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## Anger, Hostility and Other Forms of Negative Affect: Relation to Cardiovascular Disease

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### 1. Introduction

The link between psychological factors and cardiovascular disease goes far beyond well-established psychiatric diagnoses such as major depressive disorder, generalized anxiety disorder or panic disorder. The literature describes several mental and behavioral concepts which are not captured in the current nomenclature as independent mental disorders but show some degree of association with cardiovascular disease. We will discuss them in this chapter under the larger category of “negative affect”. The most common constructs we subsume in this category are Anger, Hostility, Aggressiveness, Negative Emotion, Negative Affectivity, Vital Exhaustion (VE), Type D Personality, and Type A Behavior Pattern (TABP). We chose the “negative affect” category as a mean to discuss together these different mood states having in common their potential negative impact on the cardiovascular system.

Some of these constructs have different definitions and are measured by diverse instruments. This variety of approaches reflects the complexity of the field and explains, at least in part, some disparity in results relating them to cardiovascular disease.

In this chapter, we review these constructs included in “negative affect” and the instruments that have been developed to assess them. Additionally, we will review the studies investigating their relationship with cardiac conditions, emphasizing the pathophysiological mechanisms that could mediate the relationship between negative affect and cardiac pathology. Finally, we will discuss potential treatments of negative affect and their eventual impact on cardiac conditions.

### 2. The mix of concepts: Hostility, anger, aggression and other negative affect

Over the past decades, a large number of studies have investigated the association between negative affect and coronary heart disease (CHD). Many were cross-sectional case-control studies, which have been criticized for the recall bias of the CHD diagnosis and for the memory distortion (Chida and Steptoe 2009). More recently, several prospective longitudinal studies with more rigorous methodology have also been developed. Notwithstanding, results from these studies are not homogeneous, with both positive and negative results. Although more rigorous in their methodology, the prospective studies use

diverse and partially overlapping concepts to define negative affect associated with CHD (Table 1). Since each study analyzes only a single psychological construct at a time and since these concepts are only partially overlapping, it is not surprising to note the conflicting results in the literature. In addition, the single-factor approach ignores the clustering of psychosocial risk factors for physical disease, which may act synergistically (Suls and Bunde 2005). Another view, from a twin-designed study, is that some of this negative affect concepts may have a single common genetic factor and a nonshared environmental factor, i.e., environments uncorrelated between twins, such as accidents. (Raynor, Pogue-Geile et al. 2002).

| Type A Behavior Pattern  | Type D Personality   | Vital exhaustion  | Hostility  | Anger  | Aggression   | Negative Affectivity   | Negative emotions  |
|--|--|---|--|--|--|--|--|
| An action-emotion complex induced by environmental factors, involving psychomotor mannerisms, vigorous voice, hard-driving, time involvement-pressured job, competitiveness, impatience and easy triggering anger and hostility (Friedman and Rosenman 1959) | Negative affectivity, social inhibition and feeling of distress (Denollet 1998). | An unusual tiredness, increased irritability and feelings of demoralization (Appels, Hoppener et al. 1987). | A tendency to view the world in a negative, cynical fashion; a primarily cognitive construct involving negative attitude toward others, consisting of enmity, denigration, and ill will (Smith, Glazer et al. 2004). | An affective experience, ranging in intensity from mild annoyance to fury and outrage. Two subtypes "anger-out", a combination of anger and aggression and "anger-in", a tendency to feel anger and suppress it (Schulman and Stromberg 2007). | A physical or verbal behavior including attacking destructive or hurtful actions, may be considered a personality trait. | Abroadband personality dimension characterized by a general disposition to chronically experience anxiety, sadness, guilt, anger, irritability, and other negative emotions. | Depression, anger, anxiety and hostility are emotions that range from normal to pathological in a continuum (Kubzansky and Kawachi 2000; Kubzansky, Davidson et al. 2005; Kubzansky 2007). |

Table 1. Concepts.

Some authors have proposed that anger, hostility and aggression should be considered a syndrome and other include anger and hostility in the concept of aggression. For others, hostility is characterized by interrelated elements of cynical beliefs and attributions, angry emotional states, and aggressive or antagonistic behaviors. Martin et al. advocate for the standardization of these concepts emphasizing that anger corresponds to *affect*, aggression to *behavior*, and hostility (or cynicism) to *cognition*. Together the three constructs form a three-factor "ABC" model of trait anger (Martin, Watson et al. 2000).

Aside from hostility, anger and aggression, VE and distressed personality are more complex concepts. Although they overlap partially, these constructs include specific patterns and aspects not captured by general scales for hostility, anger and aggression. Last but not least, the concept of negative affectivity posits that these symptoms represent markers of a trait

characterized by hypersensitivity to negative stimuli (Watson and Clark 1984) and the concept of negative emotions postulate the existence of a continuum across these affective states.

