Physiological Influences of Active and Passive Acute Mental Stress on Cardiac Repolarization: A Preliminary Investigation into Pathophysiological Mechanisms of Adult Cardiac Arrhythmias

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ABSTRACT

Physiological Influences of Active and Passive Acute Mental Stress on Cardiac Repolarization: A Preliminary Investigation into Pathophysiological Mechanisms of Adult Cardiac Arrhythmias

Candace Raddatz

Background: Adult cardiac arrhythmias cause adverse health effects including death. While the underlying mechanisms of arrhythmiogenesis have yet to be elucidated, the cardiac autonomic nervous system (ANS) is suggested to play a notable role. As part of the stress response the cardiac ANS is activated under conditions of acute mental stress, yet, little is known about the cardiac ANS stress response and adult arrhythmiogenesis in acute mental stress conditions. This systematic review offers insight into the influences of acute mental active and passive stress and their potential roles in generating proarrhythmic environments, and provides a primary foundation for future clinical research investigating prospective arrhythmiogenic pathophysiological pathways for the prediction, prevention and treatment of adult arrhythmias.

Methods: An extensive literature search was performed by two independent reviewers using Pubmed, PsycINFO, and Scopus electronic databases (up to December 2018). All English language articles which assessed adult cardiac electrophysiological, autonomic, and hemodynamic responses, to acute mental stress conditions were included.

Results: Eleven studies were identified; 5 studies included active stress tasks, 3 studies included passive stress tasks, and 3 studies included both active and passive stress tasks. Both active and passive stress were associated with pro-arrhythmic electrocardiographic changes, along with increased hemodynamic and autonomic responses.

Conclusions*:* Active and passive stress create a pro-arrhythmic environment through repolarization alterations, increased sympathetic nervous system activity, and concurrent diminished parasympathetic activity. Further studies should include distinctions between active and passive stress cardiac electrophysiology profiles to better understand how mental stress contributes to cardiac arrhythmia etiology.

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Author Contributions for the Manuscript

Candace Raddatz is the primary author of the manuscript of this thesis. She was responsible for developing the idea for this systematic review, data extraction, analysis and assembly of the manuscript.

Dr. Simon Bacon is the main supervisor of the primary author and oversaw all stages of the systematic review and related manuscripts. As the primary editor of the manuscript included in the present thesis, he also ensured the accurateness and completeness of its content.

Emilie Dolan is the second independent reviewer of the systematic review. She was responsible for the secondary abstract screening and data extraction of included studies.

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List of Acronyms and Abbreviations

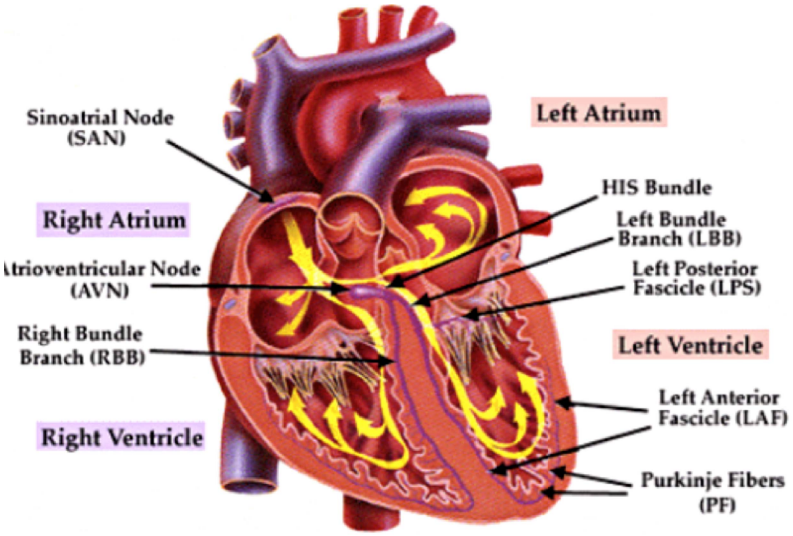
ANS	autonomic nervous system
AVN	atrioventricular node
BP	blood pressure
CAD	coronary artery disease
CI	cardiac index
CO	cardiac output
DBP	diastolic blood pressure
ECG	electrocardiograph
ECNS	extrinsic cardiac nervous system
GP	ganglionic plexi
HF-HRV	high frequency component heart rate variability
HR	heart rate
ICD	implantable cardioverter defibrillator
ICNS	intrinsic cardiac nervous system
LVEF	left ventricular ejection fraction
PNS	parasympathetic nervous system
SAM	sympathomedullary pathway
SAN	sino-atria node
SBP	systolic blood pressure
SCD	sudden cardiac death
SNS	sympathetic nervous system
SV	stroke volume
T-amp	t-wave amplitude
T-area	t-wave area
TCRT	total cosine R to T
TRP	total peripheral resistance
TWA	t-wave alternans
TWR	t-wave residua

1.0 Introduction

1.1 Cardiac Arrhythmias

Broadly defined, cardiac arrhythmias are disruptions in the normal rate and/or rhythm of the heart where they can manifest as bradycardia (<60 bpm), tachycardia (>100 bpm), irregular rhythms, or a combination thereof. Proper cardiac contractions, from atria to ventricle, are perpetuated by electrical impulses that follow a specific electrical pathway, see **Figure 1** (1). Initiated by an action potential depolarizing the sino-atria node (SA node) a cascade of depolarizations propagates the electrical signal to the atrio-ventricular node (AV node) to the left and right bundles and terminates at the purkinje fibres(2). The electrical impulse stimulates the timely sequence of atrial to ventricular contractions, however when the normal duration of these cyclic myocyte depolarizations, repolarizations, and refractory periods is changed, an arrhythmiogenic state is fostered. The topography of the cardiac electrical pathway allows arrhythmias to originate in the atria, ventricle, or AV node, yielding many different types of arrhythmias manifesting as rate and/ or rhythm irregularities (3).

Figure 1. Significant Structures for the Electrical Conduction of the Heart

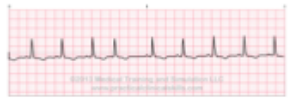
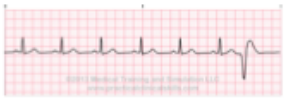
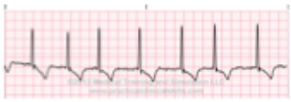
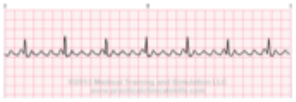
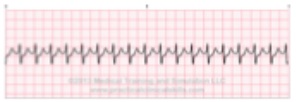
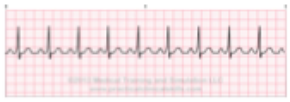
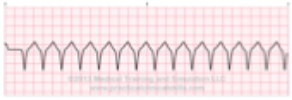
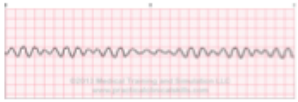
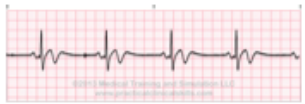


Action Potentials start in the SA node, travel to the AV node,
through the left and right bundles, and terminates at the Purkinje fibres (4).
Reprinted from EXCI 259 Lab Manual. Figure use permission from publisher, Concordia University (Appendix C)

1.1.1 Cardiac Arrhythmia Risks Factors and Outcomes

Each type of arrhythmia changes the normal cardiac electrical conductivity differently, producing distinguishable wave patterns that can be identified through an electrocardiograph (ECG**)** see **Figure 2** (5**).** The various arrhythmias differ in prevalence between age groups, however arrhythmias are less common in children (6) and most common in older adults, with a greater risk of arrhythmia occurring with aging (7). Internally initiated arrhythmic risk factors include: underlying structural heart disease (8); congestive heart failure; hypertension; and diabetes (9), while externally initiated risk factors include: exercise (10) and psychological stress (11). The spectrum of severity for arrhythmias ranges from harmless to fatal, with more serious and life-threatening arrhythmias causing brain, heart, and organ damage, and/or death, due to the hearts impeded ability to circulate sufficient blood throughout the body (9, 10). A potential, yet lethal arrhythmic outcome is sudden cardiac death (SCD). Sudden cardiac death is defined to be an unexpected death due to an abrupt loss of cardiac function within a short period (< 1 hour) of symptom onset, where the mechanism is a perturbation in cardiac electrical stability leading to fatal cardiac arrhythmias such as ventricular fibrillation and ventricular tachycardia (12-14). While antecedent arrhythmiogenic activity is sometimes difficult to determine in SCD, it is accepted that the majority of SCD cases occur via cardiac arrhythmias (15-17). Globally, SCD and arrhythmias account for 15-20% of all deaths, and in the US the annual incidence is approximately 180,000-300 000/ year (18-20).

Figure 2. Summary Chart of Arrhythmias

	Name	Type	Origin	Severity	Description	Complications	Sample ECG
Premature (Extra) Beats	Premature atrial contractions	Irregular Rhythm	Atria	Not Serious	Atrial contraction without sequential ventricle contraction	None	
	Premature ventricular contractions	Irregular Rhythm	Ventricles	Not Serious (acutely) Serious (chronicly)	Ventricle contraction without previous atrial contraction	can lead to ventricular arrhythmias	
Supraventricular Arrhythmias	Atrial fibrillation	Irregular rhythm	Atria	Serious	Electrical signal does not begin in SA node Fast and irregular atria contraction	Stroke Heart Failure	
	Atrial Flutter	Irregular Rhythm	Atria	Serious	Fast and regular atria contraction	Stroke Heart Failure	
	Paroxysmal supraventricular tachycardia	Tachycardia	Atria	Not Serious	Electrical signal travels from atria to ventricles and back to atria Fast heart rate that suddenly begins and then stops Most common and best tolerated in young adults	Death	
	Wolf Parkinson White Syndrome	Tachycardia	Atria	Serious	Extra electrical pathway from atria to ventricles Ventricles beat very fast Most common in children	Death	
Ventricular Arrhythmias	Ventricular Tachycardia	Tachycardia	Ventricles	Serious	Fast and regular contraction of ventricles	Ventricular fibrillation	
	Ventricular Fibrillation	Tachycardia	Ventricles	Very Serious	Fast and irregular contraction of ventricles Ventricles unable to pump blood out	Cardiac Arrest Death	
Bradyarrhythmias	Bradyarrhythmia	Bradycardia	Atria	Serious	Very slow heart rate	Syncope	

Summary chart of various cardiac arrhythmias including where the conduction disorder originates, the risks, and sample ECG image. (5)

1.2 Acute Mental Stress

Stress can be defined as a real or anticipated disturbance to one's physiological and /or psychological homeostasis (21). Stress can be categorized as chronic or acute, where acute can be defined as a time-limited stressful event (22). Acute stress can be classified into active or passive. Active stress can be considered as stimuli where the individual has the ability to influence the outcome to some degree using psychological or behavioural coping methods (23-25). Passive stress is stimuli where the individual has no opportunity to influence the outcome using active coping methods (25, 24, 26). The ambiguity of the term "stress" creates different conceptualizations across scientific disciplines, making a precise one-size fits all definition challenging. Within the literature on stress and arrhythmias, *psychological stress, mental stress, emotional stress, stress event, psychosocial factors,* and *emotional states* have been used interchangeably. However, after some scrutiny, certain studies associate arrhythmiogenesis with the stressor/stimulus, which is the actual cause of stress, e.g. work, natural disaster, isolation (27). Others refer to the stress responses, which are the mental and physical changes elicited from the stressors e.g. anger, fear, loneliness (27). Therefore, for the review with in this thesis, a definition of stress was created such that it was broad enough to include the heterogenous terminology found with in studies, but with enough precision to remain exclusive to the aforementioned terms and reviewed articles. From here on, the term *acute mental stress* will be used and is defined as a short-term (< 1 week) experience causing an abrupt change in one's current psychological state, without an equivalent increase in metabolic demand relative to physiological reactivity.

1.2.1 Acute Mental Stress and Cardiac Arrhythmias

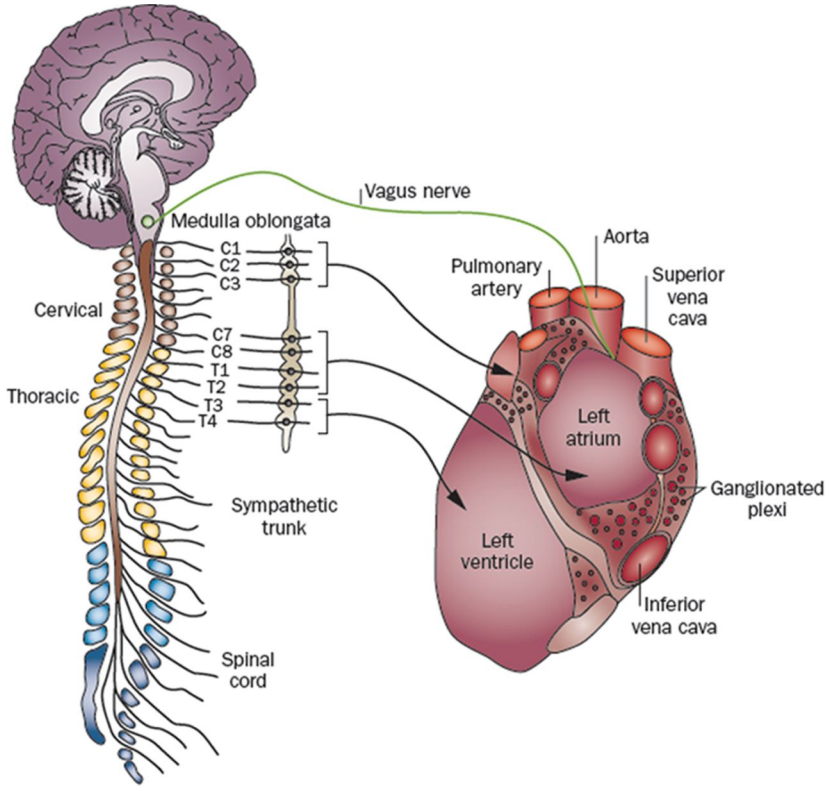
It is well known and accepted that acute mental stress contributes to adverse cardiac events and cardiovascular disease progression (14, 28, 29) and that cardiovascular reactivity to acute mental stress is associated with cardiovascular disease risk (30). It has also been shown that acute mental stress can precede arrhythmic events (31, 32). In patients with implanted cardioverters (ICD's), active mental stress tasks such

as anger recall tasks and mental arithmetic tasks precipitated changes in T-wave patterns indicative of changes in the cardiac electrophysiology (33). Electrophysiological changes and increases in arrhythmic activity have also occurred during periods of physical stress, as increases in ICD shock administration have been observed (34). In efforts to investigate the underlying mechanism between acute stress and arrhythmiogenic activity, Critchley and colleagues used neuroimaging during acute mental and physical stress tasks and found asymmetrical mid brain activation suggesting that this disrupts efferent cardiac activity and could cause problems in cardiac repolarizations, inducing potential arrhythmic activity (35).

