

## Anxiety, Autonomic Control of the Heart, and Cardiac Dysrhythmogenesis in Patients with Acute Coronary Syndrome

Mohannad E. AbuRuz, PhD, RN

Nursing Education and Development Department. King Fahad Specialist Hospital-Dammam-KSA  
[mohannadeid@yahoo.com](mailto:mohannadeid@yahoo.com)

**Abstract:** Coronary heart disease (CHD) is the number one killer in the United States. Acute coronary syndrome (ACS) is the primary consequence of CHD. Anxiety is very common among ACS patients and has been shown to affect their outcomes. High anxiety levels are associated with more cardiac complications and poor quality of life. To date, the mechanisms by which anxiety enhances these complications are not clear. In this review, we will discuss: First, the basics of the cardiac conduction system and the effect of the autonomic nervous system on cardiac function; second a review of the relationship among anxiety, ACS, and cardiac dysrhythmias; third, an amplification of the mechanisms of cardiac dysrhythmias early after ACS; and fourth a clarification of the relationship among anxiety, heart rate variability and dysrhythmias after ACS.

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### 1. Introduction

Despite improvements in the treatment of cardiovascular diseases, coronary heart disease (CHD) remains the number one cause of death in the United States and is predicted to become the number one cause of death worldwide by the year 2020. (Chockalingam et al. 2000; Go et al 2013.; Reddy et al. 1998) Acute coronary syndrome (ACS) the primary consequence of CHD is a spectrum of cardiovascular conditions that include angina, non-Q wave and Q-wave myocardial infarction. (Go et al. 2013; Yeghiazarians et al. 2000) Approximately every 44 seconds, an American will have an MI. It is estimated that 1.2 million Americans will have a new or recurrent acute myocardial infarction (AMI) in the year 2013. (Go et al. 2013) Of these, approximately 340,000 will die prior to hospitalization or in the emergency department. Most of these deaths are sudden cardiac deaths due to asystole resulting from ventricular fibrillation or ventricular tachycardia. (Go et al. 2013) For those who initially survive, future morbidity will be 15 times higher than the general population. (Go et al. 2013)

Anxiety is the earliest, most common psychological response to ACS including AMI. (Crowe et al. 1996; Herrmann et al. 2000; Januzzi et al. 2000; Ketterer et al. 2004; Kubzansky et al. 1998; Malan 1992; Moser et al. 1996) In patients suffering ACS the prevalence of anxiety may be as high as 70-80%. (Abu Ruz et al. 2010; Abu Ruz et al. 2011; Crowe et al. 1996; Moser & Dracup 1996) This anxiety stems from fear of death, a strange intensive care unit environment, loss of personal control, unpredictable consequences, diagnostic or therapeutic procedures,

cost of treatment, and potential inability to return to work. (Abu Ruz et al. 2010; Abu Ruz et al. 2011.; Moser & Dracup 1996) Anxiety has been shown to significantly impact recovery during hospitalization for AMI and to increase the severity of chest pain in anginal patients. (Bengtson et al. 1996; Costa et al. 1985; Crowe et al. 1996; Davies et al. 1993; Ketterer et al. 2000) Patients with high anxiety during the first 48 hours after AMI have up to 6 times higher risk of developing in-hospital complications such as reinfarction, recurrent ischemia, ventricular fibrillation or tachycardia, and sudden cardiac death. (Moser & Dracup 1996; Watkins et al. 2002) They were also two times higher risk for atrial complications. (Moser & Dracup 1996; Watkins et al. 2002) An understanding of the physiological and pathophysiological mechanisms by which anxiety leads to these complications will help health care providers effectively manage ACS patients. Consequently, their overall prognosis may be improved. The purpose of this paper is to review the effect of the autonomic nervous system (ANS) on the cardiovascular system and to show the relationship between anxiety and dysrhythmogenesis. This paper is divided into two sections. The first section is an overview of the ANS control of the heart. The second section describes how anxiety enhances fatal dysrhythmias either by stimulating the sympathetic nervous system (SNS) and/or inhibition of parasympathetic nervous system (PSNS) and gives a basic idea about the relationship among anxiety, heart rate variability (HRV), and dysrhythmogenesis.

**ANS control of the heart****A) Overview of the conduction system:**

The internal pacemaker of the heart, the sinoatrial node (SA node), can initiate a heart beat and maintain regular rhythm without extrinsic neural input. However, under normal physiological conditions, heart rate is regulated by the ANS. Thus, while external neural input is not necessary to initiate a heart beat, the rate at which the heart beats is primarily under the external control of the ANS. This means that any stimulus affects the ANS can subsequently affect heart rate.

The SA node is made up of a specialized myocytes which initiate electrical impulses (i.e. action potentials) at rate about 60 beats/minute at rest. These electrical impulses travel at speed of ~1m/second through the atrium, generating atrial systole. When these impulses reach the atrioventricular node (AV node), which is a small mass of cells and connective tissue in the lower posterior region of the atrial septum, they are delayed for approximately 0.1 second. This delay allows atrial contraction to occur before ventricular contraction begins.(Neurocardiology 1988; Paris et al. 1992; Zipes 2000) Tachyarrhythmias caused by SNS stimulation decrease the delay time preventing the atria from having enough time to fill the ventricles. The end result of this process is a reduction in ventricular end diastolic volume and stroke volume.(Neurocardiology 1988; Paris et al. 1992; Zipes 2000) This might explain why some ACS patients have dizziness when they have high rate tachycardia. On the other hand stimulation of PSNS decreases SA node activity and AV nodal conduction velocity, resulting in sinus bradycardia and prolongation of the AV delay (i.e., more than 0.2) ending in an AV block.

