sup> However, few such tools have been developed explicitly for the acute care setting with a focus on the perception of life threat during medical evaluation. Recently, a brief ED based self-report 7-item screening tool for acute psychological stress (e.g. threat perception) was validated in a cohort of ED patients treated for ACS events, which may show promise, though future work in other patient samples and disease processes is required.<sup>64,65</sup> Additionally, is screening for anxiety, depression, or threat perception sufficient as single domains to be used as predictive tools or should they be paired sequentially with posttraumatic screening tools such as the Posttraumatic Adjustment Scale (PAS) which has demonstrated specific utility in the ED for the identification of patients at risk for developing PTSD post evaluation?<sup>66</sup> Moreover, how does this approach compare with multi-domain assessment in the ED using computer adaptive screening tools such as the Computerized Adaptive Test for Mental Health (CAT-MH) which can assess multiple domains such as anxiety, depression, substance abuse and PTSD simultaneously? <sup>67,68</sup>

After optimizing bedside assessments and identification of at-risk ED patients, the next major research questions should focus how best to assess near and long-term psychological and cardiovascular outcomes. What is the role for ecological momentary assessment (more frequent brief contact via phone or text messaging) in assessing post-evaluation psychological sequelae which can be prone to recall bias if solely evaluated at 4–6 weeks? Further, with regard to cardiovascular outcomes, are there surrogate markers that can be identified which may inform our understanding of the relationship of acute and chronic psychological stress on the development of cardiovascular diseases? Areas for further investigation may include secondary cardiovascular behaviors (tobacco abuse, poor diet, inadequate physical activity, and medication non-adherence), acute on chronic systemic inflammation, vascular endothelial dysfunction, as well as persistent autonomic dysfunction as pathophysiologic mechanisms whereby psychological stress influences CVD event.<sup>49,69</sup> Additionally, further investigation is needed regarding the relative contributions of both patient centered and environmental factors, such as ED crowding and length of stay to CVD outcomes. There may also be significant differences amongst the diverse demographics of patients with cardiac disease. Factors such as Age, Sex, Gender, Ethnicity, and Race may all have some moderating factors in the development of psychological stress during and following an acute cardiac event. Future work should be aimed at exploring any potential subgroup differences and processes.

Finally, the end-goal of this work should be to develop ED interventions and processes of care that help to mitigate these adverse CVD outcomes. Accessible options include scripted communication and shared decision-making discussions initiated by the ED provider or support staff such as social workers as a part of a screening intervention and referral to treatment (SBIRT) model. Existing evidence has found that bedside communication between emergency clinician and patients is an important contributor of ED based threat perception and threat. For example, a sample of 474 patients treated for ACS found that perceived positive clinician-patient communication was associated with lower acute stress/posttraumatic stress symptoms at 30-day follow-up.<sup>13</sup> Other recent work has found that patient perception of provider compassion was associated with decreased subsequent PTSD symptoms at followup.<sup>70</sup> Taken together, such bedside interventions may help reduce the development of such adverse psychological outcomes following acute illness in the ED setting. Beyond bedside communication, there should be exploration of multidisciplinary treatment options such as early behavioral health consultation for a subset of high-risk patients being treated for CVD. Further, the feasibility of referral of at-risk patients, particularly without a CVD diagnosis, directly to cognitive behavioral therapy or mindfulness-based stress reductions either in-person or app-based options should be examined.

## Limitations

Given the scope of our topic, our narrative review was necessarily broad in scope and attempted to encompass literature from a diverse group of fields both within emergency medicine, as well as behavioral medicine and psychology. Unlike a systematic review, where we had a single focused question with outcome, our concepts paper drew on multiple questions and processes to succinctly summarize for readers several key points. While we

had three separate searches for this study, articles may have been overlooked or not included in this narrative review.

## Conclusions:

Being evaluated and treated for life threatening events such as CVD is frightening for many patients, which may have significant adverse effects on physiological and psychological recovery. An increased awareness of the presence of such psychological effects during CVD is an important first step to identifying and assessing patient risk during cardiovascular events. Building on this evidence, an interdisciplinary program of work aimed at supporting CVD disease in the context of acute medical stabilization and psychological support may ultimately lead to improvements in both patient psychological and cardiovascular well-being.

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