1.3 Cardiac Autonomic Nervous System

The cardiac autonomic nervous system (ANS) modulates cardiac electrophysiology. A brief overview of cardiac neuroanatomy is necessary in understanding the ANS role in arrhythmiogenesis. The heart is innervated by both the extrinsic and intrinsic ANS. The extrinsic ANS is the primary relay between the heart and central nervous system, where the intrinsic ANS mediates inter autonomic cardiac information to the extrinsic ANS (36). The extrinsic cardiac ANS is a paravertebral structure of both sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) fibers situated on the surface of the heart, that receive bilateral efferent and afferent input. Sympathetic nerves originate in the stellate, cervical and thoracic ganglia and are dispersed throughout the heart in a gradient format, with a higher density in the atria and apex compared to the ventricles (37). Stimulation of the SNS increases heart rate and cardiac contractility via interactions of the neurotransmitter norepinephrine on alpha (α) and beta (β) adrenergic receptors. Parasympathetic innervation is from the vagus nerve originating in the medulla, with high localization around the SAN and AVN, and liberally distributed throughout the atria. Stimulation of the PNS decreases heart rate and cardiac contractility by interactions of acetylcholine and cardiac receptors, see **Figure 3** (37-39).

Figure 3. Cardiac Autonomic Innervation

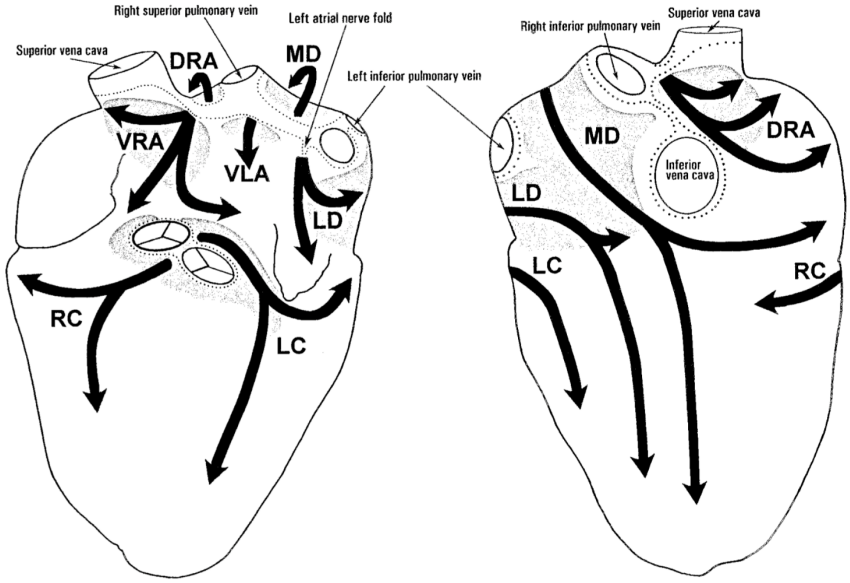


Sympathetic innervation originates from stellate, cervical and thoracic ganglia. Parasympathetic innervation originates from the vagus nerve (40).
Figure taken from Shen et al 2014. Figure use permission from publisher, Springer Nature (Appendix C)

The intrinsic ANS is a complex system of autonomic nerve fibers within the pericardium. Extrinsic nerves entering at the heart hilum become intrinsic nerves. Intrinsic nerves from the arterial portion of the hilum tend to proceed to the ventricles, whereas nerves from the venous portion continue to both the atria and ventricles. Human hearts have approximately 43000-94000 intrinsic neurons, depending on age. These neurons lie predominantly on the epicardium and are arranged into collections of ganglionic plexi (GP) that are concentrated throughout various regions of the heart. There are seven identified sub-plexuses that innervate specific cardiac areas; Left Coronary (LC), Right Coronary (RC), Ventral Right Atrial (VRA), Ventral Left Atrial (VLA), Left Dorsal (LD), Middle Dorsal (MD), Dorsal Right Atrial (DRA). Two sub plexuses innervate the right atrium, three sub plexuses innervate the left atrium, the right ventricle is innervated by one sub plexus the left ventricle is innervates by two sub plexuses, see **Figure 4**. While the

topography of the sub plexuses remains consistent throughout the lifespan, the structure of each has an age-related variability (41, 42). Both the intrinsic and extrinsic neural circuits function intra-dependently as well as an interdependently of which propagates an extremely complex network of efferent and afferent feedback loops.

Figure 4. Ganglionic Plexi (GP) of Human Heart



General schematic of intrinsic GP arrangement within the human heart (41).
Figure taken from Pauza at al 2000. Figure use permission from publisher, John Wiley and Sons (Appendix C)

1.3.1 Cardiac Autonomic Nervous System and Cardiac Arrhythmias

It is accepted that the SNS play a part in arrhythmiogenic mechanisms (43, 44) and the intricacy of the cardiac SNS and PNS interplay may impact the complexity of arrhythmic activity. It has been shown that the SNS is generally pro-arrhythmic for both atrial and ventricular chambers due to the similar effects SNS stimulation has on atrial and ventricular myocytes (45). In cases of atrial fibrillation (AF), animal studies have shown that simultaneous activation of the SNS and PNS precedes AF episodes, (46, 47) and this relationship has been observed in human AF as well (48-50). However, in ventricular fibrillation (VF) the SNS has been observed to be pro-arrhythmic and the PNS has been anti-arrhythmic (51, 52).

Cardiac arrhythmias arising from genetic predisposition, known as inherited arrhythmia syndromes (IAS), such as brugada syndrome and J-wave syndrome seem to have SNS stimulation that is anti-arrhythmic, (53-55) but in other IAS such as long QT syndrome (LQTS), the SNS appears to be pro-arrhythmic. (40) The pro-arrhythmic SNS role depends on its influence on ventricular repolarization. In ventricular fibrillation the SNS has been shown to be responsible for changes in repolarizations that can reduce the fibrillation threshold in the ventricles, which can trigger ventricular fibrillation (51). This has also been observed in long QT syndrome (LQTS), as SNS stimulation causes prolonged QT intervals, again, the ventricular repolarizations and depolarizations are affected, potentially leading to VF and sudden cardiac death (40). Adding another layer of complexity is the understanding that the pro arrhythmic nature of the SNS may be modified by the disease status of the heart (i.e. healthy or unhealthy) (40). In a normal healthy heart, the SNS can cause shortened action potentials,(44) can reduce transmural dispersion of repolarization (longest depolarization time in the left ventricle (LV)- shortest depolarization time in the LV) and shortens QT intervals (56). However in unhealthy hearts, it has been shown that the SNS increases ventricular dispersion of repolarization, which can be pro-arrhythmic (57). These ventricular effects seem to be enhanced in damaged myocardium (i.e. ischemia) because of changes in SNS innervation density in different cardiac regions (58).

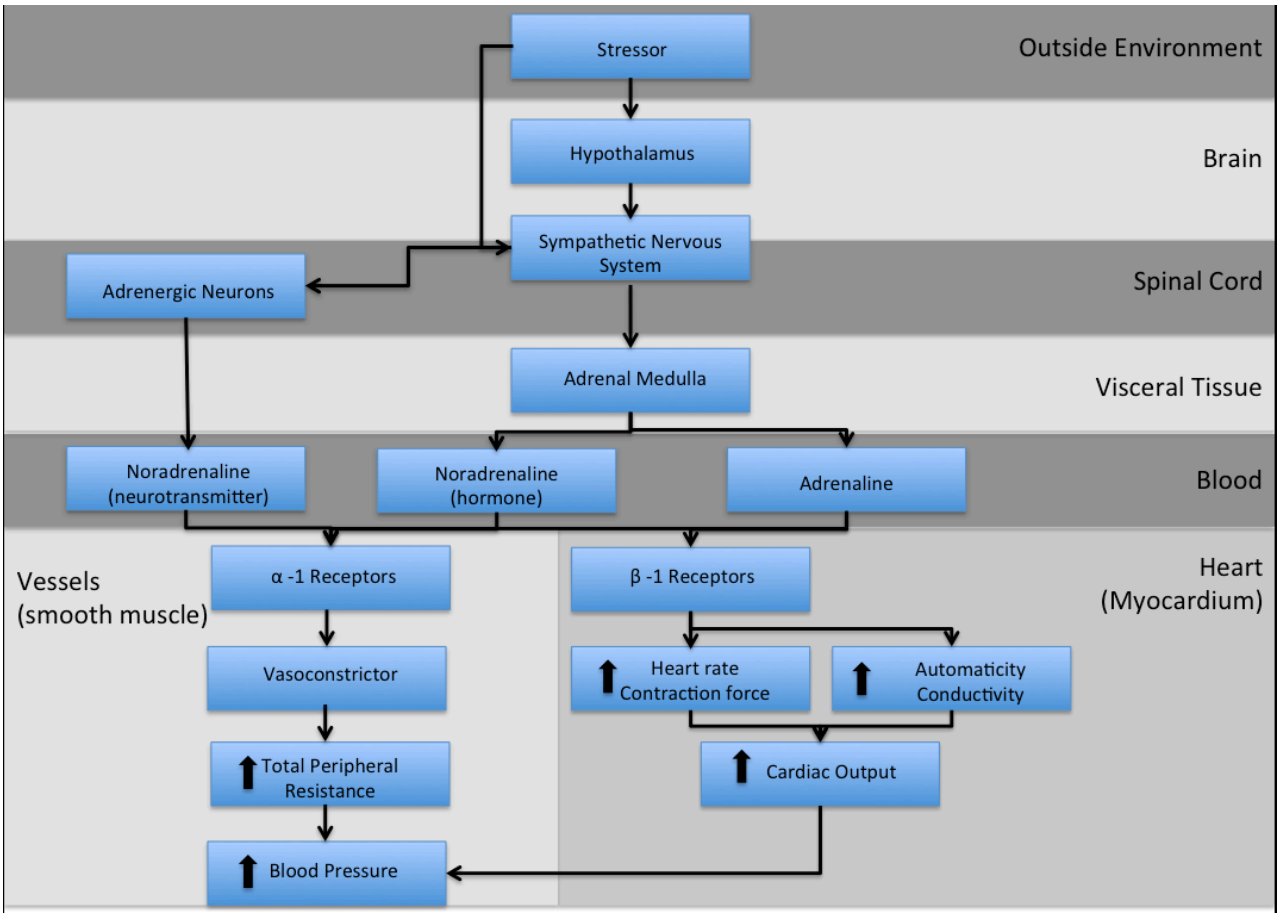
1.3.2 Cardiac Autonomic Nervous System and Acute Mental Stress

It is known that stress influences cardiac ANS activity (59). Often, physical and mental stress can be differentiated between the degree of reactivity relative to the metabolic demand, where demand tends to equate to reactivity for physical stressors but are inconsistent in mental stress (60). As part of the stress response, the SNS is activated causing a coordinated cascade of reactive physiologic events to mitigate the stress effects, see **Figure 5**. Briefly, the basic cardiac responses under sympathetic stimulation are increased heart rate and stroke volume, vascular responses are increased, e.g., blood pressure, while endocrine responses lead to catecholamine release. Cardiac parasympathetic outcomes are demonstrated by decreased heart rate, which is achieved through the inhibitory action of the vagus nerve (61). After exposure to an acute

stressor, the SNS can be activated by cells in the medulla via the hypothalamus, known as the sympathomedullary pathway (SAM), or directly by afferent neurons synapsing in the spinal cord (61). The adrenal medulla is stimulated and releases the hormones adrenaline and noradrenaline into the blood stream. Noradrenaline is also released as a neurotransmitter by adrenergic neurons. Both adrenaline and noradrenaline can bind to adrenergic receptors on the effector tissue (62). Adrenergic receptors are classified as α receptors and β receptors which can further be broken down into α-1,2 and β-1,2(60). Activation of α-1 and β-1 causes excitation of visceral tissues; conversely activation of α-2 and β-2 causes inhibition of visceral tissues. Adrenaline binds to α and β receptors and noradrenaline binds primarily to α receptors (63). It is the binding of adrenaline and noradrenaline on the receptors of cardiac tissue that produces the increased chronotropic (rate) and inotropic (contractility) effects of the heart (62). This increase in HR and SV increases the cardiac output. The large amounts of adrenaline and noradrenaline in the blood act as general constrictors of peripheral vessels and vasodilators of coronary arteries. This vasoconstriction of the peripheral vasculature increases the total peripheral resistance (TRP), this, coupled with increased cardiac output causes an increase in blood pressure (63). The sympathetic stress response as described above is a general depiction of the cardiovascular reactivity, and although cardiovascular responses tend to have the same directional end point (HR increases, BP increases), differences in the patterns of response between active mental and passive physical stress have been observed (64, 65). For example, pattern differences in BP, CO, HR and TPR between mental arithmetic tasks (active mental stress) and cold pressor tasks (passive mental stress) have been observed. Cardiovascular patterns in active mental stress tasks have had evidence of combined α- and β-adrenergic activity, where the passive mental stress tasks have had evidence of primarily α -adrenergic activity (61). Winzer and colleagues administered mental arithmetic tasks and cold pressor tasks in placebo and beta-blockade conditions, and found the cardiovascular responses to the mental arithmetic differed in beta blockade conditions, where cold pressor tasks did not (65). In an analogous study, Ring and colleagues investigated the stress tasks with alpha-blockade and found different cardiovascular response profiles within cold pressor tasks (64). These results agree with prior theories that the pattern

differences in achieving the overall stress response may be due to greater beta-adrenergic activity and decreased parasympathetic stimulation in active stress tasks, and passive stress tasks arousing greater alpha-adrenergic activity and increased parasympathetic stimulation (63).