### 3. Depression: The mix beyond the negative affects

Beyond negative affect, depression and, secondarily, anxiety have the strongest evidence for associations with CHD, even after controlling for traditional CHD risk factors, such as serum cholesterol, blood pressure, and smoking. Intriguingly, as it has been pointed out by Suls and Bunde, there is an appreciable construct and measurement overlap across anger, anxiety, and depression, which creates ambiguity both for theory testing and for interpretation of available evidence (Suls and Bunde 2005). Ravaja et al., have proposed that depression would be a moderator of the relationship between cardiovascular risk factors and anger (Ravaja, Kauppinen et al. 2000). They reported a negative association between hostility and cardiovascular risk factors in patients with high depressive tendencies. Patients with severe depression and lack of anger or hostility would represent the most severe form of exhaustion where the individual had "given-up" (Ravaja, Kauppinen et al. 2000).

Irritability has been considered a diagnostic feature of MDD in children and adolescents (American Psychiatric Association 1994). Actually, a hostile depressive subtype has been proposed in 1966 (Overall, Hollister et al. 1966). However, unfortunately, most standard rating scales of depressive symptom severity do not specifically measure irritability (Hamilton 1960; Montgomery and Asberg 1979). A particular form of irritable depression marked by recurrent anger attacks, spontaneous episodes characterized by feelings of rage and symptoms of physiologic arousal similar to panic attacks and accompanied by chronic irritability, has been reported to occur in 20-60% of patients with unipolar depression and nearly two-thirds of patients with bipolar depression (Perlis, Smoller et al. 2004) (Baker, Dorzab et al. 1971; Overall, Goldstein et al. 1971; Snaith and Taylor 1985) (Gould, Ball et al. 1996; Fava, Uebelacker et al. 1997; Morand, Thomas et al. 1998; Mischoulon, Dougherty et al. 2002; Posternak and Zimmerman 2002; Dougherty, Rauch et al. 2004). Data have suggested that depression with anger may be associated with distinct abnormalities of subcortical white matter structure (Iosifescu, Renshaw et al. 2007) and brain metabolism (Dougherty, Rauch et al. 2004), and possibly with increased serotonergic dysfunction (Fava, Vuolo et al. 2000). It is possible that anger may be a marker of a depressive variant with increased cardiovascular risk (Fava, Abraham et al. 1996; Painuly, Sharan et al. 2005; Fraguas, Iosifescu et al. 2007). Anger attacks in MDD patients were independently associated with smoking (for periods >11 years) and with total serum levels of cholesterol  $\geq 200\text{mg/dL}$ , after adjusting for age, gender, BMI, and baseline severity of depression (Fraguas, Iosifescu et al. 2007).

Major depression is a mental disorder and has reliable operational diagnostic criteria. However, the limit between major depressive disorder and subsyndromal depressive symptoms and the relevance of irritability/anger/hostility in depressed patients involve multiple non answered questions. For example, little is known about the distinction between irritable depression and depression with comorbid personality disorders or other psychiatric diagnoses associated with high rates of irritability. The interaction between temperament, personality is a complex phenomenon (Clark, Watson et al. 1994). The nature of depressive symptoms may be influenced by personality traits; in this model, irritability

may be one manifestation of sensitivity to negative stimuli (Watson and Clark 1984), or interpersonal sensitivity (Bagby, Kennedy et al. 1997). Also, increased anxiety levels may define a specific subtype of MDD (Fava, Alpert et al. 2004) and irritability is often manifested in the presence of increased anxiety (as an inadequate response of individuals overwhelmed by stress and anxiety); in a factor analysis, this continuum of symptoms in depression appears to be best captured by a common anxiety/irritability factor (Gullion and Rush 1998).

#### 4. Instruments

The variety of instruments (Table 2) used to evaluate negative affect makes standardization or even comparison between studies difficult (Davidson 2008). We describe the instruments when addressing each "negative affect" construct separately (Item 6). However, some general limitations should be discussed. For example, some instruments are composed of multidimensional items mixing several concepts and including definitional caveats. For example, the Potential for Hostility subcomponent of the Structured Interview for the TABP