The large diameter muscle fibers of the Bundle of His pass the electrical impulse from the AV node to the upper part of the interventricular septum. The main bundle fibers split into the right and the left bundle branches. These branches are broad, fast-conducting myocytes that terminate at Purkinje fibers. Purkinje fibers are the widest fiber set of connections in the subendocardium. The role of these fibers is to spread the electrical impulse rapidly through the ventricles. Within the ventricular wall the impulse is transferred from myocyte to myocyte in an outward direction (i.e. endothelium to epithelium) until the whole wall is excited resulting in ventricular contraction.(Neurocardiology 1988; Paris et al. 1992; Zipes 2000)

**B) Neural control of the heart:****Afferent innervation**

The heart is innervated by the SNS and PSNS divisions of the ANS. The afferent cardiac nerves of the SNS enter the spinal cord through the upper 4-5

thoracic roots and terminate in the dorsal funiculus on the same cell receiving afferent nerves from jaw, arms, neck and shoulders. This explains why ACS patients may perceive pain from these sites during cardiac ischemia.(Foreman et al. 1980; Talman et al. 1993) The afferent cardiac nerves of SNS innervate almost all portions of the heart: ventricular and atrial myocardium, pacemaker, and conduction system. On the other hand, the parasympathetic afferent cardiac nerves originate from cells within the nodose ganglia. Their sensory endings primarily innervate the atria. They project to the medulla oblongata where they terminate in the nucleus tractus solitarii (NTS). (Kalia et al. 1980; neurocardiology 1988; Paris et al. 1992; Zipes 2000)

**Efferent control**

Cardiac efferent preganglionic parasympathetic fibers originate in the brainstem. Their axons pass via the tenth cranial nerves (i.e. right and left vagus nerves) to the heart where they terminate on neurons of the intracardiac ganglia. (Armour et al. 1997; neurocardiology 1988; Paris et al. 1992; Zipes 2000) Cardiac efferent preganglionic sympathetic fibers originate from nerves at segmental levels of T1 to T5. (neurocardiology 1988; Paris et al. 1992; Zipes 2000) Sympathetic and parasympathetic fibers are distributed differently in the heart. Sympathetic fibers are distributed widely over the heart.(Kent et al. 2001; Talman & Kelkar 1993) In contrast, parasympathetic fibers are concentrated in the SA node, AV nodes, and atrial muscle. Consequently, sympathetic nervous system affects heart rate, atrial and ventricular contractility, while the parasympathetic nervous system affects mostly heart rate AV-nodal conduction velocity and atrial contractility.

**Autonomic influences on cardiac function**

The stimulating effect of the SNS neurons is characterized by slow onset (1 to 3 second latency) and long duration.(Talman & Kelkar 1993; Zipes 2000) Conversely, PSNS stimulation has a very short onset latency (200 to 400 msec) (neurocardiology 1988; Paris et al. 1992; Zipes 2000) and resolves quickly. This difference depends on the inactivation of the transmitter released from each. The inactivation of the catecholamines of sympathetic stimulation usually occurs slowly by reuptake and diffusion, while acetylcholine released by the vagal nerves is inactivated quickly (2.5 seconds) by acetylcholinesterase. (neurocardiology 1988; Paris et al. 1992; Zipes 2000) Therefore, tachyarrhythmias which are due to SNS stimulation are characterized by a slow onset and a sustained (> 30 second)(Philip 2001) activity requiring the health care team members administer medications to control heart rate and to decrease the work load of the heart.(Kennedy 1997)

Conversely, changes in PSNS activities is responsible for rapid changes in heart rate as slowing of the heart rate with each expiration "sinus dysrhythmia".

Sympathetic activation stimulates the medulla of the adrenal gland to secrete epinephrine into the blood stream and the sympathetic fibers in the heart to release nor-epinephrine. Epinephrine and nor-epinephrine (catecholamines) bind at both alpha ( $\alpha$ ) and beta ( $\beta$ )-receptors. These receptors are further subclassified into  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ , and  $\beta_2$ . Most of  $\alpha$  receptors are found on blood vessels. Peripherally,  $\beta_1$  receptors concentrated in the heart and  $\beta_2$  receptors in the lung.(Frederick 1991) Among these 4 receptors,  $\alpha_1$  and  $\beta_1$  are the ones that have the major influence on the cardiovascular function.

Catecholamines activate  $\beta_1$ -receptors resulting in increased heart rate (positive chronotropic effect), increased contractile force (positive inotropic effect), increased AV node conduction velocity (positive dromotropic effect).(neurocardiology 1988; Paris et al. 1992; Zipes 2000) Stimulation of post junctional/synaptic  $\alpha_1$  receptors by catecholamines will lead to contraction of the smooth muscle layer of blood vessels resulting in vasoconstriction. This includes coronary arteries, and may explain why anxious ACS patients have lower coronary perfusion and chest pain during high anxiety periods.

Parasympathetic stimulation releases acetylcholine which binds to muscarinic  $M_2$ -receptors on the myocyte membrane. This produces bradycardia by two electrophysiological actions: first, by reducing the slope of the pacemaker potential which will reduce the movement of the  $Na^+$  and  $Ca^{+2}$  into the cell during different phases in the action potential. This will prolong the time needed to reach the threshold and prolongs the plateau phase. The second action is making the cell membrane potential more negative at rest by moving more  $K^+$  extracellularly.(neurocardiology 1988; Paris et al. 1992; Zipes 2000) This will result in a prolongation of the time needed by the action potential to reach the threshold, and so the heart rate will decrease resulting in bradycardia.(neurocardiology 1988; Paris et al. 1992; Zipes 2000)

#### **Relationship among anxiety, ACS, and cardiac dysrhythmias**

Although the relevant pathophysiological mechanisms of the relationship between anxiety and dysrhythmias in ACS are not fully understood, (Kubzansky et al. 1998) our understanding about the role of ANS in the genesis of cardiac dysrhythmias is sufficient to highlight key events.(Shusterman et al. 1998) There is evidence that SNS is responsive to external stimuli such as anxiety. Anxiety neurotransmitters include catecholamines which also can be released as a result of SNS stimulation.(Frederick 1991)