Figure 5. The Stress Response



Overview of the stress response and the levels at which they occur.(66)

1.4 Rationale

There is evidence linking cardiac arrhythmias to acute mental stress, with studies suggesting that the cardiac ANS is a mediating factor, yet there are many unknowns about the precise arrhythmiogenic mechanisms that acute mental stress initiates. While risk factors such as pre-existing heart disease and physical exertion can be directly measured, acute mental stress has a less empirical nature making it an enigmatic risk factor and prompting further research of how it contributes to the etiology of cardiac arrhythmias. Previous studies have observed different physiological response profiles between active and passive stress, suggesting that active and passive stress influence the cardiac ANS differently. Therefore, it is proposed that if active and passive stress have independent impacts on the cardiac ANS, then perhaps this can be used as a pathophysiological stimuli to help elucidate how the cardiac ANS influences and generates proarrhythmic cardiac environments during acute mental stress conditions.

1.5 Research Objectives and Hypotheses

1) To investigate if any notable differences exist between acute mental active stress and acute mental passive stress's relationship with the potential for cardiac arrhythmias in adults. It is hypothesized that acute mental active stress will have a greater impact on arrhythmiogenesis compared to acute mental passive stress.

2) To observe how the electrocardiographic, hemodynamic and autonomic responses differ between acute mental active stress and acute mental passive stress tasks. It is hypothesized that electrocardiographic, hemodynamic and autonomic responses will be amplified in acute mental active stress compared to passive stress.

3) To observe the relative relationships between electrocardiographic, hemodynamic and autonomic responses in both acute mental active and acute mental passive stress to discern differences that may lead to plausible arrhythmiogenic mechanisms. This objective is exploratory and as such, there are no potential hypotheses.

2.0 Article: Acute Mental Stress Effects on Cardiac Repolarization and their Potential Role in Adult Arrhythmiogenesis: A Systematic Review

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2.1 Abstract

Objective: Research demonstrates a link between acute mental stress and cardiac arrhythmias; however, the pathophysiological mechanism is unknown. Different physiological response patterns have been observed between acute mental *active* and *passive* stress suggesting that these stressors may have independent impacts on cardiac electrophysiology. This systematic review summarizes and evaluates available evidence of acute *active* and *passive* mental stress effects and their roles in potentiating arrhythmiogenic environments.

Methods: A systematic literature review was conducted by two independent authors in PubMed, PsycInfo, and Scopus databases (up to December 2018). All English language publications consisting of laboratory acute mental stress tasks and cardiac electrophysiological outcomes in adults were eligible for review.

Results: Eleven studies were identified; 5 studies included active stress tasks, 3 studies included passive stress tasks, and 3 studies included both active and passive stress tasks. Studies indicated that active stress is associated with increased heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), t-wave amplitude (T-amp), t-wave area (T-area), t-wave residua (TWR) and circulating epinephrine (EPI) and norepinephrine (NE) levels, and simultaneous shortened QT intervals and high frequency (HF) component decreases. Passive stress tasks, appeared to have less impact on electrocardiographic, hemodynamic and autonomic responses compared to active stress tasks.

Conclusions*:* The literature suggests that acute mental active and passive stress creates a pro-arrhythmic environment through repolarization alterations, increased sympathetic nervous system activity, and concurrent diminished parasympathetic activity. Further studies should include distinctions between active and passive stress cardiac electrophysiology profiles to better understand how mental stress contributes to cardiac arrhythmia etiology.

This Systematic review is registered through PROSPERO
Registration number: CRD42017062698

Key Words: Arrhythmia, acute mental stress, active stress, passive stress,

2.2 Introduction

Cardiac arrhythmias are disruptions in normal cardiac electrical conductance, impairing automaticity, and rhythmicity. The sequence of atrial and ventricular contractions occurs via action potentials depolarizing in the sino-atria node (SAN), propagating electrical signals to the atrioventricular node (AVN), the left and right bundles, and terminating at the purkinje fibres. When the duration of myocyte depolarizations, repolarizations and refractory periods is changed, an arrhythmiogenic state is fostered (67). Arrhythmic severity ranges from harmless (e.g., premature atrial contractions) to fatal (e.g., ventricular tachycardia), with potential complications including syncope, stroke, heart failure, cardiac arrest, developing other life threatening arrhythmias, and sudden cardiac death (68) (12). It estimated that cardiac arrhythmias are responsible for 250,000 deaths annually in the US (69) (13). Cardiac electrophysiological mechanics coupled with the neuronal topography of the heart, gives a variety of arrhythmias with different outcomes, making arrhythmias a diverse yet pertinent health care issue (70). However, the knowledge gap of arrhythmic pathogenesis impedes risk stratification and prevention measures of many types of arrhythmia (13, 71)

Acute mental stress preceding arrhythmic episodes and events is well documented in animal and human studies (31, 32, 72-75). Epidemiological studies and post mortem investigations reported acute disturbances from real-life stressors, such as natural disasters and war, as the cause of sudden cardiac death (SCD) (76-80). While antecedent arrhythmiogenic activity is sometimes difficult to determine in SCD, it is accepted that the majority of SCD cases occur via cardiac arrhythmias (16, 17, 81). Holter monitoring and implantable cardioverter defibrillator (ICD) studies have found associations between every day, real-life acute mental stress and increased arrhythmic event frequency (31, 32, 72, 34, 82). In another example, Hansson et al reported that 54% of arrhythmias were caused by acute mental stress (83). The heterogeneity of populations and stress conditions discussed above is evidence that acute mental stress is a potential putative precipitant of arrhythmiogenesis.

The pathophysiological connection between acute mental stress and arrhythmia lies within the cardiac autonomic nervous system (ANS), with both the extrinsic and intrinsic ANS being core mediators in inducing proarrhythmic states (42- 49).The extrinsic ANS is the primary relay between the heart and central nervous system, whereas the intrinsic ANS mediates inter autonomic cardiac information to the extrinsic ANS (36). The paravertebral structure of the extrinsic cardiac ANS has both sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) fibers situated on the surface of the heart, receiving bilateral efferent and afferent input. After exposure to acute mental stress the SNS is activated by afferent neurons synapsing in the spinal cord (61) or by the sympathomedullary pathway, with epinephrine and norepinephrine being released into the blood stream, binding to alpha and beta adrenergic receptors on effector tissues (60, 62, 84) . Increased SNS activity causes chronotropic and inotropic cardiac effects, measurable by changes in heart rate, stroke volume, total peripheral resistance, and blood pressure (60).

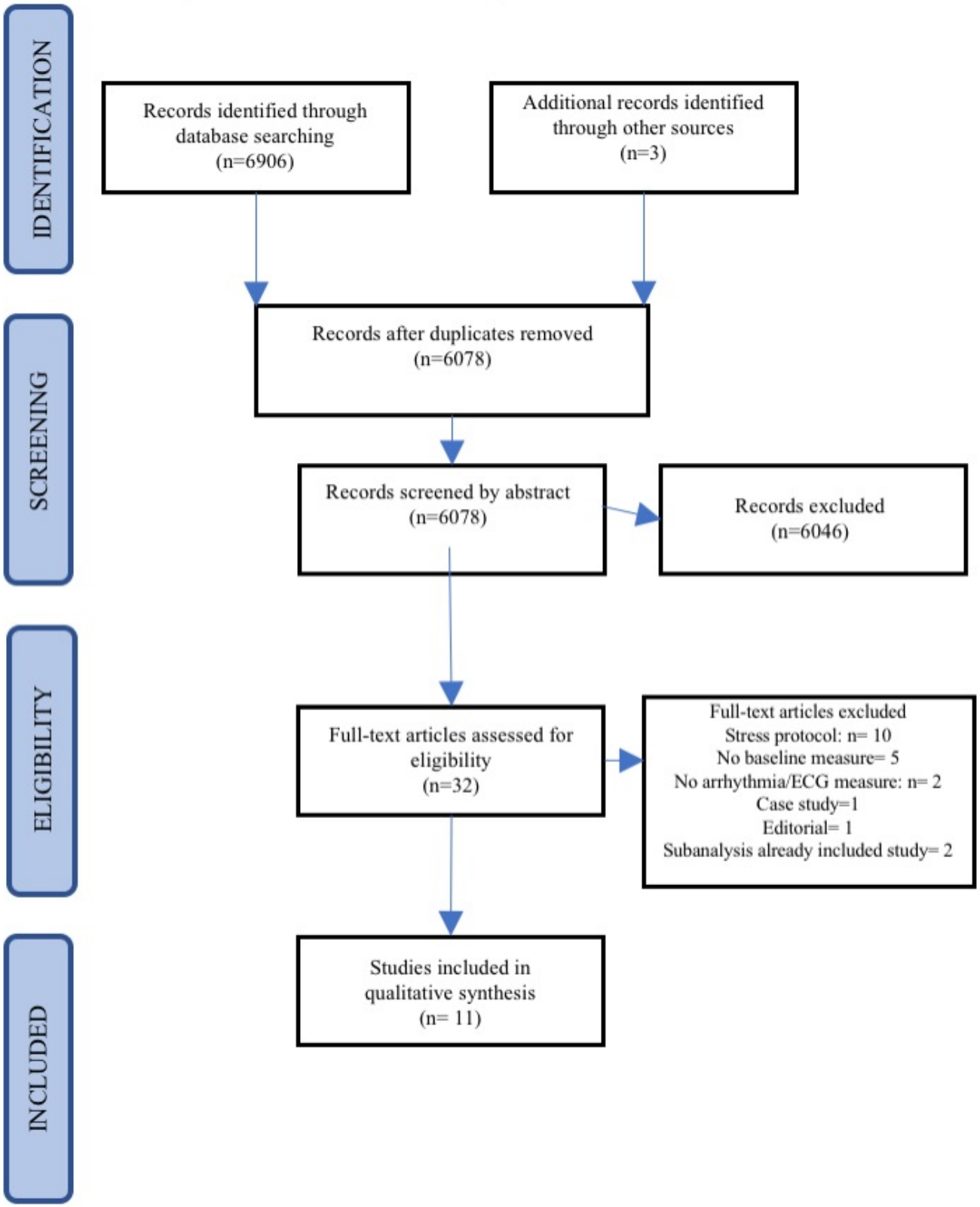
Although cardiovascular reactivity responses to acute mental stress tend to have the same directional end-point (HR increases, BP increases), different response profiles between active (stimuli where the individual influences the outcome through physical or mental effort, such as public speaking, or solving arithmetic problems (24)) and passive (stimuli where there is no opportunity to influence the outcome, such as recalling events that induce negative emotions such as anger or fear (25)) mental stress have been observed (64, 65). For example, stress response pattern differences in BP, cardiac output (CO), HR and TPR between mental arithmetic tasks (active stress) and cold pressor tasks (passive stress) have been documented (64, 65). Cardiovascular reactivity patterns in active stress tasks reveal combined alpha- and beta-adrenergic activity along with decreased parasympathetic stimulation, whereas passive stress tasks are driven primarily by alpha-adrenergic activity and increased parasympathetic stimulation (61, 63). Applying this concept to arrhythmias, differential cardiac electrophysiological changes and concomitant hemodynamic and autonomic changes between acute active and passive stress may help disentangle stress-induced arrhythmiogenic mechanisms. This review assesses the differential impact of laboratory induced acute active and passvie

mental stress on cardiac electrophysiology, hemodynamic and autonomic responses and their potential roles in generating arrhythmic activity.

2.3 Methods

The present systematic review was registered in PROSPERO (record CRD42017062698) and conducted per the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (85). A literature search was conducted August 01 2016, and updated December 01 2018, in Pubmed, PsycInfo and Scopus. Keywords searched were a combination of: "acute stress"; "stress response"; "arrhythmia"; and "dysrhythmia" (see online supplement for details). The search was conducted by an independent reviewer (CR). Eligibility criteria for this review included; adult populations, non-exercise laboratory induced stress, baseline or resting period, and a defined cardiac arrhythmia status. Laboratory induced stress was categorized into active and passive stress using the definitions above (24). Cardiac arrhythmia status was determined by electrocardiograph assessments and/or specific arrhythmia identification during stress conditions. Two independent reviewers (CR and ED) read and screened abstracts with the following exclusion criteria; 1) Not Human; 2) Not English; 3) Not Adults; 4) No Laboratory Mental Stress; 5) Only Exercise Stress; 6) No Arrhythmia/ECG data; and 7) Case Study's, Reviews, or Meta-Analysis. Bibliographies of prospective studies and relevant reviews were examined for additional potential studies. Following abstract screening, the full text of eligible studies was read and assessed by CR and ED with an inter-rater reliability (IRR) score of 1 on the agreement of the included studies. A flow chart of the identified and reviewed articles for final inclusion can be found in **Figure 6**. Data extraction was independently performed (CR and ED), with discrepancies resolved by third party (SLB). Authors were contacted to obtain the missing data, seven authors were contacted (86, 35, 87-91) with one response (89), where means and SD were unavailable.