| Type A Behavior Pattern  | Type D Personality  | Vital exhaustion  | Hostility   | Anger   | Aggression   |
|--|---|---|---|---|--|
| Among the self-report instruments there is the Jenkins Activity Scale (JAS) (Jenkins, Rosenman et al. 1967) and the Framingham Type A scale (FTAS) (Levenkron, Cohen et al. 1983). Among the instruments used by an interviewer there is the Rosenman and Friedman structured interview (MacDougall, Dembroski et al. 1979). | The Type D Scale-14 (DS14) evaluate the two components of Type D, the negative affectivity and social inhibition (Denollet 2005). | The 21-item Maastricht Questionnaire evaluates VE including factors such as depressive symptoms, sleep problems and lack of concentration (Appels, Hoppener et al. 1987). | The Cook and Medley Hostility scale (CMHS, or Ho scale) includes 50 items, true or false, evaluates cynicism and distrust (Smith, Glazer et al. 2004); the Buss-Durkee Hostility Inventory (Buss and Durkee 1957) assesses expressive hostility or antagonism (physical and verbal aggression) and neurotic or experiential hostility; the Interpersonal Hostility Assessment Technique (IHAT) is a structured interview that classifies the hostile behavior in four styles (Brummett, Maynard et al. 2000). | The Anger Expression scales (Spielberger et al., 1985), and Framingham Anger Reaction or Expression Scales (Haynes, Feinleib et al. 1980; Eaker, Pinsky et al. 1992); the Spielberger State-Trait Anger Expression Inventory is a self-report Inventory and assess anger expression ("anger-in" and "anger out"); the Anger Attacks Questionnaire evaluates the presence of anger attacks, spells of anger that are inappropriate to the situation and have physical features resembling panic attacks (Fava, Rosenbaum et al. 1991). | The Aggression Questionnaire (AQ), developed by Buss and Perry (1992) contains subscales to measure anger, hostility and verbal and physical aggression (Buss and Perry 1992). |

Table 2. Instruments

has elements of hostile cynicism and anger affect, although it primarily assesses antagonistic expression (Dembroski, MacDougall et al. 1989). In addition, the same questionnaires identified as measures of anger and hostility by some authors are described as measures of aggression by others (Felsten and Hill 1999).

Raynor et al., using twin analyses, found that covariation among the Beck Depression Inventory, the Interpersonal Support Evaluation List and the Cook-Medley Hostility Scale could be explained by a single common genetic factor and a common nonshared environmental factor. They challenged the conventional approach of examining these psychosocial variables as independent risk factors for cardiovascular disease and argued for the importance of investigating specific causes for their covariation (Raynor, Pogue-Geile et al. 2002).

Davidson et al. (Davidson 2008) performed a comparative analysis between the association of different instruments for measuring anger and hostility and CHD. The Minnesota Multiphasic Personality Inventory (MMPI) and the Cook-Medley Hostility Scale (CMHS) were positively associated with CHD in populations with and without psychiatric pathology. The Spielberger Trait Anger Scale (TAS) tended to show higher association with CHD compared with the overall effect in disease studies, while the Spielberger anger expression scale showed no association with CHD.

## **5. Neurophysiological bases for the relationship between negative affect and the cardiovascular system**

Many authors attribute the possible influence of psychological traits on CHD to the impact of these affect states on promoting cardiovascular high-risk behaviors such as smoking, poor eating habits, low physical activity, poor sleep quality and low adherence to drug treatment (Scherwitz, Perkins et al. 1992). However, physiological pathways have been studied, suggesting that these affective constructs may be associated with autonomic, inflammatory and neuroendocrine changes that increase the risk for CHD (Table 3). Aspects of the proposed mechanisms of impact on the cardiovascular system are also discussed in the each of the negative affect categories in section 6.

The *reactivity hypothesis* offers a comprehensive model to understand the mechanisms connecting negative affect and increased cardiovascular morbidity. This hypothesis states that exaggerated physical or psychological responses can identify individuals at increased risk of cardiovascular disease. Based on this model, psychological traits and states would lead to increased risk through cardiovascular and neuroendocrine responses to environmental stressors. Lovallo and Gerin (2003) (Lovallo and Gerin 2003), divided the physiological mechanisms responsible for cardiovascular reactivity in three levels: 1) exaggerated cognitive-emotional responses; 2) increased brain stem and hypothalamus responsiveness; 3) Abnormalities in peripheral tissue modifications. In this paper, we discuss the first level, since it concerns the influence of personality traits on physiological responses of the organism.

Neurophysiologically, Lovallo and Gerin (2003) (Lovallo and Gerin 2003), outline two brain circuits through which the frontal lobe modulates and controls emotions. The first one includes the premotor region of the frontal cortex, connected to the anterior cingulate cortex,

responsible for the selection of motor responses due to a motivated behavior. The second involves the orbital prefrontal cortex, which regulates the activity of the brain stem and hypothalamus secondary to the conscious evaluation of external events. It is worth mentioning the important connection of the orbital prefrontal cortex to the ventromedial prefrontal cortex, which has extensive dopaminergic and serotonergic areas, and is activated by signals ascending from the amygdala, the bed nuclei of the stria terminalis and septal regions. Thus, this second circuit would provide "emotional color" to the experiences.