Situation that known to produce anxiety, such as public speaking, being in a large crowd, or frightening situation such as a sudden earthquake, can lead to an increase in plasma catecholamines levels by 40-200%. (Bhat et al. 1979; Heninger et al. 1988; Nadeau et al. 1979) High levels of catecholamines were found at the time AMI patients complained of anxiety or pain. These times were associated with significant high rates of ventricular tachycardia, premature ventricular contractions, and sinus tachycardia. (Bhat et al. 1979; Nadeau & de Champlain 1979)

When anxiety stimulates the sympathetic nervous system or decreases parasympathetic activity,(Kawachi et al. 1995; Kennedy 1997; Shusterman et al. 1998; Thayer et al. 1996; Watkins et al. 2002; Watkins et al. 1998) a cascade of physiological responses that increase myocardial oxygen consumption,(Kamarck et al. 1991; Muller et al. 1989) enhance cardiac vascular reactivity,(Panza et al. 1991) platelet aggregation,(Brezinski et al. 1988) lower threshold for dysrhythmias,(Kamarck & Jennings 1991; Kennedy 1997; Muller et al. 1989) decrease heart rate variability (HRV), and make the atherosclerotic plaque more susceptible for rupture(Davies et al. 1984; Falk 1983; Falk et al. 1995; Kennedy 1997; Kubzansky et al. 1998) is generated. As a result, persons faced with untreated anxiety are particularly prone to cardiac dysrhythmias or sudden cardiac death.(Gorman et al. 2000; Kennedy 1997; Kubzansky et al. 1998; Moser & Dracup 1996; Voriadis et al. 1983) For this reason, mechanisms linking anxiety to dysrhythmias can be clarified by two major dimensions: stimulation of SNS and inhibition of PSNS (Figure.1).

#### **A) Stimulation of SNS**

When anxiety stimulates the SNS, there is an increase in the catecholamine levels in the plasma and in the cardiac tissue itself. (Bacaner et al. 2004; Kennedy 1997; Newton et al. 1996; Talman & Kelkar 1993) With sufficient SNS stimulation, catecholamine may, in fact, reach a toxic level in cardiac tissue.(Bacaner et al. 2004; Kennedy 1997; Newton & Parker 1996; Talman & Kelkar 1993) The actual mechanism for this is unknown, but evidence suggests that it is related to the intrinsic release of nor-epinephrine from cardiac sympathetic nerves.<sup>20</sup> The final results of this process is an activation of the myocyte calcium channel leading to hypercalcemia intracellularly.(Kennedy 1997) This hypercalcemia can generate a new action potential during the refractory period of the original action potential, and this phenomenon called after depolarization. These after depolarizations can result in ventricular and supraventricular tachyarrythmias.(Kennedy 1997; Priori et al. 1990) In an animal study,(Priori et al.

1988) administration of calcium channel antagonists was shown to prevent the occurrence of fatal dysrhythmias following myocardial ischemia. This suggests that catecholamine-induced hypercalcemia in the myocardium is a primary cause of ventricular dysrhythmias following an ACS.

**Ischemia:** The sympathetic stimulation from emotional anxiety is considered responsible for producing  $\alpha$ -adrenergic coronary vasoconstriction. This vasoconstriction may increase cardiovascular resistance and decrease coronary blood flow.(Billman et al. 1981) In patients with coronary artery disease, this vasoconstriction may lead to the development of ACS events and make these patients more vulnerable to ischemic damage and life threatening complications.(Kamarck & Jennings 1991; Pozzati et al. 1996; Vallance et al. 1990)

It is known that the electrocardiogram (ECG) changes and dysrhythmias observed during coronary vasoconstriction and during periods of increased oxygen demand are directly caused by nor-epinephrine released from sympathetic nerves.(Talman & Kelkar 1993) Elevated left cardiac sympathetic activity (induced by anxiety) can reduce the ventricular myocyte's refractory period (Gorman & Sloan 2000; Talman & Kelkar 1993) and lower ventricular fibrillation threshold,(Brezinski et al. 1988; Kennedy 1997) regardless of whether the cardiac muscle is well perfused or ischemic. Anxiety is associated with decreased beta-endorphin production resulting in lowered pain threshold.(Light et al. 1991) Ischemia, which usually occurs in ACS, is also associated with decrease beta-endorphin production.(Ketterer et al. 2004) Therefore, anxious patients would be expected to experience more pain, which in turn would increase SNS activity making them more susceptible to further ischemia and complications than non-anxious patients.(De Jong et al. 2004; De Jong et al. 2005)

### B) Inhibition of PSNS

Traditionally, health care team members concentrated on the role of SNS as a dysrhythmogenic mechanism.(Shusterman et al. 1998) However, it is necessary to have an appropriate balance between sympathetic and parasympathetic activities to maintain normal cardiac stability, and to avoid excessive sympathetic cardiac excitability which leads to complications.(Talman & Kelkar 1993) The parasympathetic system control dominates at rest, or at times when there is no psychological distress.(Gorman & Sloan 2000; Kubzansky et al. 1998; Paris et al. 1992) When patients develop an acute coronary event, high levels of anxiety cause a greater reduction in PSNS control.(Watkins et al. 2002)

This results in increased heart rate and myocardial ischemia due to increased myocardial workload. Combined, these factors play a significant

role in the development of malignant ventricular dysrhythmias(Hohnloser et al. 1994; Watkins et al. 1998) and sudden cardiac death in these patients.(Schwartz et al. 1992) Conversely, stimulation of the vagus nerve (Lucreziotti et al. 2000; Schwartz et al. 1984) have worked as antifibrillatory through  $M_2$ -receptors and inhibition of presynaptic nor-epinephrine release.(Verrier et al. 1997)