Figure 6. PRISMA Flow Diagram of Included Studies



2.4 Results

A total of 6,906 articles were identified in databases and 3 articles were found in bibliographic records of prospective studies, 831 were duplicates and an abstract screen eliminated 6078 articles. The remaining 32 full text articles were assessed for eligibility where 21 articles were excluded for the following reasons: ten did not have laboratory induced stress (92, 93, 31, 94-100), seven did not report baseline measures (101-107), two were sub-analysis studies of an already included study (108, 109), one was an editorial (110), and one was a case study (111). Finally, 11 studies met all inclusion criteria for this review (86, 35, 87, 88, 112, 89, 90, 113, 91, 114, 115).

2.4.1 Study Characteristics

As seen in **Table 1**, three studies (88, 91, 115) used a control group defined as healthy participants with no history of CAD or other cardiac conditions. Seven studies included both men and women (86, 35, 88, 112, 89, 113, 91) with 4 including only men (87, 90, 114, 115). Average ages of participants ranged from 25 (90) to 64 years (112) with one study not reporting age (114). Seven studies included participants taking antiarrhythmic medications (86, 35, 87, 88, 112, 113, 91). Five studies reported if participants had previous arrhythmic episodes (35, 88, 89, 113, 115). Seven studies (86, 35, 87, 88, 112, 89, 91) included participants with pre-existing heart disease

Table 1 Study Characteristics

First Author (year)	Location	N of total Patients	Age (years) M (SD)	% Women	ICD	Type of Anttiarrhythmic Medication (% patients)	N Patients with Previous Arrhythmia	N Participants with Heart Disease	N of Stress Tasks	Type of Stress Task	Study Quality Score
Abisse (2011)	USA	56	63.6 (11.9)	12	Yes	Beta-Blocker (86)	n/a	54	1	Serial Seven Subtraction (A)	14
Critchley (2005)	UK	10	57 (6.6)	20	No	Beta-Blockers (70)	1	13	2	Serial Seven Subtraction (A) Isometric Hand Grip Squeeze*	12
Gray (2007)	UK	10	59 (11)	0	No	Beta-Blockers (90) Ca-Blockers (40)	n/a	24	1	Serial Seven Subtraction (A)	12
Kop (2004)	USA	ICD 23 Controls 17	62.1 (12.3) 54.2 (12.1)	9 47	Yes No	Beta-Blockers (56)	23	62	3	Serial Seven Subtraction (A) Ironson Anger Recall (P) Bicycle Ergometry*	13
Lache (2007)	Germany	55	64 (12)	15	Yes	Beta-blockers (58) Sotalol (18)	n/a	55	2	Serial Seven Subtraction (A) Anger Recall (P)	9
Lampert (2005)	USA	33	58.8 (12.7)	25	Yes	Beta-Blockers (88)	17	29	2	Serial Seven Subtraction (A) Anger Recall (P)	11
Souza (2013)	Brazil	50	25.4 (5.99)	0	No		n/a		2	Trier Social Stress Test Speech (A) Trier Social Stress Test Mental Arithmetic (A)	11
Suresh (2017)	USA	148	39.5 (13.1)	29	No	Beta-Blockers (0.7)	6		1	Human Centrifuge (P)	18
Taggart (2009)	UK	CAD** 14 Controls** 14	42 (n/a) 64 (n/a)	21 14	No	Beta-Blockers (71) Ca^{+}-Blockers (21)	n/a	14	2	Serial Seven Subtraction (A) Speech (A)	16
Whinnery (1988)	USA	24	n/a	0	No		n/a		1	Human Centrifuge (P)	11
Whinnery (1983)	USA	Stress Panel 20 Nondysrhythmia 20 Dysrhythmia 20	27 (9) 36.6 (8) 37.8 (7)	0	No		n/a		2	Human Centrifuge (P) Treadmill Testing*	14

CAD: Coronary Artery Disease, ICD: Implantable Cardio Defibrillator, MI: Myocardial Infarction, VF: Ventricular Fibrillation, VT: Ventricular Tachycardia, A; Active Stress Task, P; Passive Stress Task, * The exercise stress component of this study was not considered for this review, ** Study included placebo and NTG conditions, but this data was not considered for the review.

2.4.2 Stress task characteristics

Five studies included active stress (86, 35, 87, 90, 91), three included passive stress (113-115) and three included both stress tasks (88, 112, 89). Two studies included an exercise stress task, which was not included in the current review (35, 88). One study had a placebo and nitro-glycerin condition for each stress task, however only the placebo data was used for this review (91). Mental arithmetic (Serial Seven Subtraction and TSST Mental Arithmetic component) was the most common active stress task. Passive stress tasks included anger recall and human centrifuge (acceleration stress). The average duration of active stress tasks was 4.7 minutes (±0.76; range 3-5 minutes) and 4.5 minutes (±0.71; range 3-7 minutes) for passive stress. The average duration of baseline was 5.6 minutes (±4.1; range 1-15 minutes).

2.4.3 Study Quality

Study quality was assessed using an adapted version of the Downs and Black checklist (116). Items 13, 15, 19, 23 and 24 were not used as they applied to studies with interventions and/or treatments, leaving a possible 21 points for scoring. The power item was modified to a binary score (1=study addressed power calculation, 0=study did not address power calculation). Overall scores ranged from 9- 18 with a M ± SD score of 12.8 ± 2.6. See Appendix A for further details.

2.4.4 Outcomes

Overall electrocardiographic responses, hemodynamic responses, and autonomic nervous system responses are summarized in **Figure 7**. Only findings which were consistent in two or more studies were included.

Figure 7. Overall Electrocardiographic, Hemodynamic and Autonomic Outcomes

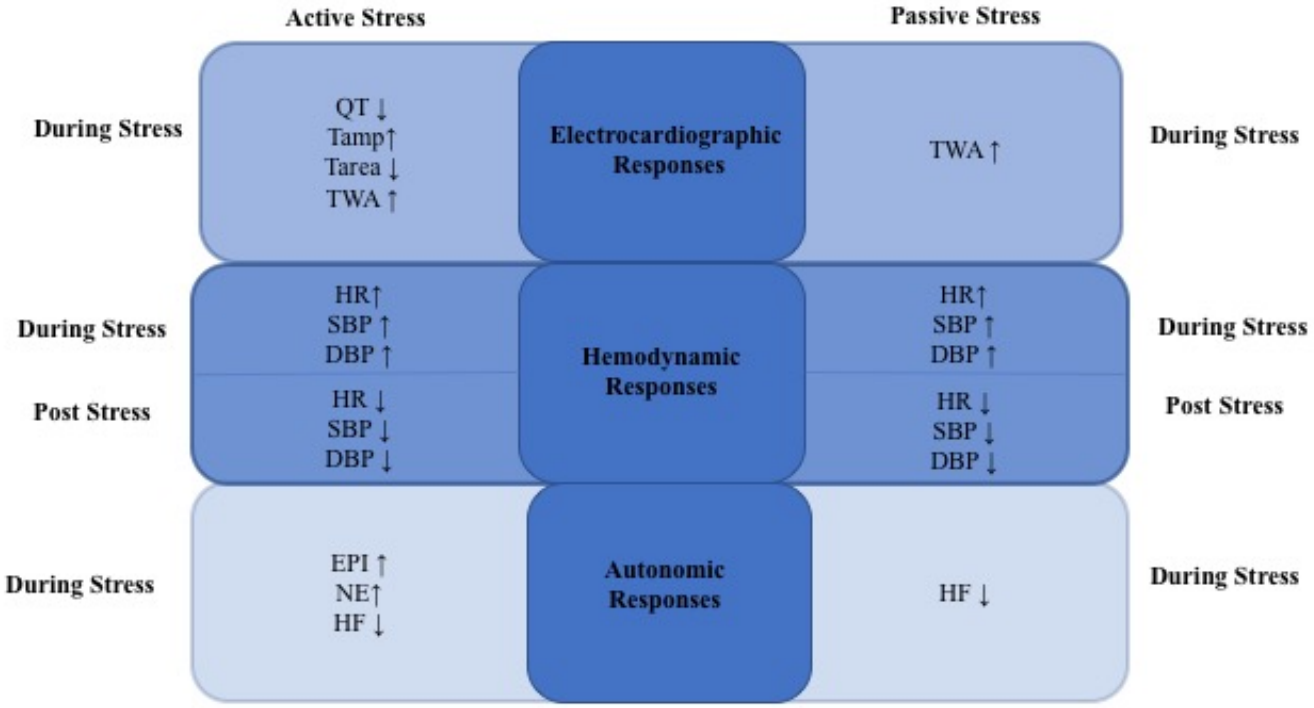


Figure 7. Overall outcomes for electrocardiographic, hemodynamic and autonomic nervous system responses. Depicted measures are for only those that had at least two consistent studies with the same outcome.

2.5 Electrocardiographic Responses

Electrocardiographic responses *during* active and *post* active stress tasks are summarized in **Tables 2** and **3**, respectively, and *during* passive and *post* passive stress tasks summarized in **Table 4** and **5,** respectively. Due to the broad range of ECG measurements throughout the studies, the electrocardiographic measurements are trichotomized into cardiac depolarization, cardiac repolarization indices, and arrhythmia occurrence.

Table 2 Electrocardiographic Measures During Active Stress

			Depolarization Indices			Repolarization Indices										
Author (year)	Group	Active Stressor	QRS	QT	Δ QT	Tamp	Δ Tamp	Tamp Var.	Tarea	Δ Tarea	TCRT	Twave	TWR	TWA	HP	ST
Abisse (2011)	All Patients	Serial Seven Subtraction	↑ x	↓↓	↓x	↑ x	↑ x	↑ x	↑ x	↑ x						
Critchley (2005)	All Patients	Serial Seven Subtraction									↓		↑			
Gray (2007)	All Patients	Serial Seven Subtraction				↑↑									↑↑	
Kop (2004)	ICD Controls	Serial Seven Subtraction												↑* ↑		
Lampert (2005)	All Patients	Serial Seven Subtraction		↓**		↑↑**			↑↑ **			-**	↑↑	↑↑		- **
Taggert (2009)	CAD Controls CAD Controls	Serial Seven Subtraction		? ? ? ?		↑ ↓ ↑ ↓			↑ ↓ ↑ ↓							

QRS; QRS interval (ms), QT; QT interval (ms), deltaQT; change in QT interval, Tamp: T- wave amplitude (mV), deltaTamp; change in T-wave amplitude, Tampvar; varaiance of T-wave amplitude, Tarea; T-wave area (ms x mV), deltaTarea; change in T-wave area, TCRT; total cosine R to T, TWR; T-wave residua, HP; Hill parameter, TWA; T-wave alternans, ST; ST segment, ↑; Increased and no report on significance, ↓; Decreased and no report on significance, ↑ x; increased and not significant , ↓x; Decreased and not significant, ↑↑; increased and significant, ↓↓; Decreased and significant *; significantly higher compared to control group,**; combined active and passive stress task results ?; no comparison to baseline measurements reported, -; no change relative to baseline

Table 3 Electrocardiographic Measures Post Active Stress Tasks

			Depolarization Indices			Repolarization Indices										
Author (year)	Group	Active Stressor	QRS	QT	Δ QT	Tamp	Δ Tamp	Tamp Var.	Tarea	Δ Tarea	TCRT	Twave	TWR	TWA	HP	ST
Abisse (2011)	All Patients	Serial Seven Subtraction	$\downarrow^{x}$	$\uparrow^{x}$	$\downarrow^{x}$	$\downarrow^{x}$	$\uparrow^{x}$	$\downarrow^{x}$	$\downarrow^{x}$	$\downarrow^{x}$						
Kop (2004)	ICD Controls	Serial Seven Subtraction												Remained Elevated		

QRS; QRS interval (ms), QT; QT interval (ms), deltaQT; change in QT interval, Tamp: T- wave amplitude (mV), deltaTamp; change in T-wave amplitude, Tampvar; varaiance of T-wave amplitude, Tarea; T-wave area (ms x mV), deltaTarea; change in T-wave area, TCRT; total cosine R to T, TWR; T-wave residua, HP; Hill parameter, TWA; T-wave alternans, ST; ST segment, ↑; Increased and no report on significance, ↓; Decreased and no report on significance, $\uparrow^{x}$; increased and not significant , $\downarrow^{x}$; Decreased and not significant, ↑↑; increased and significant, ↓↓; Decreased and significant *; significantly higher compared to control group,**; combined active and passive stress task results ?; no comparison to baseline measurements reported, -; no change relative to baseline

Table 4 Electrocardiographic Measures During Passive Stress Tasks

Author (year)	Group	Active Stressor	Depolarization Indices			Repolarization Indices					Arrhythmia Occurrence				
			QRS	QT	PR	Tamp	Tarea	Twave	TWA	ST	Atrial	Junctional	RB	Ventricular	Other
Kop (2004)	ICD	Ironson Anger Recall							↑						
	Controls								↑						
Lampert (2005)	All Patients	Anger Recall		↓**		↑↑**	↑↑**	-**	↑↑	-**					
Suresh (2017)	All Patients	Centrifuge											↑		
Whinnery (1998)	All Patients	Centrifuge	↓	↓	↓										
Whinnery (1983)	Stress Panel	Centrifuge									↑	↓		↑	↑
	Non-Dysrhythmia										?	?		?	?
	Dysrhythmia										?	?		?	?