After the cognitive and emotional evaluation, such areas send signals to the hypothalamus and brain stem, originating a wide range of physiological, endocrine, visceral and motor changes. Thus, specific cognitive and affective dispositions would lead to specific (and possibly persistent) changes in these systems (Lovallo and Gerin 2003).

This model is supported by several studies (Everson, McKey et al. 1995; Drevets 1999; Schaefer, Abercrombie et al. 2000; Pizzagalli, Pascual-Marqui et al. 2001) which indicate the importance of the quality of the stressor event (and not just its intensity) in the increased reactivity in susceptible individuals.

### **5.1 Proposed mechanisms: Chronic versus acute risk**

The impact of negative affect on the cardiovascular system may be chronic or acute. For instance, hostility may be a personality trait with considerable stability across years and can be considered a character trait. In this situation the negative affect may chronically contribute to the morbidity of the cardiovascular system such as an association with increased levels of cholesterol (Table 3) (Dujovne and Houston 1991). On the other hand, anger attacks occurring episodically may acutely damage the cardiovascular system, such as an anger attack causing a heart attack (Mittleman, Maclure et al. 1995).

Regarding emotional states precipitating acute cardiac events, the evidence is very robust. Epidemiological studies have shown a significant increase of sudden cardiac death in populations submitted to disasters such as wars or earthquakes. In records of patients with implantable cardioverter-defibrillator (ICD), it was noticed that individual intense emotions such as anger or anxiety could trigger arrhythmias in susceptible patients. Lampert R et al, 2002, (Lampert, Joska et al. 2002) conducted a controlled prospective study, where ICD patients were requested to record in a diary the intensity of their emotions in the 15 minutes before shocks and, also, during the two hours to 15 minutes before the shock. As a control, the study assessed the diaries of the same patients during the same periods, one week after the shocks registration. Patients identified anger significantly more in the 15 minutes before the shock than during the control period. The association between the shocks and acute anger showed to be higher than the association with other measured emotions such as joy, sadness, worry and anxiety. The same group had previously reported that induced arrhythmias in patients undergoing mental stress (eg, performing arithmetic calculation or remembering stressful events) were faster in onset and more difficult to be extinguished than in those without such exposure.

Regarding psychological precipitants for acute myocardial infarction (MI), Culic V., et al, 2005 (Culic, Eterovic et al. 2005), performed a meta-analysis which found that emotional stress could immediately precedes MI in 7% of all cases of MI.

The relevance of considering both patterns is that affective traits may increase the frequency of acute subtle cardiovascular episodes.

| Type A Behavior Pattern  | Type D Personality   | Vital exhaustion   | Hostility  | Anger   |
|--|--|--|--|---|
| <p>-Short-term responses to stress in physiological variables that are controlled by sympathetic nervous system(Oishi, Kamimura et al. 1999);</p> <p>- Increased cardiovascular risk factors as atherogenic lipid profile(Niaura, Stoney et al. 1992),</p> <p>-Increased thickness of the carotid intima-media (Keltikangas-Jarvinen, Hintsala et al. 2007).</p> | <p>-Overstated cardiovascular activity in daily life, mediated by an enhanced sympathetic drive and decreased vagal control of the heart including endothelial function, platelet function, altered lipid profile, altered activity of the hypothalamus-pituitary-adrenal cortex (HPA) axis and enhanced inflammatory activity of the immune system;</p> <p>-Increased negative behavioral factors; enhanced cortisol reactivity to stress and heightened blood pressure reactivity (Habra, Linden et al. 2003).</p> | <p>-Decreased ACTH and cortisol activation of inflammation; decreased slow wave sleep; reactivated cytomegalovirus fosters growth of atherosclerosis;</p> <p>-Increased production of cytokines and decreased negative feedback from the HPA-axis upon the sympathetic adrenomedullary system.</p> | <p>-Increased blood pressure, heart rate, and levels of norepinephrine, cortisol and testosterone after stress (Suarez, Kuhn et al. 1998);</p> <p>-Decreased adaptation of blood pressure and heart rate to different stressors (mainly those related to interpersonal activities).(Everson, McKey et al. 1995).</p> | <p>-Increased levels of catecholamines and decreased vagal stimulation; increased risk of cardiac arrhythmias (Verrier, Calvert et al. 1975; Stopper, Joska et al. 2007; Ziegelstein 2007; Yu-Wai-Man, Griffiths et al. 2010);</p> <p>-Increased hypertension (Ohira 2010).</p> |

Table 3. Proposed Mechanisms

## 6. The negative affects

### 6.1 Type A Behavior Pattern (TABP)

The TABP was described by Meyer Friedman and Ray Rosenman, two American cardiologists in the decade of 1950. The TABP is an action-emotion complex induced by environmental factors, involving psychomotor mannerisms, vigorous voice, hard-driving, time involvement-pressured job, competitiveness, impatience and easy triggering anger and hostility (Friedman and Rosenman 1959) (Table 1). During the decades of 1960 and 1970 various studies demonstrated a significant association between high levels of TABP measures and the development of cardiovascular disease (Jenkins, Rosenman et al. 1974; Rosenman, Brand et al. 1976). However, subsequent studies found did not confirm the relevance of the TABP as a predictor of CHD (Ragland and Brand 1988; Ragland and Brand 1988; Schulman and Stromberg 2007). Therefore, many researchers changed the focus of their research to assess whether some aspects of the TABP, particularly anger and hostility, would be more closely linked with the development of heart disease.