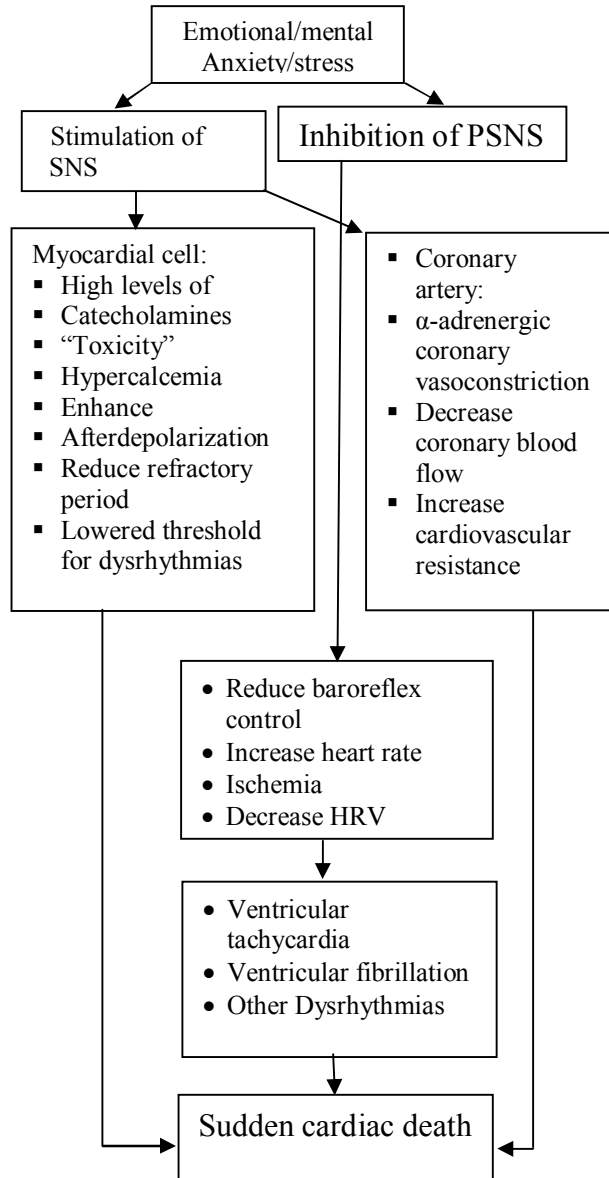


Figure 1: Pathophysiology of relationship among anxiety, ACS, and cardiac complications. ACS: Acute coronary syndrome. SNS: Sympathetic nervous system. PSNS: Parasympathetic nervous system. HRV: Heart rate variability.

In order to have a clearer understanding of the effect of anxiety on the mechanisms responsible for

these dysrhythmias early after ACS events, descriptions of the cardiac action potential phases and the effect of ischemia on these phases are presented next.

### Phases of action potential

The action potential is a change in electrical activity along the cell membrane. At rest (polarized state) a high intracellular negative (from -70 to -90 mV) charge exists relative to the extracellular region. (Weller et al. 1989) At this time, the cell membrane is essentially impermeable to sodium ions ( $\text{Na}^+$ ) and permeable to potassium ions ( $\text{K}^+$ ). This allows  $\text{K}^+$  to move freely outside while  $\text{Na}^+$  is prevented from entering.

When an electrical stimulus from the action potential of an adjacent cell reaches the threshold at approximately -60 to -65 mV,  $\text{Na}^+$  channels open which increase the sarcolemmal permeability to  $\text{Na}^+$ . With the fast  $\text{Na}^+$  channels open, the inward rush of  $\text{Na}^+$  is extremely rapid and briefly causes the cell to depolarize and flip to a positive potential of +20 to +30 mV. (Weller & Noone 1989) This is known as Phase 0 (fast-response) of the action potential. After a very short period of time, the fast  $\text{Na}^+$  channels are automatically inactivated. At this point,  $\text{Na}^+$  no longer rushes into the cell and the cell has an early repolarization period (phase 1) at about 0 mV. During this phase (phase 1)  $\text{K}^+$  continue to move outside via a class of  $\text{K}^+$  channels that open transiently in response to depolarization then quickly inactivate. This phase usually occurs in epicardial myocytes and Purkinje fibers. Sino-atrial and AV nodes don't have this phase.

During the plateau phase (phase 2) another set of channels, the L-type calcium ( $\text{Ca}^{+2}$ ) channels, slowly open and allow the influx of  $\text{Ca}^{+2}$ . Also during phase 2,  $\text{K}^+$  tends to diffuse out of the cell, balancing the slow inward flux  $\text{Ca}^{+2}$ , thereby maintaining the plateau of the action potential.

Phase 3 is the final repolarization phase and depends on two processes. The first is the inactivation of the  $\text{Ca}^{+2}$  channels, thereby preventing further influx of  $\text{Ca}^{+2}$ . The other is continued efflux of  $\text{K}^+$  out of the cell. Both of these processes cause intracellular environment to become more negative, thereby reestablishing resting membrane potential. Phase 4 is the return to resting membrane potential. The excess  $\text{Na}^+$  that entered the cell during the depolarization is now removed from the cell in exchange for  $\text{K}^+$  by means of  $\text{Na}^+/\text{K}^+$  pump. This mechanism returns intracellular concentration of  $\text{Na}^+$  and  $\text{K}^+$  to the levels before depolarization and is essential for normal ionic balance.

### Ischemia and action potential

Ischemia raises transmembrane potential (the difference in the charge between intracellular and extracellular) to a less negative state. In this situation,

the fast response ( $\text{Na}^+$  inward current) is depressed and the conduction relies primarily on the slow response ( $\text{Ca}^{+2}$  inward current). This mechanism is referred to as "slow-response" action potential. (Weller & Noone 1989) The results of these changes are immediate (2 to 10 minutes) decreased amplitude and increased duration of action potential. (Philip 2001; Pogwizd et al. 1990) Within 12 to 30 minutes after ischemia, electrophysiological alterations such as slow conduction throughout the ischemic tissue and variable degrees of conduction block occur. (Philip 2001; Pogwizd & Corr 1990) Most of these electrophysiological changes occur due to slow response action potential.