Atrial; atrial dysrhythmias including premature atrial contractions, ectopic atrial rhythm, sinus arrhythmia, and atrial tachycardia, Junctional; junctional dysrhythmias including premature junctional contractions and supraventricular tachycardia, Ventricular; ventricular dysrhythmias, QRS; QRS interval (ms), QT; QT interval (ms),Tamp: T-wave amplitude (mV), Tarea; T-wave area (ms x mV), TWA; T-wave alternans, ST; ST segment, ↑; Increased and no report on significance, ↓; Decreased and no report on significance, $\uparrow^{x}$; increased and not significant , $\downarrow^{x}$; Decreased and not significant, ↑↑; increased and significant, ↓↓; Decreased and significant *; significantly higher compared to control group,**; combined active and passive stress task results ?; no comparison to baseline measurements reported, -; no change relative to baseline

Table 5 Electrocardiographic Measures Post Passive Stress Tasks

			Depolarization Indices			Repolarization Indices					Arrhythmia Occurrence				
Author (year)	Group	Active Stressor	QRS	QT	PR	Tamp	Tarea	Twave	TWA	ST	Atrial	Junctional	RB	Ventricular	Other
Kop (2004)	ICD Controls	Ironson Anger Recall							Remain Elevated						
Suresh (2017)	All Patients	Centrifuge											↓		
Whinnery (1988)	All Patients	Centrifuge	↑	↓	↑										
Whinnery (1983)	Stress Panel Non-Dysrhythmia Dysrhythmia	Centrifuge									↓ ↓ ↓	↑ ↓ ↓		↓ ↓ ↓	↓ ↓ ↓

Atrial; atrial dysrhythmias including premature atrial contractions, ectopic atrial rhythm, sinus arrhythmia, and atrial tachycardia, Junctional; junctional dysrhythmias including premature junctional contractions and supraventricular tachycardia, Ventricular; ventricular dysrhythmias, QRS; QRS interval (ms), QT; QT interval (ms),Tamp: T- wave amplitude (mV), Tarea; T-wave area (ms x mV), TWA; T-wave alternans, ST; ST segment, ↑; Increased and no report on significance, ↓; Decreased and no report on significance, ↑ ^{x}; increased and not significant , ↓^{x}; Decreased and not significant, ↑↑; increased and significant, ↓↓; Decreased and significant *; significantly higher compared to control group,**; combined active and passive stress task results ?; no comparison to baseline measurements reported, -; no change relative to baseline

2.5.1 Active Stress Responses

Three studies included measures of cardiac depolarization (86, 89, 91). The time of ventricular depolarization measured by the QRS complex increased, yet not significantly, during active stress (86). The time of ventricular depolarization to ventricular repolarization, measured by the QT interval was found to shorten significantly in two studies (86, 89), see Table 3. One study (Table 4) found that both the QRS and QT interval reverted towards baseline levels post active stress (86). A variety of indices were used to measure cardiac repolarization. The most common were T-amp, T-area and TWA. T-amp and t-area measure ventricular repolarization and provide different facets of ventricular repolarization. T-amp reflects transmural dispersion of repolarization and T-area is the repolarization across the epicardium only (117-119). TWA measures beat-to-beat fluctuations in the T-wave, and is a diagnostic tool with high negative predictive values for ventricular arrhythmias (120). All six studies measuring cardiac repolarization reported acute stress-induced changes towards proarrhythmic states (86, 35, 87-89, 91), see Table 3. T-wave amplitude increased in patient cohorts with heart disease (86, 87, 89, 91), yet decreased in patient cohorts free of heart disease (91), with similar results for T wave area (86, 89, 91). Active stress increased TWA (88, 89) with significantly larger increases in ICD patients compared to health participants. In addition, the Total Cosine R to T decreased, and the T-Wave Residual (35), the Hill Parameter, and T-wave alterations increased (87) during active stress conditions, all indicating a proarrhythmic change. As seen in table 4, post active stress cardiac repolarization measures were in two studies (86, 88), where T-amp and T-area decreased (86) and TWA remained elevated in ICD patients' compared to controls (88).

2.5.2 Passive Stress Responses

As seen in table 5, two studies included measures of cardiac depolarization during passive stress tasks (89, 114), with both reporting a significant decrease in QT interval, and one finding that the QRS and PR intervals significantly decreased during passive stress tasks (114).

Post passive stress task, the QRS complex and PR intervals increased towards basal values, though, QT interval remained significantly shorter, see Table 6, (114). Two studies measured cardiac repolarization during passive stress tasks (88, 89), both observing TWA increases, with one of the studies also seeing increases in T-amp and T-area, see Table 5 (89). As seen in **Table 5**, TWA remained elevated in ICD patients compared to controls post passive stress (88).

2.5.3 Active vs. Passive Stress

The above studies demonstrate that active and passive stress have similar impacts on the QT interval causing a quicker rate of ventricular depolarization to ventricular repolarization during both stressors. Only one study measured the QRS response to active stress and a separate study measured the passive stress response with seemingly different effects on the time of ventricular depolarization. Additionally, the contrasting QT recovery responses between post active and post passive stress tasks indicate again that active and passive stress may impact arrhythmia etiology differently. Collectively, active and passive stress tasks produce proarrhythmic tendencies in cardiac repolarization, and these proarrhythmic shifts diminished post stress. As per Kop et al (88), active stress appears to induce a larger magnitude of proarrhythmic change compared to passive stress. Of note, evidence suggests that cardiac disease status is a factor in the proarrhythmic vulnerability regardless of stress task type.

Two studies measured arrhythmia type outcome during passive stress tasks (113, 115), with increases in relative bradycardia RB episodes (113) and atrial, ventricular and other dysrhythmias, but decreases in junctional arrhythmias (115). However, it should be noted that both these studies did not report baseline values, thus it is unknown if the quantity of arrhythmic episodes increased, decreased, or did not change relative to baseline (115).

2.6 Hemodynamic Responses

A summary of the reported hemodynamic responses from each study can be found in **Table 6**.

2.6.1 Active Stress Responses

As would be expected, there were active stress-induced increases in HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP), which returned to baseline levels post stress (86, 35, 87, 88, 112, 89-91). Interestingly, one study found no significant difference in stress-induced HR increases between the CAD and control group (91). One study found left ventricular ejection fraction (87), an index of sympathetic activity, and another found cardiac index (CI) (112), a measure of cardiac output relative to body surface area, to significantly increase in response to stress. Additionally, CI decreased towards baseline during the post stress period.

2.6.2 Passive Stress Responses

There was also passive-stress induced increases in HR, SBP, and DBP, which returned to baseline levels post stress (88, 112, 89, 114, 115). One study noted that recovery SBP and DBP remained higher for the ICD group compared to the control group, suggesting that heart disease status may impact the efficiency of blood pressure recovery (88) .

2.6.3 Active vs. Passive Stress

Both stress tasks were associated with significant increases in HR, SBP and DBP. Though three studies used both kinds of tasks, due to the nature of reporting, comparing the magnitude of change between tasks was limited. However, there is a suggestion that active stress tasks may increase the magnitude of hemodynamic change more than passive stress tasks (112).

Table 6 Hemodynamic Measures During and Post Active and Passive Stress Tasks

Author(year)	Group	Measurement Time	Active Stress Task	HR	SBP	DBP	Passive Stress Task	HR	SBP	DBP
Abisse (2011)	All Patients	During	Serial Seven Subtraction	↑↑						
		Post		↓↓						
Critchley (2005)	All Patients	During	Serial Seven Subtraction	↑						
Gray (2007)	All Patients	During	Serial Seven Subtraction	↑	↑	↑				
Kop (2004)	ICD	During	Serial Seven Subtraction	↑	↑	↑	Ironson Anger Recall	↑	↑	↑
		Post		↓	↓	↓		↓	↓*	↓*
	Control	During		↑	↑	↑		↑	↑	↑
		Post		↓	↓	↓		↓	↓	↓
Lache (2007)	All Patients	During	Serial Seven Subtraction	↑	↑	↑	Anger Recall	↑	↑	↑
		Post		↓	↓	↓		↓	↓	↓
Lampert (2005)	All Patients	During**	Serial Seven Subtraction	↑	↑	↑	Anger Recall	↑	↑	↑
Sousza (2013)	All Patients	During	Trier Social Stress Task Speech	↑						
		Post		↓						
		During	Trier Social Stress Task Arithmetic	↑						
		Post		↓						
Taggert (2009)	CAD	During	Serial Seven Subtraction	↑						
	Control			↑						
	CAD	During	Speech	↑						
	Control			↑						
Whinnery (1988)	All Patients	During					**Centrifuge**	↑		
		Post						↓		
Whinnery (1983)	Stress- Panel	During					**Centrifuge**	**?**		
	Dysrhythmia	During						**?**		
	Non-Dysrhythmia	During						**?**		

HR; Heart Rate, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, LVEF; Left Ventricular Ejection Fraction, CI; Cardiac Index, ↑; Increased and no report on significance, ↓; Decreased and no report on significance, ↑↑; increased and significant, ↓↓; decreased and significant *; higher compared to control group, **; based on maximum response out of both tasks and did not distinguish between active and passive stressor ?; no comparison to baseline measurements reported -; no change relative to baseline

2.7 Autonomic Responses

An overview of the autonomic responses to active and passive stress are summarized in **Table 7**.

2.7.1. Active Stress Responses

There was a general suggestion that active stress increased sympathetic drive (86, 35, 112, 89, 90) as demonstrated by increases in epinephrine, norepinephrine, and the ratio of low frequency and high frequency components of heart rate variability (LF/HF) (86, 35, 89). There also seemed to be a parasympathetic withdrawal (121), with stress-induced decreases in HF power (89, 112) and root mean square of successive RR intervals (RMSSD) (90) being observed. The post-stress period was characterised by a still elevated sympathetic drive (86) with a return to normal parasympathetic levels (112, 90).

2.7.2 Passive Stress Responses

As with active stress, the two studies which assessed passive stress (112, 89) indicate that it leads to increased sympathetic drive (increases in epinephrine and norepinephrine) and parasympathetic withdrawal (decreased HF), and that post-stress there was a normalisation of parasympathetic activity (89).

2.7.3 Active vs Passive Stress

Overall, both active and passive stress tasks increased sympathetic stimulation with simultaneous decreases in parasympathetic activity, with no indication of either type of stress having a greater magnitude of change compared to the other during the stress tasks. However, after the removal of active and passive stress stimuli, parasympathetic drive resumed baseline function yet sympathetic stimulation still persisted for active stress, suggesting that active stress has a longer lasting impact on autonomic responses compared to passive stress.

Table 7 Autonomic Measures During and Post Active and Passive Stress Tasks

Author (year)	Group	Measurement Time	Active Stressor	EPI	HF	RMSSD	LF/ HF	NE	Passive Stressor	EPI	HF	RMSSD	NE
Abisse (2011)	All Patients	During	Serial Seven Subtraction	↑↑				↑↑					
		Post		↑↑				↑↑					
Critchley (2005)	All Patients	During	Serial Seven Subtraction				↑						
Lache (2007)	All Patients	During	Serial Seven Subtraction		↓				Anger Recall		↓		
		Post			↑						↑		
Lampert (2005)	All Patients	During	Serial Seven Subtraction	↑	↓*			↑	Anger Recall	↑	↓*		↑
Sousza (2013)	All Patients	During	Serial Seven Subtraction			↓			↑				
		Post				↑			↓				
		During	Trier Social Stress Task Arithmetic			↓			↑				
		Post				↑			↓				

EPI; Epinephrine (pmol/L), HF; High-Frequency component, HF-HRV%; High-Frequency Percentage Heart Rate Variability, HRV; Heart Rate Variability, LF/HF; Low Frequency to High Frequency ratio, NE; Norephinephrine (mmol/L) ↑; Increased and no report on significance, ↓; Decreased, ↑↑; increased and significant ,*; reported maximum response out of both tasks and did not distinguish between active or passive stressor

2.8 Electrocardiographic, Hemodynamic, And Autonomic Relationships During Acute Mental Stress

Relationships between electrocardiographic, hemodynamic, and autonomic responses were assessed. Factors from each of these physiological response systems, that had consistent outcomes in two or more studies were used for this evaluation.

During active stress tasks, observed increases in electrocardiographic responses measured by T-amp, T-area and TWA (88, 89) were associated with increases in hemodynamics, measured by HR, SBP, and DBP (89, 112, 88, 87). These elevated electrocardiographic and hemodynamic responses were associated with increased autonomic responses, measured by higher circulating epinephrine and norepinephrine(86, 89). Additionally, these aforementioned increases correlated with shortened QT intervals (electrocardiographic), and HF component (autonomic) reductions (112, 89, 114). Overall, these interactions demonstrate higher sympathetic drive with corresponding reduction in parasympathetic activity during active stress.

Throughout passive stress tasks, similar relationships were found compared to active stress tasks. Increased electrocardiographic responses represented by TWA, were associated with increased hemodynamic responses (HR, SBP, DBP) and decreased HF component. Although there is less evidence surrounding passive stress task responses, there is still a suggestion that passive stress causes amplified sympathetic activity with a simultaneous decrease in parasympathetic drive.

Correlations between hemodynamic, electrocardiographic and autonomic parameters were unable to be evaluated for post active and post passive active stress conditions due to limited data.

2.9 Discussion

This review's purpose was to assess all available literature on cardiac electrophysiological changes in response to acute mental active and passive stress and the simultaneous hemodynamic and autonomic changes, to better understand how acute stress may contribute to arrhythmia etiology. Overall, both kinds of stress cause shifts in cardiac depolarization and repolarizations towards a proarrhythmic state with simultaneous increases in hemodynamics and sympathetic drive. These influences were more pronounced in diseased hearts. The results also demonstrate that active stress had a larger impact on the magnitude of hemodynamic increase and proarrhythmic change than passive stress. Additionally, the findings indicate that active and passive stress have differential effects on the timing of ventricular depolarization.