Both self-report and investigator-administered instruments have been developed to recognize TABP. Among the self-report instruments are the Jenkins Activity Scale (JAS) (Jenkins, Rosenman et al. 1967) and the Framingham the Type A scale (FTAS) (Levenkron, Cohen et al. 1983). A reliable investigator-administered instrument is the Rosenman and Friedman structured interview (MacDougall, Dembroski et al. 1979). Use of this structured interview may result in different association with CHD than the self report evaluation (Dembroski, MacDougall et al. 1985; Schulman and Stromberg 2007), raising questions on the reliability of the self-report instruments.

## 6.2 Hostility

Various studies combine under the single label of hostility a variety of manifestations of anger and aggression. Nevertheless, those represent distinct cognitive, emotional and behavioral characteristics. Essentially, hostility generally reflects a person's tendency to view the world in a negative, cynical fashion. Smith et al (Smith, Glazer et al. 2004) define hostility as a primarily cognitive construct involving "negative attitude toward others, consisting of enmity, denigration, and ill will". The author describes its components: the cynicism (i.e., a belief that others are motivated primarily by selfish concerns); the mistrust (an expectation that people will tend to be hurtful); and denigration (i.e., a devaluation of other people's motivation and goals). Other authors define hostility as "antagonistic interpersonal attitude" including cognitions (cynicism and hostile attributions), affect (hostile emotions) and behaviors (aggressive responses) (Barefoot JC LI. The assessment of anger and hostility. In: Siegman AW, Smith TW, eds Anger, Hostility, and the Heart Hillsdale, NJ: Lawrence Erlbaum 1994:43- 66.

It is clear that these definitions, as well as the personality traits they originate from, are highly correlated and overlapping. Smith and Glazer (Smith, Glazer et al. 2004) point out the correlation among these phenomena, emphasizing that anger, hostility and aggression are not just different names for the same construct. Consequently, one could not presume that they have similar associations with cardiovascular pathology. Suarez et al (Suarez, Kuhn et al. 1998) conducted a randomized study in which men, stratified by high or low scores on the Ho scale, underwent an anagram-solving task while experiencing alternatively harassing and not harassing comments from the researcher. It was observed that, compared to men with low levels of hostility, those with higher scores on Ho scale showed greater increase in blood pressure, heart rate, and levels of norepinephrine, cortisol and testosterone. Interestingly, such increase occurred only during (and shortly after) the aversive comments. In a similar study Everson et al (Everson, McKey et al. 1995) evaluated men with high and low levels of hostility. They found that men with low levels of hostility experienced rapid adaption of heart rate and blood pressure elevations to task repetition, while men with high hostility experienced even larger increases in their rates of heart rate and blood pressure after repetitions of aversive tasks. From these two studies it can be concluded that personality traits influence physiological responses to different stressors, particularly those related to interpersonal activities. Smith and Glazer (Smith, Glazer et al. 2004) point out other social stressors also related to high reactivity among hostile individuals, such as recalling and discussing past anger-inducing events, discussions, watching anger-inducing movies and self-disclosure of personal problems. Some authors have emphasized the relevance of higher cynical hostility (Chaput, Adams et al. 2002). Various studies and meta-analyses have supported the role of hostility in increasing the risk of CHD and even cardiac

death (Booth-Kewley and Friedman 1987; Friedman and Booth-Kewley 1987; Miller, Smith et al. 1996).

A variety of instruments have been used to evaluate hostility and the differences among them indicate the distinction among the subjacent concepts.

The Cook and Medley Hostility scale (CMHS, or Ho scale) consists of 50 items taken from the Minnesota Multiphasic Personality Inventory to be answered true or false. CMHS can be interpreted as a measure of cynicism and distrust (Smith, Glazer et al. 2004). This is a comprehensive scale that has been correlated with other features outside of the concept of hostility, such as neuroticism, depression and anxiety (Barefoot, Dodge et al. 1989; Steinberg and Jorgensen 1996). Although frequently used, its internal reliability is low and some authors advise to analyze its subscales separately (Barefoot, Dodge et al. 1989).