### Mechanisms of cardiac dysrhythmias

Cardiac dysrhythmias associated with ischemia-related changes in the action potential that occur early after ACS events have two major mechanisms: reentry and abnormal impulse formation. (Lazzara et al. 1988; Rosen 1988) Reentry, which is reexcitation of previously activated cardiac tissue, is believed to be the major mechanism underlying lethal cardiac dysrhythmias that occur early after ACS events. (Mandel 1987; Philip 2001; Rosen 1988) Among the mechanisms responsible for abnormal impulse formation are enhanced automaticity and triggered activity. Automaticity is divided into normal and abnormal. Triggered activity is further divided into two subcategories: early after depolarization (EADs) and delayed after depolarization (DADs) (Figure.2).

**Reentry:** Reentry is the return of the impulse to excite previously activated myocardial tissue that has passed the absolute refractory period. (Weller & Noone 1989) Reentry occurs when there is an appropriate anatomic or functional tissue loop. For reentry to occur, a block must exist in one portion of the loop and conduction must be slow enough (conduction delay) through the rest of the loop to permit recovery (repolarization) of the blocked area to restore sufficient excitability to respond to the impulse. (Mandel 1987) To achieve critical block and conduction delay, a premature beat is usually required to initiate reentry because premature beats are more likely to encounter refractory tissue and are propagated with much slower conduction velocity.

### Abnormal impulse formation

**Automaticity:** Normal automaticity is defined as the ability of pacemaker cells and cells in the conduction system to generate spontaneous action potential. Spontaneous activity is the result of depolarization during diastole caused by a net inward current that progressively brings the membrane potential to threshold. The ionic mechanisms

underlying normal sino-atrial node and Purkinje fibers automaticity include a hyperpolarization activated inward  $\text{Na}^+$  current (DiFrancesco 1985; DiFrancesco 1995) and decay of outward  $\text{K}^+$  current. (Vassalle 1995)

Abnormal automaticity or depolarization-induced automaticity is observed under conditions of reduced resting membrane potential, such as ischemia or infarction that occur in ACS events. During ischemic states, the resting membrane potential of ventricular muscle may decrease from normal value of about -90 mV to -60 mV. This may cause spontaneous diastolic depolarization. The ionic basis for diastolic depolarization in abnormal automaticity may be similar to that of normal automaticity in sino-atrial node, consisting of decay of outward  $\text{K}^+$  current with progressive activation of  $\text{Ca}^{+2}$  inward current.

#### After-depolarization and triggered activity:

These are generally divided into early after depolarization (EAD) and delayed after depolarization (DAD) subclasses. EADs interrupt repolarization during phase 2 or phase 3 (or both) of the cardiac action potential, whereas DADs arise after full repolarization (Phase 4). When an EAD or DAD amplitude brings the membrane potential to its threshold potential, a spontaneous action potential referred to as a *triggered response* is the result. (Philip 2001) These triggered responses are responsible for some of tachyarrhythmias. (Philip 2001)

**EADs:** EADs are observed in isolated cardiac tissues exposed to injury, (Lab 1982) altered electrolytes, hypoxia and acidosis, (Adamantidis et al. 1986; Coraboeuf et al. 1980) catecholamines (Priori & Corr 1990; Volders et al. 1997) and pharmacological agents including anti-dysrhythmic drugs. (Davidenko et al. 1989; Philip 2001) Ventricular hypertrophy also predisposes to the development of EADs. (Nuss et al. 1999; Philip 2001; Volders et al. 1998) It has been shown that anxious individuals with family history of coronary heart disease have a higher left ventricular mass, which predisposes them to this type of mechanism if they develop ACS events. (Piccirillo et al. 1999) Although specific mechanisms of EAD may differ, a critical prolongation of repolarization accompanies most of EADs. This usually occurs because of reduction of net outward current; either due to an increase in inward ( $\text{Ca}^{+2}$  current) current or decrease in outward current ( $\text{K}^+$  Current), leading to increase intracellular positivity. Since ischemia developed in ACS events prolongs action potential duration, it provides the ideal situation for EADs to occur.

**DADs:** DADs that reach the threshold give rise to spontaneous responses referred to as triggered activity. (Philip 2001) DADs and DAD-triggered

activity are observed under conditions that cause increase in intracellular  $\text{Ca}^{+2}$ . This hypercalcemia occurs either via: (a) enhancement of  $\text{Ca}^{+2}$  entry by catecholamines, pharmacological agents as digoxin and quinidine; or (b) reduction of reuptake and/or increase release of  $\text{Ca}^{+2}$  from sarcoplasmic reticulum. (Priori & Corr 1990) Agents that prolong repolarization facilitate the induction of DAD activity by augmenting  $\text{Ca}^{+2}$  entry.

DADs are always induced at relatively rapid rates. Therefore, clinical dysrhythmias that might be caused by DADs include: idiopathic ventricular tachyarrhythmias (i.e., ventricular tachycardia), supraventricular tachycardia, and accelerated idioventricular rhythm that occurs in a setting of myocardial infarction. (Cardinal et al. 1986; Cardinal et al. 1992)

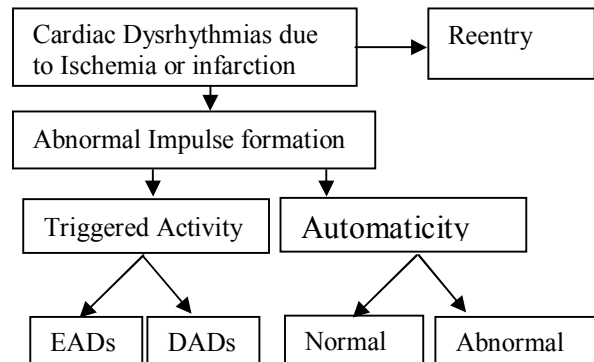


Figure 2. Classification of cardiac dysrhythmic mechanisms after ACS events.