2.9.1 Stress Influences on Arrhythmiogenesis

Active stress tasks were associated with cardiac repolarization changes. This is strongly connected to arrhythmias as inhomogeneous repolarization generates electrical instability, temporally and/or spatially, promoting arrhythmiogenic environments (122-125) and preceding arrhythmic episodes in animals and vulnerable patients (126-128). Furthermore, active stress repolarization inhomogeneity has been associated with subsequent arrhythmic events in ICD patients (33), as well as ventricular arrhythmias and SCD (129, 130). Thus, active stress proarrhythmic repolarization changes is a supported link in the pathophysiology of acute mental stress-induced arrhythmiogenicity. However, *why* repolarization inhomogeneity occurs remains unclear, though it is suggested that it is due to shifts in ANS balance (131). Our results reflect this as HR, BP, and catecholamines increased, while QT interval decreased concurrently with repolarization changes, all of which are manifestations of SNS activity. Additionally, there was simultaneous parasympathetic withdrawal as evidenced by the decreases in HF and RMSSD. This kind of ANS pattern has been associated with proarrhythmic repolarization instability and initiating lethal arrhythmias in other studies (132, 98, 133, 88, 89, 134, 135).

In addition to the SNS-PNS balance, the extrinsic and intrinsic cardiac neuroanatomy may also play a role. The extrinsic ANS is the primary relay between the heart and central nervous system, and the intrinsic ANS mediates inter-autonomic cardiac information to the extrinsic ANS (36). Extrinsic cardiac sympathetic nerves are distributed in gradient format, with a higher density in the atria and apex compared to the ventricles(37) while parasympathetic nerves are highly localized around the SAN and AVN, and liberally distributed throughout the atria (37-39). This heterogeneous arrangement of cardiac autonomic nerves is very influential on ANS efferent activity, and spatially effects cardiac repolarization (136). Furthermore, the intrinsic cardiac nervous system functions independently from the extrinsic cardiac nervous system and can produce autonomous chemical and mechanical changes based on efferent input from the extrinsic nervous system (42). Individual intrinsic cardiac nervous system ganglionic plexi not only have local cardiac region influence, but are also capable of remote cardiac effects from overlapping other intrinsic plexes inputs. These inter- and intra–plexes interactions within the intrinsic cardiac nervous system can cause changes in local electrophysiology, ultimately altering cardiac performance, and therefore generating an extremely complex network of feedback loops both *within* and *between* the intrinsic cardiac nervous system and extrinsic cardiac nervous system, which may temporally effect cardiac repolarization (42, 37).

Passive stress tasks demonstrated similar patterns of repolarization changes and concomitant hemodynamic increases, SNS increases, and PNS decreases (88, 89, 112, 114) as active stress. We speculate that alterations in cardiac repolarization from passive stress is mechanistically similar to active stress, except that passive stress did not impact repolarization inhomogeneity as much as active stress. This may be consequence of the brain-heart link and the laterality hypothesis. Brain lateralization influences cardiac control (137) and cortical mapping studies have shown that brain-lateralization has a role in arrhythmiogenesis, with disproportionate mid-brain activation disrupting efferent cardiac activity causing problems in cardiac repolarizations and therefore being proarryhthmic (35, 87). In the context of emotions, it is well established that left and right brain lateralization occurs (138) and that different emotions elicit

distinctive autonomic patterns (139-143). Asymmetric brain activity patterns likely differ in response to active and passive stress. In animal studies, distinctive neural circuits have been identified in active stress and passive stress that are both functionally and anatomically different (144). If this is also the case in humans, then perhaps different cortical processes contribute to a range of phenotypes of ANS imbalances and in turn cause different inhomogeneous repolarization profiles that vary in magnitude. This may explain why it appears that passive stress has less of an arrhythmiogenic foot print than active stress. However, with few studies including passive stress tasks, an assessing their cardiac repolarization effects is limited.

2.9.2 Cardiac Pathology Influences and Arrythmiogenesis

The pathological condition of cardiac tissue may exacerbate these above ANS imbalances making it a potential mediating factor in arrhythmiogenesis. Our results support this as repolarization changes differed between CAD and healthy aged matched participants, for example, there were exaggerated repolarization changes, both in magnitude and duration, in ICD participants compared to healthy participants (88, 91). A plausible explanation for this is cardiac tissue remodelling (57, 145), which causes alterations in the electrical pathway, resulting in heterogeneous repolarizations and increased arrhythmia vulnerability (44). Generally, increased SNS activity is pro-arrhythmic for both atrial and ventricular chambers (45, 132), yet the PNS appears to be pro-arrhythmic only in the atria (146, 147, 81) and anti-arrhythmic in the ventricles (44, 148, 149). Therefore, if cardiac tissue remodelling occurs, then perhaps these differential chamber-dependent arrhythmiogenic effects from each arm of the cardiac ANS are altered and produce a variety of electrophysiological phenotypes. Previous studies have observed that in the presence of a previous injury (e.g., ischemia) or a pre-existing condition (e.g., Long QT Syndrome) the SNS appears to have an intensified proarrhythmic effect as evidenced by changing repolarization duration and magnitude and decreasing the threshold at which fibrillation can occur (150, 151, 57). The apparent exacerbated SNS proarrhythmic influence may be from alteration in cardiac nerve density (152, 153). The autonomic innervation in CAD patients tends to be even more non-uniform, due to nerve damage and regional hyper-innervation, thus

causing excessive uneven sympathetic activity where healthy subjects have relatively evenly increased sympathetic activity due to uniform innervation dispersion (57, 91). Although this difference between patient cohorts was a consistent observation, it was only investigated among a few of the included studies with varying methodology and inconsistent repolarization analysis techniques.

2.10 Limitations and Future Directions

This systematic review provides a broad understanding of the impact of active and passive stress on arrhythmiogenesis, yet there are several limitations to consider. Firstly, there were a limited amount of studies eligible for the review. Secondly, the included studies have small sample sizes. Thirdly, many of the studies were a one group design and lacked control groups, which is evident by the low internal validity–confounding score in the Downs and Black checklist. Fourthly, while most of the studies scored fairly well individually in the reporting sub scale according to Downs and Black, the lack of consistent measures and analyzed physiological indices between studies limit the comparability of results, including an inability to conduct any meaningful meta-analyses. Finally, many of the studies included only active stress tasks, a smaller number included only passive stress tasks, with only a few including both tasks. Among the few studies with analagous methodology, the general outcomes appeared to be consistent. While the general finding is that active stress causes fluctuations in cardiac repolarization that are proarrhythmic, to fully determine the differential role of active and passive stress tasks in arrythmiogenesis, further research is required with larger sample sizes, consistent methodologies, and the use of constant repolarization indices. In spite of the limitations, this review has some notable strengths. Firstly, to the best of our knowledge this is the first systematic review assessing laboratory active stress and passive stress in arrhythmiogenesis. Secondly, the assessment of multiple physiological responses allowed for a broad understanding of the systemic relations and their relevant roles in stress induced arrhythmias. Thirdly, this review addressed gaps within the literature and made recommendations for future research.

Identified gaps within the literature that should be addressed, include: Directly assessing the impact of passive stress on arrhythmias; Comparing the proarrhythmic difference between active and passive stress in the same cohort; and Comparing the difference in the degree of active and passive stress proarrhythmic influences between heart-healthy patients and cardiac patients.

2.11 Conclusion

The findings from this systematic review suggest that acute active and passive stress trigger proarrhythmic shifts in cardiac electrophysiology by altering repolarization homogeneity. This seems to occur via ANS imbalances, specifically, increased SNS activity with simultaneous decreased PNS reactivity, which may be exacerbated by naturally occurring disparities in cardiac neuro-anatomy. The amplified proarrhythmic response within CAD and ICD patients compared to healthy patients, suggests that cardiac tissue pathology acts as a substrate in arrhythmiogenesis. However, the lack of studies including and differentiating results between active and passive stress tasks, the small sample sizes, and inconsistent analysis techniques weakens the strength of these conclusions. It would be beneficial for future studies to include more passive stress tasks and focus on investigating the different electrophysiological, autonomic, and hemodynamic effects arising from active and passive stress tasks to advance the knowledge of underlying arrhythmiogenic mechanisms.

3.0 References

1. M. J, S. B. Heart Failure. New England Journal of Medicine. 2003;348:2007-18.
2. McMurray J, Pfeffer, MA. Heart Failure. The Lancet. 2005;365:1877-89.
3. Anzelevitch C, Burashnikov, A. Overview of Basic Mechanisms of Cardiac Arrhythmia. Cardiac Electrophysiology Clinics. 2011;3:23-45.
4. Desaulniers P. Cardiovascular and Respiratory Physiology Laboratory Manual. [Laboratory Manual]. In press 2013.
5. Keroes J, Erikson, B., Lieberman, D., Wrigley, D., Mazzini, M., O'Brien, T., French, W.,. Practical Clinical Skills: EKG 2019 [cited 2016 March 01].
6. Sekar RP. Epidemiology of arrhythmias in children. Indian pacing and electrophysiology journal. 2008;8:S13.
7. Chow GV, Marine JE, Fleg JL. Epidemiology of arrhythmias and conduction disorders in older adults. Clinics in geriatric medicine. 2012;28:539-53.
8. Gillespie H, Lin C, Prutkin J. Arrhythmias in Structural Heart Disease. Current Cardiology Reports. 2014;16:1-10.
9. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent Risk Factors for Atrial Fibrillation in a Population-Based Cohort: The Framingham Heart Study. JAMA. 1994;271:840-4.
10. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaëlsson K, Sundström J. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. European heart journal. 2013;34:3624-31.
11. Peacock J, Whang W. Psychological Distress and Arrhythmia: Risk Prediction and Potential Modifiers. Progress in Cardiovascular Diseases. 2013;55:582-9.
12. Chugh SS, Kelly KL, Titus JL. Sudden cardiac death with apparently normal heart. Circulation. 2000;102:649-54.
13. Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. J Cardiovasc Electrophysiol. 2002;13:709-23.
14. Steptoe A, Kivimäki M. Stress and cardiovascular disease: an update on current knowledge. Annual review of public health. 2013;34:337-54.
15. Zipes DP, Wellens HJJ. Sudden Cardiac Death. Circulation. 1998;98:2334-51.
16. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y, American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117:e25-146.
17. Myerburg, Rj, Castellanos A. Cardiac Arrest and Sudden Cardiac Death. Braunwalds Heart Disease: A Textbook of Cardiovascular Medicine2012. p. 845-84.
18. Srinivasin N, Schilling, R. Sudden Cardiac Death and Arrhythmias. Arrhythmia & Electrophysiology Review. 2018;7:111-7.
19. Chugh S, Reinier, K., Teodorescu, C. et al. . Epidemiology of Sudden Cardiac Death: Clinical and Research Implications. Progress in Cardiovascular Diseases. 2008;51:213-25.
20. Adabag A, Luepker, RV., Roger VL., Gersh, BJ. . Sudden Cardiac Death: Epidemiology and Risk Factors. Nature Reviews Cardiology. 2010;7:216-25.
21. Committee NRCU. Recognition and Alleviation of Distress in Laboratory Animals. Washington, DC: National Academies Press (US); 2008. Available from: https://www.ncbi.nlm.nih.gov/books/NBK4027/.
22. Cohen S, Kessler, RC., Underwood, LG. . Measuring Stree: A Guide for Health and Social Scientists. New York: Oxford University Press; 1995.

23. Carroll L. Active Coping. In: M.D. Gellman JRT, editor. Encylopedia of Behavioral Medicine. New York: Springer New York; 2013. p. 21.
24. Plourde A, Lavoie KL, Raddatz C, Bacon SL. Effects of acute psychological stress induced in laboratory on physiological responses in asthma populations: A systematic review. Respir Med. 2017;127:21-32.
25. Sherwood A, Dolan CA, Light KC. Hemodynamics of blood pressure responses during active and passive coping. Psychophysiology. 1990;27:656-68.
26. Carroll L. Passive Coping Strategies. In: M.D. Gellman JRT, editor. Encyclopedia of Behavioural Medicine. Ne York: Springer New York; 2013. p. 1442-.
27. Suzuki SI, Ito D. Psychological Stress. 2013.
28. Steptoe A. Stress Resposivity and Socioeconomic Status: A Mechanism for Increased Cardiovascular Disease Risk? European heart journal. 2002;23:1757-63.
29. Chida Y, Steptoe A. Greater Cardiovascular Responses to Laboratory Mental Stress Are Associated With Poor Subsequent Cardiovascular Risk Status: A Meta-Analysis of Prospective Evidence. Hypertension. 2010;55:1026-32.
30. Dimsdale JE. Psychological Stress and Cardiovascular Disease. Journal of the American College of Cardiology. 2008;51:1237-46.
31. Lampert R, Joska T, Burg MM, Batsford WP, McPherson CA, Jain D. Emotional and physical precipitants of ventricular arrhythmia. Circulation. 2002;106:1800-5.
32. Steinberg JS, Arshad A, Kowalski M, Kukar A, Suma V, Vloka M, Ehlert F, Herweg B, Donnelly J, Philip J, Reed G, Rozanski A. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. J Am Coll Cardiol. 2004;44:1261-4.
33. Lampert R, Shusterman V, Burg M, McPherson C, Batsford W, Goldberg A, Soufer R. Anger-induced T-wave alternans predicts future ventricular arrhythmias in patients with implantable cardioverter-defibrillators. J Am Coll Cardiol. 2009;53:774-8.
34. Fries R, Konig J, Schafers HJ, Bohm M. Triggering effect of physical and mental stress on spontaneous ventricular tachyarrhythmias in patients with implantable cardioverter-defibrillators. Clin Cardiol. 2002;25:474-8.
35. Critchley HD, Taggart P, Sutton PM, Holdright DR, Batchvarov V, Hnatkova K, Malik M, Dolan RJ. Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism. Brain. 2005;128:75-85.
36. Kawashima T. The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. Anat Embryol (Berl). 2005;209:425-38.
37. Fukuda K, Kanazawa H, Aizawa Y, Ardell JL, Shivkumar K. Cardiac innervation and sudden cardiac death. Circ Res. 2015;116:2005-19.
38. Gabella G. Structure of the Autonomic Nervous System. 1 ed. Dordrecht: Springer; 1976.
39. Levick JR. An Introduction to Cardiovascular Physiology. GB: Butterworth Heinemann; 1991.
40. Shen M, Zipes D. Role of the Autonomic Nervous System in Modulating Cardiac Arrhythmias. Circulation Research. 2014;114:1004-21.
41. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. The Anatomical Record. 2000;259:353-82.
42. Wake E, Brack K. Characterization of the intrinsic cardiac nervous system. Auton Neurosci. 2016;199:3-16.
43. McEachern CG, Manning GW, Hall GE. SUDDEN OCCLUSION OF CORONARY ARTERIES FOLLOWING REMOVAL OF CARDIOSENSORY PATHWAYS: AN EXPERIMENTAL STUDY. Archives of Internal Medicine. 1940;65:661-70.
44. Martins JB, Zipes DP. Effects of sympathetic and vagal nerves on recovery properties of the endocardium and epicardium of the canine left ventricle. Circ Res. 1980;46:100-10.
45. Gilmour RF. Modulation of Cardiac Arrhythmias by the Autonomic Nervous System.