The Buss-Durkee Hostility Inventory (Buss and Durkee 1957) assesses mainly two interconnected dimensions: the expressive hostility or antagonism (physical and verbal aggression) and the neurotic or experiential hostility, which involves subjective experiences like resentment, suspicion, mistrust and irritation.

The Interpersonal Hostility Assessment Technique (IHAT) developed by Barefoot and colleagues (Brummett, Maynard et al. 2000) is a structured interview that classifies hostile behaviors in four types, based on the style (rather than content) of the responses to interviewer: direct challenges to the interviewer, indirectly or more subtle challenges, hostile withholding of information or evasion of the question, and irritation (Brummett, Maynard et al. 2000).

Although consistently associated with increased cardiovascular morbidity, the effect size of hostility has been considered low and its clinical relevance has been questioned by some authors (Myrtek 2001).

### 6.3 Anger

The concept of anger usually refers to an unpleasant emotion ranging in intensity from irritation or annoyance to fury or rage. Feelings of anger are elicited in situation of being treated unjustly and is accompanied by subjective arousal. As a personality trait it can be defined as the characteristic to experience frequent and pronounced episodes of this emotion.

Another relevant aspect of anger is its expression. In this context, two subtypes have been defined: "anger-out", a personality trait derived from a combination of anger and aggression (i.e, the expression of aggressive behavior when angry) and "anger-in", a tendency to feel anger and suppress it (Schulman and Stromberg 2007). Anger is viewed by other authors (Norlander and Eckhardt 2005) as a multidimensional construct, involving physiological, behavioral, cognitive and phenomenological components. Scales have been developed to evaluate various aspects of anger. The Anger-Out scale of the Spielberger et al. (1985) Anger-Expression Questionnaire evaluates tendencies to express aggression outwardly using a self-report questionnaire format, whereas the Anger-In scale purportedly measures tendencies to suppress or withhold anger.

Evaluated as a trait, anger significantly predicted occurrence of another MI (Denollet and Brutsaert 1998). More recently, Ohira (Ohira 2010), 2010, in the Circulatory Risk in

Communities Study (CIRCS), evaluated the association of depressive symptoms, tension and anger expression with the incidence of cardiovascular disease in Japanese population. It was a pioneering study, since all previous relevant data are mostly limited to Western populations. As an instrument for measuring tension and anger expression, Ohira and colleagues used the Spielberger anger expression scale and the Framingham Tension Scale to evaluate 6292 men and women. In a cross-sectional examination, "anger-out" was inversely associated with hypertension in men. In longitudinal observation, anger-in score was positively associated with hypertension in men, even after further adjustment for BMI, alcohol intake and systolic blood pressure levels at baseline.

Besides working chronically as a personality trait, episodes of anger may acutely cause negative impact on the cardiovascular system. Anger attacks have been associated with sudden cardiac death, MI and ventricular arrhythmias.

Among the pathophysiological mechanisms linking anger attacks and acute cardiovascular changes, two are most studied: modifications in autonomic regulation and electrophysiological changes. The autonomic dysregulation caused by anger and other emotions is well described. Experimental studies show that intense emotional factors increase the level of catecholamines and decrease vagal stimulation. Other findings suggest that cardiac sympathetic activation (and the decrease of vagal stimulation) is arrhythmogenic (Lampert 2010). Of note, Verrier et al (Verrier, Calvert et al. 1975) reported the stimulation of the posterior hypothalamus (which increases sympathetic cardiac stimulation) produced a 40% reduction of the threshold for induction of ventricular fibrillation in dogs. Regarding arrhythmogenic electrophysiological changes induced by stress, interesting results were obtained by analyzing the T-wave alternation. This measure is considered a marker of the heterogeneity of repolarization and therefore to have a major role in arrhythmogenesis. T-wave alternation was enhanced during mental stress (Kovach, Nearing et al. 2001). In a previous study, increased T-wave alternation among patients experiencing emotional stressors correlated to a higher incidence of shocks of implantable cardioverter-defibrillator (ICD) which were in turn induced by acute ventricular arrhythmias (Stopper, Joska et al. 2007). Moreover, it is noteworthy that recent evidence obtained from neuroimaging studies using positron emission tomography suggest that the laterality of brain activity during stress is related to an increased susceptibility to ventricular arrhythmias (Ziegelstein 2007).

Psychological interventions may be used to improve the management of anger, and anger attacks may also decrease significantly with antidepressant treatment, particularly in those with depression (Fava, Rosenbaum et al. 1991; Fava, Alpert et al. 1996).