#### Anxiety, heart rate variability, and dysrhythmias

HRV refers to an increase and/or decrease over time in the RR interval which is an indication of beat-to-beat variability in heart rate. (Kara et al. 2003) Several studies have advocated HRV as an index of cardiac autonomic function as influenced by the brain. (Gorman & Sloan 2000; Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996; Kara et al. 2003) Many investigators have reported that specific changes in HRV are related either to reduction in parasympathetic stimulation or to an increase in sympathetic autonomic stimulation. (Carney et al. 1988; Gorman & Sloan 2000; Kawachi et al. 1995) Reduced HRV can result from either by parasympathetic system suppression or by increase sympathetic nervous system stimulation. On the contrary, HRV increases when there is an increase in the parasympathetic activity or reduction in sympathetic nervous system activity.

Many investigators have shown that anxiety decrease HRV resulting in tachycardia among different

populations such as: generalized anxiety disorder,(Thayer et al. 1996) posttraumatic stress disorder,(Cohen et al. 1997) panic disorder,(Yeragani et al. 1993) phobic anxiety, and even in young healthy people with high trait anxiety.(Watkins et al. 1998) One attractive possibility is that anxiety decreases HRV via a reduction in vagal stimulation, thereby leaving the heart exposed to unopposed stimulation by the SNS, making it more vulnerable to fatal dysrhythmias and sudden cardiac death.(Bigger et al. 1992; Gorman & Sloan 2000; Huikuri et al. 1992; Levy 1997) In patients suffering coronary artery disease the incidence of dysrhythmias ( i.e. ventricular tachycardia or ventricular fibrillation) was highest at 9 am and 6pm.(Shusterman et al. 1998) These times coincide with circadian peaks in catecholamine levels.(Bigger et al. 1992; Kamarck & Jennings 1991; Muller et al. 1989) Another possible explanation is the elevation of the catecholamine level due to SNS stimulation from anxiety which is associated with the day time activities in comparison with the night time activities.

Interestingly, sudden changes in the HRV just prior to fatal ventricular dysrhythmias and sudden cardiac death among ACS patients have been observed.(Bigger et al. 1992; Huikuri et al. 1992) Therefore, some health care team researchers have considered these changes as a warning marker for these dysrhythmias. Moreover, reduced HRV has been shown to independently predict sudden cardiac death due to dysrhythmias.(Bigger et al. 1992; Huikuri et al. 1992)

### Summary

There is accumulating evidence for a functional relationship among anxiety, imbalance of sympathetic, and parasympathetic control of the heart, and the occurrence of fatal cardiac dysrhythmias. This imbalance can, most of the time, lead to increase in SNS stimulation which is associated with different mechanisms at the cellular level and blood vessels leading to fatal dysrhythmias. Electrical changes at cellular level include: reduced refractory period, lowered dysrhythmias threshold, high catecholamine levels, and hypercalcemia, predisposing ACS patients for dysrhythmias. Coronary arteries are also affected by the imbalance between the sympathetic, parasympathetic control. Alpha-adrenergic coronary vasoconstriction, leading to an increase in cardiovascular resistance and a decrease in coronary blood flow, is the apparent mechanism for the development of cardiac ischemia and dysrhythmias in ACS patients. However, the suppression of PSNS by anxiety is playing an important role in the dysrhythmogenesis in ACS. This suppression will increase heart rate and myocardial work load, decrease

HRV leading to ischemia and dysrhythmias.

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### Corresponding Author:

Dr. Mohannad Eid AbuRuz  
Nursing Education and Development Department  
King Fahad Specialist Hospital-Dammam, KSA  
E-mail: [mohannadeid@yahoo.com](mailto:mohannadeid@yahoo.com)

### References

1. Abu Ruz ME, Lennie TA, Moser DK. Effects of beta-blockers and anxiety on complication rates after acute myocardial infarction. *Am J Crit Care* 2011; 20 (1):67-73; quiz 4.
2. Abu Ruz ME, Lennie TA, Riegel B et al. Evidence that the brief symptom inventory can be used to measure anxiety quickly and reliably in patients hospitalized for acute myocardial infarction. *J Cardiovasc Nurs* 2010; 25 (2):117-23.
3. Adamantidis MM, Caron JF, Dupuis BA. Triggered activity induced by combined mild hypoxia and acidosis in guinea-pig Purkinje fibers. *J Mol Cell Cardiol* 1986; 18 (12):1287-99.
4. Armour JA, Murphy DA, Yuan B-X et al. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anatomical Record* 1997; 247:289-98.
5. Bacaner M, Brietenbucher J, LaBree J. Prevention of ventricular fibrillation, acute myocardial infarction (myocardial necrosis), heart failure, and mortality by bretylium: is ischemic heart disease primarily adrenergic cardiovascular disease? *Am J Ther* 2004; 11 (5):366-411.
6. Bengtson A, Herlitz J, Karlsson T et al. Distress correlates with the degree of chest pain: a description of patients awaiting revascularisation. *Heart* 1996; 75 (3):257-60.
7. Bhat PS, Udupa KN, Vaish SK. Plasma catecholamines during arrhythmias following acute myocardial infarction. *Indian Heart J* 1979; 31 (6):345-8.
8. Bigger JT, Jr., Fleiss JL, Steinman RC et al. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992; 85 (1):164-71.
9. Billman GE, Randall DC. Mechanisms mediating the coronary vascular response to behavioral stress in the dog. *Circ Res* 1981; 48 (2):214-23.
10. Brezinski DA, Tofler GH, Muller JE et al. Morning increase in platelet aggregability. Association