46. Tan A, Zhou, S., Ogawa, M. et al. Neural Mechanisms of Paroxysmal Atrial Fibrillation and Paroxysmal Atrial Tachycardia in Ambulatory Canines. Circulation. 2008;118:1772-9.
47. Ogawa M, Tan, AY., Song, J. et al. . Cryoblation of Stellate Ganglia and Atrial Arrhythmia in Ambulatory Dogs with Pacing-Induced Heart Failure. Heart Rhythm. 2009;6:1772-9.
48. Amar D, Zhang, H., Miodownik, S., Kadish, AH. Competing Autonomic Mechanisms Precede the Onset of Postoperative Atrial Fibrillation. Journal of American College of Cardiology. 2003;42:1262-8.
49. Bettoni M. Autonomic Tone Variations Before the Onset of Paroxysmal Atrial Fibrillation. Circulation. 2002;105.
50. Tomita T, Takei, M., Saikawa, Y. et a. Role of Autonomic Tone in the Initiation and Termination of Paroxysmal Atrial Fibrillation in Patients without Structural Heart Disease. Journa of Cardiovascular Electrophysiology. 2003;14:559-64.
51. Yanowitz F, Preston, JB., Abildskov, JA. Functional Distributation of Right and Left Stellate Innervation to the Ventricles: Production of Neurogenic Electrocardiographs changes by Unilateral Alteration of Sympathetic Tone. Circulation Research.18:416-28.
52. Zhou S, Jung, B-C., Tan, AY. et al. . Spontaneous stellate ganglion nerve activity and ventricular arrhythmia in a canine model of sudden death. Heart Rhythm. 2008;5:131-9.
53. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. Journal of the American College of Cardiology. 1996;27:1061-70.
54. Abe AMD, Ikeda TMDF, Tsukada TMD, Ishiguro HMD, Miwa YMD, Miyakoshi MMD, Mera HMD, Yusu SMD, Yoshino HMD. Circadian variation of late potentials in idiopathic ventricular fibrillation associated with J waves: Insights into alternative pathophysiology and risk stratification. Heart Rhythm. 2010;7:675-82.
55. Mizumaki KMD, Nishida KMD, Iwamoto JMD, Nakatani YMD, Yamaguchi YMD, Sakamoto TMD, Tsuneda TMD, Kataoka NMD, Inoue HMD. Vagal activity modulates spontaneous augmentation of J-wave elevation in patients with idiopathic ventricular fibrillation. Heart Rhythm. 2012;9:249-55.
56. Dukes I, Wiliams, EMV. Effects of selective alpha 1-, alpha 2-,beta-1-and beta 2- adrenoceptor stimulation on potentials and contractions in the rabbit heart. The Journal of physiology. 1984;355:523-46.
57. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J Clin Invest. 2005;115:2305-15.
58. Barber M, Mueller, T M, Henry, DP., Felten, SY., Zipes, DP. Transmural myocardial infarction in the dog produces sympathectomy in noninfarcted myocardium. Circulation. 1983;67:787-96.
59. Ziegler M. Psychological Stress and the Autonomic Nervous System. Primer on the Autonomic Nervous System: Elsevier; 2012.
60. Carroll D, Phillips AC, Balanos GM. Metabolically exaggerated cardiac reactions to acute psychological stress revisited. Psychophysiology. 2009;46:270-5.
61. Cacioppo JT. Social neuroscience: autonomic, neuroendocrine, and immune responses to stress. Psychophysiology. 1994;31:113-28.
62. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol. 2003;24:151-80.
63. Obrist PA. Cardiovascular Psychophysiology : a perspective. 1 ed. United States: Springer US; 1981.
64. Ring C, Harrison LK, Winzer A, Carroll D, Drayson M, Kendall M. Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: effects of alpha-adrenergic blockade. Psychophysiology. 2000;37:634-43.
65. Winzer A, Ring C, Carroll D, Willemsen G, Drayson M, Kendall M. Secretory immunoglobulin A and cardiovascular reactions to mental arithmetic, cold pressor, and exercise: effects of beta-adrenergic blockade. Psychophysiology. 1999;36:591-601.
66. Craft J, Gordon, C., Tiziani, A. Understanding pathophysiology. Chatswood, N.S.W.: Elsevier Australia; 2011.

67. Antzelevitch C, Burashnikov A. Overview of Basic Mechanisms of Cardiac Arrhythmia. Card Electrophysiol Clin. 2011;3:23-45.
68. Lip GY. Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why? Eur Heart J. 2013;34:1041-9.
69. Albert CM, Stevenson WG. The Future of Arrhythmias and Electrophysiology. Circulation. 2016;133:2687-96.
70. Grace AA, Roden DM. Systems biology and cardiac arrhythmias. The Lancet. 2012;380:1498-508.
71. Deyell MW, Krahn AD, Goldberger JJ. Sudden cardiac death risk stratification. Circ Res. 2015;116:1907-18.
72. Stamler JS, Goldman ME, Gomes J, Matza D, Horowitz SF. The effect of stress and fatigue on cardiac rhythm in medical interns. J Electrocardiol. 1992;25:333-8.
73. Kirby DA, Pinto JM, Hottinger S, Johnson DA, Lown B. Behavioral arousal enhances inducibility and rate of ventricular tachycardia. Am J Physiol. 1991;261:H1734-9.
74. Reich P. Psychological predisposition to life-threatening arrhythmias. Annu Rev Med. 1985;36:397-405.
75. Reich P, DeSilva RA, Lown B, Murawski BJ. Acute psychological disturbances preceding life-threatening ventricular arrhythmias. JAMA. 1981;246:233-5.
76. Lecomte D, Fornes P, Nicolas G. Stressful events as a trigger of sudden death: a study of 43 medico-legal autopsy cases. Forensic Science International. 1996;79:1-10.
77. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med. 1996;334:413-9.
78. Meisel SR, Kutz I, Dayan KI, Pauzner H, Chetboun I, Arbel Y, David D. Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. Lancet. 1991;338:660-1.
79. Myers A, Dewar HA. Circumstances attending 100 sudden deaths from coronary artery disease with coroner's necropsies. Br Heart J. 1975;37:1133-43.
80. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. N Engl J Med. 1984;311:552-9.
81. Zipes DP, Mihalick MJ, Robbins GT. Effects of selective vagal and stellate ganglion stimulation of atrial refractoriness. Cardiovasc Res. 1974;8:647-55.
82. Stopper MM, Jain D, Burg M, Joska T, McPherson C, Batsford W, Lampert R. Electrophysiological characteristics of anger-triggered arrhythmias. Heart Rhythm. 2005;2:S162-S3.
83. Hansson A, Madsen-Hardig B, Olsson SB. Arrhythmia-provoking factors and symptoms at the onset of paroxysmal atrial fibrillation: a study based on interviews with 100 patients seeking hospital assistance. BMC Cardiovasc Disord. 2004;4:13.
84. Heuther S, McCance KL. Understanding pathophysiology. fourth ed. USA: Mosby Elsevier; 2008.
85. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
86. Abisse SS, Lampert R, Burg M, Soufer R, Shusterman V. Cardiac repolarization instability during psychological stress in patients with ventricular arrhythmias. J Electrocardiol. 2011;44:678-83.
87. Gray MA, Taggart P, Sutton PM, Groves D, Holdright DR, Bradbury D, Brull D, Critchley HD. A cortical potential reflecting cardiac function. Proc Natl Acad Sci U S A. 2007;104:6818-23.
88. Kop WJ, Krantz DS, Nearing BD, Gottdiener JS, Quigley JF, O'Callahan M, DelNegro AA, Friehling TD, Karasik P, Suchday S, Levine J, Verrier RL. Effects of acute mental stress and exercise on T-wave alternans in patients with implantable cardioverter defibrillators and controls. Circulation. 2004;109:1864-9.
89. Lampert R, Shusterman V, Burg MM, Lee FA, Earley C, Goldberg A, McPherson CA, Batsford WP, Soufer R. Effects of psychologic stress on repolarization and relationship to autonomic and hemodynamic factors. J Cardiovasc Electrophysiol. 2005;16:372-7.

90. Souza GG, Magalhaes LN, Cruz TA, Mendonca-De-Souza AC, Duarte AF, Fischer NL, Souza WF, Coutinho Eda S, Vila J, Gleiser S, Figueira I, Volchan E. Resting vagal control and resilience as predictors of cardiovascular allostasis in peacekeepers. Stress. 2013;16:377-83.
91. Taggart P, Batchvarov VN, Sutton P, Young G, Young S, Patterson D. Repolarization changes induced by mental stress in normal subjects and patients with coronary artery disease: effect of nitroglycerine. Psychosom Med. 2009;71:23-9.
92. Adams SL, Roxe DM, Weiss J, Zhang F, Rosenthal JE. Ambulatory Blood Pressure and Holter Monitoring of Emergency Physicians before, during, and after a Night Shift. Academic Emergency Medicine. 1998;5:871-7.
93. Alijani A, Hanna GB, Band M, Struthers AD, Cuschieri A. Cardiovascular autonomic function in patients with hemodynamic instability at induction of capnoperitoneum: a case-control study. Surg Endosc. 2004;18:915-8.
94. MacKenzie MA, Aengevaeren WR, Hermus AR, Van Der Werf T, Pieters GF, Smals AG, Kloppenborg PW. Electrocardiographic changes during steady mild hypothermia and normothermia in patients with poikilothermia. Clin Sci (Lond). 1992;82:39-45.
95. Madias C, Fitzgibbons TP, Alsheikh-Ali AA, Bouchard JL, Kalsmith B, Garlitski AC, Tighe DA, Estes NA, 3rd, Aurigemma GP, Link MS. Acquired long QT syndrome from stress cardiomyopathy is associated with ventricular arrhythmias and torsades de pointes. Heart Rhythm. 2011;8:555-61.
96. Niederseer D, Thaler CW, Egger A, Niederseer MC, Ploderl M, Niebauer J. Watching soccer is not associated with an increase in cardiac events. Int J Cardiol. 2013;170:189-94.
97. Pauli P, Hartl L, Marquardt C, Stalmann H, Strian F. Heartbeat and arrhythmia perception in diabetic autonomic neuropathy. Psychol Med. 1991;21:413-21.
98. Shusterman V, Goldberg A, London B. Upsurge in T-wave alternans and nonalternating repolarization instability precedes spontaneous initiation of ventricular tachyarrhythmias in humans. Circulation. 2006;113:2880-7.
99. Stevenson IP, Duncan CH, et al. Life situations, emotions, and extrasystoles. Psychosom Med. 1949;11:257-72.
100. Tipton MJ, Gibbs P, Brooks C, Roiz de Sa D, Reilly TJ. ECG during helicopter underwater escape training. Aviat Space Environ Med. 2010;81:399-404.
101. Follick MJ, Ahern DK, Gorkin L, Niaura RS, Herd JA, Ewart C, Schron EB, Kornfeld DS, Capone RJ. Relation of psychosocial and stress reactivity variables to ventricular arrhythmias in the Cardiac Arrhythmia Pilot Study (CAPS). Am J Cardiol. 1990;66:63-7.
102. Forbes LM, Chaney RH. Physical arousal concealed during emotional stress. Psychol Rep. 1978;42:355-60.
103. Lampert R, Jain D, Burg MM, Batsford WP, McPherson CA. Destabilizing effects of mental stress on ventricular arrhythmias in patients with implantable cardioverter-defibrillators. Circulation. 2000;101:158-64.
104. Russell DC, Smith TL, Krahn DD, Graskamp P, Singh D, Kolden GG, Sigmund H, Zhang Z. Effects of Cognitive Behavioral Stress Management on Negative Mood and Cardiac Autonomic Activity in ICD Recipients. Pacing Clin Electrophysiol. 2015;38:951-65.
105. Taggart P, Sutton P, Redfern C, Batchvarov VN, Hnatkova K, Malik M, James U, Joseph A. The effect of mental stress on the non-dipolar components of the T wave: modulation by hypnosis. Psychosom Med. 2005;67:376-83.
106. Hanada R, Hisada T, Tsujimoto T, Ohashi K. Arrhythmias observed during high-G training: proposed training safety criterion. Aviat Space Environ Med. 2004;75:688-91.
107. Mietla B. Links between parameters of long term memory and progression from paroxysmal to permanent atrial fibrillation during a five year observation period. A preliminary study.
108. Lampert R. ECG signatures of psychological stress. J Electrocardiol. 2015;48:1000-5.
109. Lampert R. Behavioral influences on cardiac arrhythmias. Trends Cardiovasc Med. 2016;26:68-77.