#### 6.4 Type D

Type D personality, also known as *distressed* personality, is a construct that has also been associated with cardiovascular disorders. The core symptoms of this construct are *negative affectivity* and *social inhibition* (Denollet 1998). The *negative affectivity* refers to a tendency to experience distress over time and in various situations (Watson and Pennebaker 1989), while *social inhibition* refers to the tendency of consciously inhibit the expression of these negative emotions in social situations. A high score on both traits denotes those with a Type D personality (Pedersen and Denollet 2003). Therefore, the base of this construct is not just

experiencing negative emotions, but the combination of negative emotion and suppressed emotional expression. Consequently, those with this personality experience distress which is not easily shared with others. Type D personality may be identified with the DS14, an instrument developed specifically to obtain standard assessment of negative affectivity and social inhibition (Denollet 2005).

Several studies established Type D personality as an independent predictor of cardiac mortality in patients with CHD (Denollet, Sys et al. 1995; Denollet, Vaes et al. 2000). It has also been reported that Type D personality increases the risk of sudden cardiac arrest (Appels, Golombeck et al. 2000) and is an independent predictor of mortality in patients with decreased left ventricular ejection fraction after MI (Denollet and Brutsaert 1998).

Direct mechanisms proposed for the impact of Type D personality in the cardiovascular system include cardiovascular autonomic nervous system activity, endothelial function, platelet function and altered lipid profile. Type D personality has been associated with greater cortisol reactivity to stress, heightened blood pressure reactivity (Habra, Linden et al. 2003) and increased circulating levels of the pro-inflammatory cytokine tumor necrosis factor (TNF- $\alpha$ ) and TNF- $\alpha$  soluble receptors 1 and 2 (Denollet, Conraads et al. 2003).

### 6.5 Vital exhaustion

The most common definition of VE characterizes this condition by an unusual fatigue, increased irritability and feelings of demoralization. The assessment of VE can be made with the 21-item Maastricht Questionnaire (Appels, Hoppener et al. 1987) and, although there is an overlap between VE and depressive symptoms, there is evidence these are distinct conditions (Kopp, Falger et al. 1998).

Various studies have associated VE with CHD and chronic heart failure (Appels, Kop et al. 1995; Pedersen and Middel 2001; Smith, Gidron et al. 2009). VE has been associated with a twofold to threefold increased risk of mortality and morbidity in patients with CHD (Kop, Appels et al. 1994; Appels, Kop et al. 1995). It has also been associated with sudden cardiac arrest and adverse cardiac events in patients that underwent successful angioplasty (Kop, Appels et al. 1994; Appels, Golombeck et al. 2000). A recent study showed that four distinct VE trajectories may be found in cardiac patients: low VE, decreasing VE, increasing VE and severe VE; the last two (increasing VE and severe VE) trajectories were predictors of poor cardiovascular prognosis (Smith, Kupper et al. 2010).

Several possible biological pathways may link VE with cardiovascular disease. VE has been associated with increased lipid metabolism (van Doornen and van Blokland 1989), reduced fibrinolytic capacity (Kop, Hamulyak et al. 1998; van Diest, Hamulyak et al. 2002), parasympathetic withdrawal (Watanabe, Sugiyama et al. 2002), reduced heart rate recovery after exercise (von Kanel, Barth et al. 2009), increased levels of cytokines (van der Ven, van Diest et al. 2003; Janszky, Lekander et al. 2005), decreased slow wave sleep, reactivated cytomegalovirus fosters growth of atherosclerosis, decreased negative feedback from the HPA-axis onto the sympathetic-adrenomedullary system (Appels 2004) and hypocortisolemia (Keltikangas-Jarvinen, Raikkonen et al. 1996; Nicolson and van Diest 2000).

Treatment of VE aims to reduce stressors causing exhaustion and to support recovery by promoting rest and by making rest more efficient. Group discussions may be used to identify stressors in the family and work domain, and to help patients to cope with these stressors. The process includes an evaluation of the optimum length of resting time, teaching relaxation exercises designed to make rest more efficient, stimulation of physical exercise and homework assignments (Appels 2004).

### 6.6 Aggression

Aggression refers to a physical or verbal behavior, typically defined as attacking, destructive, or hurtful actions. Aggressive behavior may be precipitated by anger, but it may be motivated by many other factors as well. Aggression may be considered a personality trait in those who tend to frequently exhibit such behavior. The Aggression Questionnaire (AQ), developed by Buss and Perry (1992) (Buss and Perry 1992), contains subscales to measure anger, hostility and verbal and physical aggression.

### 6.7 Negative affectivity and negative emotion

Watson & Clark (1984) have proposed the existence of a broadband personality dimension referred to as negative affectivity (Watson and Clark 1984). This construct includes all negative emotions and is characterized by a general disposition to chronically experience anxiety, sadness, guilt, anger, irritability, and other negative emotions.

These individuals tend to be internally focused and attuned to somatic sensations. This tendency leads them to experience body sensations as symptoms of physical illness.

Some data have offered a support for increased risk of CHD in individuals with increased levels of negative affectivity (Frasure-Smith and Lesperance 2003).