- with assumption of the upright posture. *Circulation* 1988; 78 (1):35-40.
11. Cardinal R, Savard P, Armour JA et al. Mapping of ventricular tachycardia induced by thoracic neural stimulation in dogs. *Can J Physiol Pharmacol* 1986; 64 (4):411-8.
  12. Cardinal R, Scherlag BJ, Vermeulen M et al. Distinct activation patterns of idioventricular rhythms and sympathetically-induced ventricular tachycardias in dogs with atrioventricular block. *Pacing Clin Electrophysiol* 1992; 15 (9):1300-16.
  13. Carney RM, Rich MW, teVelde A et al. The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. *J Psychosom Res* 1988; 32 (2):159-64.
  14. Chockalingam A, Balaguer-Vintro I, Achutti A et al. The World Heart Federation's white book: impending global pandemic of cardiovascular diseases: challenges and opportunities for the prevention and control of cardiovascular diseases in developing countries and economies in transition. *Can J Cardiol* 2000; 16 (2):227-9.
  15. Cohen H, Kotler M, Matar MA et al. Power spectral analysis of heart rate variability in posttraumatic stress disorder patients. *Biol Psychiatry* 1997; 41 (5):627-9.
  16. Coraboeuf E, Deroubaix E, Coulombe A. Acidosis-induced abnormal repolarization and repetitive activity in isolated dog Purkinje fibers. *J Physiol (Paris)* 1980; 76 (2):97-106.
  17. Costa PT, Zonderman AB, Engel BT et al. The relation of chest pain symptoms to angiographic findings of coronary artery stenosis and neuroticism. *Psychosom Med* 1985; 47 (3):285-93.
  18. Crowe JM, Runions J, Ebbesen LS et al. Anxiety and depression after acute myocardial infarction. *Heart Lung* 1996; 25 (2):98-107.
  19. Davidenko JM, Cohen L, Goodrow R et al. Quinidine-induced action potential prolongation, early afterdepolarizations, and triggered activity in canine Purkinje fibers. Effects of stimulation rate, potassium, and magnesium. *Circulation* 1989; 79 (3):674-86.
  20. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N Engl J Med* 1984; 310 (18):1137-40.
  21. Davies RF, Linden W, Habibi H et al. Relative importance of psychologic traits and severity of ischemia in causing angina during treadmill exercise. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. *J Am Coll Cardiol* 1993; 21 (2):331-6.
  22. De Jong MJ, Chung ML, Roser LP et al. A five-country comparison of anxiety early after acute myocardial infarction. *Eur J Cardiovasc Nurs* 2004; 3 (2):129-34.
  23. De Jong MM, An K, McKinley S et al. Using a 0-10 scale for assessment of anxiety in patients with acute myocardial infarction. *Dimens Crit Care Nurs* 2005; 24 (3):139-46.
  24. DiFrancesco D. The cardiac hyperpolarizing-activated current, *if*. Origins and developments. *Prog Biophys Mol Biol* 1985; 46 (3):163-83.
  25. DiFrancesco D. The pacemaker current (*I<sub>f</sub>*) plays an important role in regulating SA node pacemaker activity. *Cardiovasc Res* 1995; 30 (2):307-8.
  26. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J* 1983; 50 (2):127-34.
  27. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; 92 (3):657-71.
  28. Foreman RD, Ohata CA. Effects of coronary artery occlusion on thoracic spinal neurons receiving viscerosomatic inputs. *Am J Physiol* 1980; 238 (5):H667-74.
  29. Frederick HL. Clinical Articles: The neurophysiology of acute anxiety: A review of the literature. *The clinical forum for nurse anesthesia* 1991; 2 (2):52-61.
  30. Go AS, Mozaffarian D, Roger VL et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*; 127 (1):e6-e245.
  31. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. *Am Heart J* 2000; 140 (4 Suppl):77-83.
  32. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93 (5):1043-65.
  33. Heninger GR, Charney DS. Monoamine receptor systems and anxiety disorders. *Psychiatr Clin North Am* 1988; 11 (2):309-26.
  34. Herrmann C, Brand-Driehorst S, Buss U et al. Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. *J Psychosom Res* 2000; 48 (4-5):455-62.
  35. Huikuri HV, Linnaluoto MK, Seppanen T et al. Circadian rhythm of heart rate variability in survivors of cardiac arrest. *Am J Cardiol* 1992; 70 (6):610-5.
  36. Januzzi JL, Jr., Stern TA, Pasternak RC et al. The influence of anxiety and depression on outcomes