110. Frankel DS. Ventricular arrhythmias after cardiac surgery: failing the stress test. J Am Coll Cardiol. 2012;60:2672-3.
111. Ziegelstein RC. Acute emotional stress and cardiac arrhythmias. JAMA. 2007;298:324-9.
112. Lache B, Meyer T, Herrmann-Lingen C. Social support predicts hemodynamic recovery from mental stress in patients with implanted defibrillators. J Psychosom Res. 2007;63:515-23.
113. Suresh R, Blue RS, Mathers CH, Castleberry TL, Vanderploeg JM. Dysrhythmias in Laypersons During Centrifuge-Simulated Suborbital Spaceflight. Aerosp Med Hum Perform. 2017;88:1008-15.
114. Whinnery CC, Whinnery JE. Acceleration-induced electrocardiographic interval changes. Aviat Space Environ Med. 1988;59:102-6.
115. Whinnery JE. Dysrhythmia comparison in apparently healthy males during and after treadmill and acceleration stress testing. Am Heart J. 1983;105:732-7.
116. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology & Community Health. 1998;52:377-84.
117. Fuller MS, Sándor Gr, Punske B, Taccardi B, MacLeod RS, Ershler PR, Green LS, Lux RL. Estimates of Repolarization Dispersion From Electrocardiographic Measurements. Circulation. 2000;102:685-91.
118. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation. 1998;98:1928-36.
119. Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. J Am Coll Cardiol. 1995;25:746-52.
120. Narayan SM. T-wave alternans and the susceptibility to ventricular arrhythmias. J Am Coll Cardiol. 2006;47:269-81.
121. Garabedian C, Champion C, Servan-Schreiber E, Butruille L, Aubry E, Sharma D, Logier R, Deruelle P, Storme L, Houfflin-Debarge V, De Jonckheere J. A new analysis of heart rate variability in the assessment of fetal parasympathetic activity: An experimental study in a fetal sheep model. PLoS One. 2017;12:e0180653.
122. Batchvarov V, Hnatkova K, Ghuran A, Poloniecki JAN, Camm AJ, Malik M. Ventricular Gradient as a Risk Factor in Survivors of Acute Myocardial Infarction. Pacing and Clinical Electrophysiology. 2003;26:373-6.
123. Han J, Moe GK. Nonuniform Recovery of Excitability in Ventricular Muscle. Circ Res. 1964;14:44-60.
124. Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. Circulation. 1983;67:1356-67.
125. Antzelevitch C. Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes. Am J Physiol Heart Circ Physiol. 2007;293:H2024-38.
126. Nearing BD, Verrier RL. Progressive increases in complexity of T-wave oscillations herald ischemia-induced ventricular fibrillation. Circ Res. 2002;91:727-32.
127. Verrier RL, Kumar K, Nearing BD. Basis for sudden cardiac death prediction by T-wave alternans from an integrative physiology perspective. Heart Rhythm. 2009;6:416-22.
128. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med. 1994;330:235-41.
129. Gold MR, Bloomfield DM, Anderson KP, El-Sherif NE, Wilber DJ, Groh WJ, Estes NA, 3rd, Kaufman ES, Greenberg ML, Rosenbaum DS. A comparison of T-wave alternans, signal averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. J Am Coll Cardiol. 2000;36:2247-53.
130. Aro AL, Kentta TV, Huikuri HV. Microvolt T-wave Alternans: Where Are We Now? Arrhythm Electrophysiol Rev. 2016;5:37-40.

131. Conrath CE, Opthof T. Ventricular repolarization: an overview of (patho)physiology, sympathetic effects and genetic aspects. Prog Biophys Mol Biol. 2006;92:269-307.
132. Shusterman V, Aysin B, Gottipaty V, Weiss R, Brode S, Schwartzman D, Anderson KP. Autonomic nervous system activity and the spontaneous initiation of ventricular tachycardia. ESVEM Investigators. Electrophysiologic Study Versus Electrocardiographic Monitoring Trial. J Am Coll Cardiol. 1998;32:1891-9.
133. Brodsky MA, Sato DA, Iseri LT, Wolff LJ, Allen BJ. Ventricular tachyarrhythmia associated with psychological stress. The role of the sympathetic nervous system. JAMA. 1987;257:2064-7.
134. Schwartz PJ. The rationale and the role of left stellectomy for the prevention of malignant arrhythmias. Ann N Y Acad Sci. 1984;427:199-221.
135. Schwartz PJ, Zipes DP. Autonomic modulation of cardiac arrhythmias in Cardiac Electrophysiology. From Cell to Bedside. In: Zipes DP, J J, editors. 4th ed. Philadelphia: W.B. Saunders; 2004. p. 300-14.
136. Franciosi S, Perry FKG, Roston TM, Armstrong KR, Claydon VE, Sanatani S. The role of the autonomic nervous system in arrhythmias and sudden cardiac death. Auton Neurosci. 2017;205:1-11.
137. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992;42:1727-32.
138. Craig AD. Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn Sci. 2005;9:566-71.
139. Ekman P, Levensom RW, Friesen WV. Autonomic nervous system activity distinguishes among emotions. Science. 1983;221:1208-10.
140. Levensom RW, Ekman P, Friesen WV. Voluntary facial action generated emotion-specific autonomic nervous system activity. Psychophysiology. 1990;27:363-84.
141. Christie IC, Friedman BH. Autonomic specificity of discrete emotion and dimension of affective space: a multivariate approach. International Journal of Psychophysiology. 2004;51:143-53.
142. Rainville P, Bechara A, Naqvi N, Damasio AR. Basic emotions are associated with distinct patterns of cardiorespiratory activity. Int J Psychophysiol. 2006;61:5-18.
143. Friedman BH, Thayer JF. Autonomic balance revisted: panic anxiety and heart rate variability. Journal of Psychosomatic Research. 1998;44:133-51.
144. Bandler R, Keay KA, Floyd N, Price J. Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. Brain Res Bull. 2000;53:95-104.
145. Vaseghi M, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. Prog Cardiovasc Dis. 2008;50:404-19.
146. Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. Circulation. 1998;98:2202-9.
147. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92:1954-68.
148. Ng GA, Brack KE, Coote JH. Effects of direct sympathetic and vagus nerve stimulation on the physiology of the whole heart--a novel model of isolated Langendorff perfused rabbit heart with intact dual autonomic innervation. Exp Physiol. 2001;86:319-29.
149. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS, Jr., Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res. 1991;68:1471-81.
150. Bloomfield DM, Steinman RC, Namerow PB, Parides M, Davidenko J, Kaufman ES, Shinn T, Curtis A, Fontaine J, Holmes D, Russo A, Tang C, Bigger JT, Jr. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation. 2004;110:1885-9.

151. Opthof T, Misier AR, Coronel R, Vermeulen JT, Verberne HJ, Frank RG, Moulijn AC, van Capelle FJ, Janse MJ. Dispersion of refractoriness in canine ventricular myocardium. Effects of sympathetic stimulation. Circ Res. 1991;68:1204-15.
152. Cao JM, Chen LS, KenKnight BH, Ohara T, Lee MH, Tsai J, Lai WW, Karagueuzian HS, Wolf PL, Fishbein MC, Chen PS. Nerve sprouting and sudden cardiac death. Circ Res. 2000;86:816-21.
153. Swissa M, Zhou S, Gonzalez-Gomez I, Chang CM, Lai AC, Cates AW, Fishbein MC, Karagueuzian HS, Chen PS, Chen LS. Long-term subthreshold electrical stimulation of the left stellate ganglion and a canine model of sudden cardiac death. J Am Coll Cardiol. 2004;43:858-64.

4.0 APPENDIX A: Study Quality Assessment

Table.1 Study Quality Assessment for Included Studies

First Author (year)	Reporting (10)	External Validity (2)	Internal Validity Bias (4)	Internal Validity Confounding Selection Bias (4)	Power (1)	Total (21)
Abisse (2011)	9	0	3	2	0	14
Critchley (2005)	7	2	3	0	0	12
Gray (2007)	7	2	3	0	0	12
Kop (2004)	7	0	3	1	0	11
Lache (2007)	7	2	3	1	0	13
Lambert (2005)	6	0	3	0	0	9
Souza (2013)	6	2	3	0	0	11
Suresh (2017)	9	1	4	3	1	18
Taggart (2009)	7	2	4	3	0	16
Whinnery (1988)	6	2	3	0	0	11
Whinnery (1983)	6	2	4	2	0	14

Studies were assessed for risk of bias using a modified version of Downs & Black checklist. Items 13, 15, 19, 23 and 24 were not used as they applied to studies with interventions and/or treatments, leaving a possible 21 points for scoring

4.1 APPENDIX B: Data search strategies presented by database

PubMed

In Advanced Search Builder

Choose **Title/Abstract** for all search words

Search Term #1: Acute Mental stress **OR** Acute Psychological Stress **OR** Acute Stress **OR** Mental Stress **OR** psychological stress **OR** Stress **OR** Stress Reactivity **OR** Stress Response **OR** Stressor

Search Term #2: Arrhythmia **OR** Atrial fibrillation **OR** Atrial flutter **OR** Conductance disorder **OR** Couplet **OR** Dysrhythmia **OR** Heart Rate Variability **OR** Triplet

Search Term #3: Combine *Search Term #1* **AND** *Search Term #2*

PsycINFO

Advanced Search

Choose **Abstract** for all search words

Search Term #1: Acute Mental stress **OR** Acute Psychological Stress **OR** Acute Stress **OR** Mental Stress **OR** psychological stress **OR** Stress **OR** Stress Reactivity **OR** Stress Response **OR** Stressor

Search Term #2: Arrhythmia **OR** Atrial fibrillation **OR** Atrial flutter **OR** Conductance disorder **OR** Couplet **OR** Dysrhythmia **OR** Heart Rate Variability **OR** Triplet

Search Term #3: Combine *Search Term#1* **AND** *Search Term #2*

Scopus

Search

Choose **Article title, Abstract, Keywords** for all search words

Search Term #1: Acute Mental stress **OR** Acute Psychological Stress **OR** Acute Stress **OR** Mental Stress **OR** psychological stress **OR** Stress **OR** Stress Reactivity **OR** Stress Response **OR** Stressor

Search Term #2: Arrhythmia **OR** Atrial fibrillation **OR** Atrial flutter **OR** Conductance disorder **OR** Couplet **OR** Dysrhythmia **OR** Heart Rate Variability **OR** Triplet

Search Term #3: Combine queries *#1* **AND** *#2*

4.2 APPENDIX C: Figure Use Permission

4.2.1 **Figure 1** Significant Structures for the Electrical Conduction of the Heart ***Permission***

Candace Bell April 23, 2019 at 4:35 PM
To: patrice.desaulniers@concordia.ca Details

Dear Dr. Desaulniers,

I am a master's student at Concordia University (Montreal, Quebec, Canada) and am currently writing a systematic review titled *Investigating the Individual Influences of Acute Physical and Acute Mental Stress on Adult Arrhythmiogenesis* with Dr. Simon Bacon. I am requesting permission for use of figure labeled Significant Structures for the Electrical Conduction of the Heart, in the Cardiovascular and Respiratory Physiology Laboratory Manual from EXCI 259.

Thank you,

Candace

Candace Bell, MSc.C
Department of Health, Kinesiology and Applied Physiology
Concordia University, Montreal Quebec
Montreal Behavioural Medicine Centre (MBMC)
http://mbmc.cmcm.ca/
Hôpital du Sacré- Coeur de Montréal- Research Center

Patrice Desaulniers April 24, 2019 at 3:55 PM
RE: Figure Reprint Permission
To: Candace Bell

New contact info found in this email: Patrice Desaulniers patrice.desaulniers@concordia.ca add...

Hi Candace,

I spoke with the author of the manual, and she does not see a problem with you using that figure. That said, if this is going to be used for a published review or equivalent, please let me know.

Patrice

Patrice Desaulniers, Ph.D.
Technical Officer / Neuromuscular Physiologist
Department of Health, Kinesiology and Applied Physiology
Concordia University
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Science Pavilion Room 165-15
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Cell: (514) 462-1395
Fax: (514) 848-8681
e-mail: patrice.desaulniers@concordia.ca

4.2.2 **Figure 2.** Summary of Arrhythmias ***Permission***

Candace Bell Yesterday at 3:44 PM

To: comments@practicalclinicalskills.com Details

CB

To Whom it May Concern,

I am a Masters student at Concordia University (Montreal, Quebec Canada) and am writing a thesis entitled *Investigating the Physiological Influences of Acute Mental Stress on Adult Arrhythmiogenesis*. As part of the thesis I am including a figure and I am requesting permission to use the EKG figures for the following arrhythmias from your website https://www.practicalclinicalskills.com/ekg-reference;

Premature Atrial Complex
Atrial Fibrillation
Atrial Flutter
Supraventricular Tachycardia
Wolf-Parkinson Syndrome
Premature Ventricular Complex
Ventricular Fibrillation
Ventricular Tachycardia
Sinus Bradycardia

Of course proper reference and credit will be given in the citations and bibliography. This thesis will only be in an electronic format and will not be printed or distributed.

Thank you for your time and consideration,

Candace Bell, MSc.C
Department of Health, Kinesiology and Applied Physiology
Concordia University, Montreal Quebec
Montreal Behavioural Medicine Centre (MBMC)
http://mbmc.cmcm.ca/
Hôpital du Sacré- Coeur de Montréal- Research Center

comments comments Yesterday at 11:28 PM

Re: Figure Use Permission

To: Candace Bell

CC

We agree with your request and give our premission for such use.

Bill Kania
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4.2.3 **Figure 3.** Cardiac Autonomic Innervation ***Permission***

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4.2.4 **Figure 4.** Ganglionic Plexi (GP) of Human Heart ***Permission***

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