- of patients with coronary artery disease. *Arch Intern Med* 2000; 160 (13):1913-21.
37. Kalia M, Mesulam MM. Brain stem projections of sensory and motor components of the vagus complex in the cat: II. Laryngeal, tracheobronchial, pulmonary, cardiac, and gastrointestinal branches. *J Comp Neurol* 1980; 193 (2):467-508.
  38. Kamarck T, Jennings JR. Biobehavioral factors in sudden cardiac death. *Psychol Bull* 1991; 109 (1):42-75.
  39. Kara T, Nykodym J, Somers VK. Heart rate variability: back to the beginning. *J Cardiovasc Electrophysiol* 2003; 14 (8):800-2.
  40. Kawachi I, Sparrow D, Vokonas PS et al. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *Am J Cardiol* 1995; 75 (14):882-5.
  41. Kennedy HL. Beta blockade, ventricular arrhythmias, and sudden cardiac death. *Am J Cardiol* 1997; 80 (9B):29J-34J.
  42. Kent DM, Lau J, Selker HP. Balancing the benefits of primary angioplasty against the benefits of thrombolytic therapy for acute myocardial infarction: the importance of timing. *Eff Clin Pract* 2001; 4 (5):214-20.
  43. Ketterer MW, Mahr G, Cao JJ et al. What's "unstable" in unstable angina? *Psychosomatics* 2004; 45 (3):185-96.
  44. Ketterer MW, Mahr G, Goldberg AD. Psychological factors affecting a medical condition: ischemic coronary heart disease. *J Psychosom Res* 2000; 48 (4-5):357-67.
  45. Kubzansky LD, Kawachi I, Weiss ST et al. Anxiety and coronary heart disease: a synthesis of epidemiological, psychological, and experimental evidence. *Ann Behav Med* 1998; 20 (2):47-58.
  46. Lab MJ. Contraction-excitation feedback in myocardium. Physiological basis and clinical relevance. *Circ Res* 1982; 50 (6):757-66.
  47. Lazzara R, Scherlag BJ. Generation of arrhythmias in myocardial ischemia and infarction. *Am J Cardiol* 1988; 61 (2):20A-6A.
  48. Levy MN. Neural control of cardiac function. *Baillieres Clin Neurol* 1997; 6 (2):227-44.
  49. Light KC, Herbst MC, Bragdon EE et al. Depression and type A behavior pattern in patients with coronary artery disease: relationships to painful versus silent myocardial ischemia and beta-endorphin responses during exercise. *Psychosom Med* 1991; 53 (6):669-83.
  50. Malan SS. Psychosocial adjustment following MI: current views and nursing implications. *J Cardiovasc Nurs* 1992; 6 (4):57-70.
  51. Mandel. Cardiac arrhythmias, their mechanisms, diagnosis, and management. 2nd ed. Philadelphia: Lippincott; 1987.
  52. Moser DK, Dracup K. Is anxiety early after myocardial infarction associated with subsequent ischemic and arrhythmic events? *Psychosom Med* 1996; 58 (5):395-401.
  53. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989; 79 (4):733-43.
  54. Nadeau RA, de Champlain J. Plasma catecholamines in acute myocardial infarction. *Am Heart J* 1979; 98 (5):548-54.
  55. Neurocardiology. First ed. GF Henri E. Kulbertus, editor. Mount Kisco, New York: Futura Publishing company; 1988. (GF Henri E. Kulbertus editor).
  56. Newton GE, Parker JD. Cardiac sympathetic responses to acute vasodilation. Normal ventricular function versus congestive heart failure. *Circulation* 1996; 94 (12):3161-7.
  57. Nuss HB, Kaab S, Kass DA et al. Cellular basis of ventricular arrhythmias and abnormal automaticity in heart failure. *Am J Physiol* 1999; 277 (1 Pt 2):H80-91.
  58. Panza JA, Epstein SE, Quyyumi AA. Circadian variation in vascular tone and its relation to alpha-sympathetic vasoconstrictor activity. *N Engl J Med* 1991; 325 (14):986-90.
  59. Paris W, Woodbury A, Thompson S et al. Social rehabilitation and return to work after cardiac transplantation--a multicenter survey. *Transplantation* 1992; 53 (2):433-8.
  60. Philip P. Cardiac arrhythmia: mechanisms, diagnosis, and management Philadelphia: Lippincott, Williams & wilkins; 2001.
  61. Piccirillo G, Viola E, Bucca C et al. QT interval dispersion and autonomic modulation in subjects with anxiety. *J Lab Clin Med* 1999; 133 (5):461-8.
  62. Pogwizd SM, Corr PB. Mechanisms underlying the development of ventricular fibrillation during early myocardial ischemia. *Circ Res* 1990; 66 (3):672-95.
  63. Pozzati A, Pancaldi LG, Di Pasquale G et al. Transient sympathovagal imbalance triggers "ischemic" sudden death in patients undergoing electrocardiographic Holter monitoring. *J Am Coll Cardiol* 1996; 27 (4):847-52.
  64. Priori SG, Corr PB. Mechanisms underlying early and delayed afterdepolarizations induced by catecholamines. *Am J Physiol* 1990; 258 (6 Pt 2):H1796-805.
  65. Priori SG, Zuanetti G, Schwartz PJ. Ventricular fibrillation induced by the interaction between

- acute myocardial ischemia and sympathetic hyperactivity: effect of nifedipine. *Am Heart J* 1988; 116 (1 Pt 1):37-43.
66. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998; 97 (6):596-601.
- Rosen MR. The links between basic and clinical cardiac electrophysiology. *Circulation* 1988; 77 (2):251-63.
67. Shusterman V, Aysin B, Gottipaty V et al. 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 (7):1891-9.
68. Talman WT, Kelkar P. Neural control of the heart. Central and peripheral. *Neurol Clin* 1993; 11 (2):239-56.
69. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. *Biol Psychiatry* 1996; 39 (4):255-66.
70. Vallance SR, Randall DC, Yingling JD. Coronary alpha-adrenergic tone and contraction of ischemic myocardium in awake dog. *Int J Cardiol* 1990; 26 (3):291-302.
71. Vassalle M. The pacemaker current (I<sub>f</sub>) does not play an important role in regulating SA node pacemaker activity. *Cardiovasc Res* 1995; 30 (2):309-10.
72. Volders PG, Kulcsar A, Vos MA et al. Similarities between early and delayed afterdepolarizations induced by isoproterenol in canine ventricular myocytes. *Cardiovasc Res* 1997; 34 (2):348-59.
73. Volders PG, Sipido KR, Vos MA et al. Cellular basis of biventricular hypertrophy and arrhythmogenesis in dogs with chronic complete atrioventricular block and acquired torsade de pointes. *Circulation* 1998; 98 (11):1136-47.
74. Vouridis EM, Mallios KD, Papantonis TM. Holter monitoring during 1981 Athens earthquakes. *Lancet* 1983; 1 (8336):1281-2.
- Watkins LL, Blumenthal JA, Carney RM. Association of anxiety with reduced baroreflex cardiac control in patients after acute myocardial infarction. *Am Heart J* 2002; 143 (3):460-6.
75. Watkins LL, Grossman P, Krishnan R et al. Anxiety and vagal control of heart rate. *Psychosom Med* 1998; 60 (4):498-502.
76. Weller DM, Noone J. Mechanisms of arrhythmias: enhanced automaticity and reentry. *Crit Care Nurse* 1989; 9 (5):42-67.
77. Yeghiazarians Y, Braunstein JB, Askari A et al. Unstable angina pectoris. *N Engl J Med* 2000; 342 (2):101-14.
78. Yeragani VK, Pohl R, Berger R et al. Decreased heart rate variability in panic disorder patients: a study of power-spectral analysis of heart rate. *Psychiatry Res* 1993; 46 (1):89-103.
79. Zipes DP. *The nervous system and the heart*. first ed. GJT Horst, editor. Totowa, New Jersey: Humana Press; 2000. (GJT Horst editor).

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