Besides negative affectivity, some studies have referred to depression, anger, anxiety and hostility as negative emotions. According to Kubzansky et al. anger, anxiety and depression are the three negative emotions with the largest evidence linking them etiologically to the development of CHD (Kubzansky and Kawachi 2000; Kubzansky, Davidson et al. 2005; Kubzansky 2007). According to these authors emotions occur in a continuum ranging from normal to pathological and there is evidence of a dose response between negative emotions and CHD risk (Kubzansky and Kawachi 2000; Everson-Rose and Lewis 2005; Rozanski, Blumenthal et al. 2005). Possibly all these negative emotions work as a general stressor of the cardiovascular system (Todaro, Shen et al. 2003). In the INTERHEART, a case-control study, the authors performed an analysis using a score integrating psychosocial factors including depression, locus of control, perceived stress and life events. They found that psychosocial factors had a greater relative risk of MI than well-established risk factors such as hypertension, abdominal obesity and diabetes (Yusuf, Hawken et al. 2004).

## 7. Treatment

Various strategies have been developed to treat negative affect (Table 4). Most of them focused in reducing TABP, including education about CHD and TABP; Relaxation Training (Relaxation exercises of the "deep-muscle" or "Jacobsonian"); Cognitive Therapy including restructuring techniques such as the identification and modification of TABP cognitions (e.g.,

"I have to get there faster" is changed to "I'm going fast enough"). Specific techniques are the *Imaging* strategy that includes imagining rousing situations such as a traffic jam or confrontation with a boss and the training to apply specific coping skills such as relaxation training or cognitive restructuring; the *Behavior Modification* that includes rehearsing of Type B coping skills through role playing or behavioral prescriptions that are given to be carried out between sessions; the *Emotional Support* that includes the encouragement to ventilate the painful affects and experiences in an empathic atmosphere. There is also the *Psychodynamic Interpretation* that includes the use of psychodynamic interpretations of the unconscious motives and conflicts underlying TABP (Nunes, Frank et al. 1987). A meta-analysis of 18 controlled studies of psychological treatment of TABP revealed an effect size of  $0.61 \pm 0.21$  indicating a reduction approximately by half a standard deviation (Nunes, Frank et al. 1987).

| Type A Behavior Pattern   | Type D Personality   | Vital exhaustion  | Hostility  | Anger  | Aggression   |
|---|--|---|--|--|--|
| -Education about CHD and TABP;<br>-Relaxation Training:<br>Relaxation excercises;<br>-Cognitive Therapy including cognitive restructuring techniques and also psychodynamic interpretation (Nunes, Frank et al. 1987) | -Patients may benefit from psychological treatment to deal with threatening issues and lighten the symptoms. | -Reduction of the stressors that cause exhaustion,<br>-Support recovery by promoting rest and by making rest more efficient;<br>-Group discussions may be used to identify stressors in the family and work domain, and to help patient in coping with these stressors;<br>-Stimulation of physical exercise (Appels 2004). | -Cognitive-behavior interventions may reduce measures of hostility (Sloan, Shapiro et al. 2010);<br>-SSRIs may reduce hostile affect (Kamarck, Haskett et al. 2009). | -Cognitive-behavioral and skills-based approaches may reduce anger (Blake and Hamrin 2007).<br>-Anger attacks may decrease with SSRIs particularly in depressed patients (Fava, Rosenbaum et al. 1991; Fava, Alpert et al. 1996) | -SSRIs may reduce, physical and verbal aggression in women (Kamarck, Haskett et al. 2009). |

Table 4. Treatments

There is no well-established treatment for type D personality, but these patients may benefit from psychological treatment to deal with threatening issues and lighten the symptoms. Interventions for VE focus on reducing the stressors associated with the exhaustion and support recovery by promoting rest and by making rest more efficient. Group discussions

may be used to identify stressors in the family and work domain, to help patients to cope with these stressors and to stimulate physical exercise (Appels 2004). Kamark et al (Kamarck, Haskett et al. 2009) studied people with high hostility scores and with no Axis I diagnosis medicated with citalopram or placebo. The citalopram group showed significant reductions in state anger, and hostile affect, while physical and verbal aggression was reduced among women.

Cognitive-behavior interventions have shown to be effective in reducing measures of hostility and improving cardiac autonomic modulation (Sloan, Shapiro et al. 2010). In addition, Cognitive-behavioral and skills-based approaches may be effective in reducing anger and aggression in youth (Blake and Hamrin 2007). Anger attacks (Fava, Rosenbaum et al. 1991; Fava, Alpert et al. 1996) decreased significantly with fluoxetine treatment in depressed patients.

## 8. Discussion

Several studies have linked negative affect with cardiovascular morbidity. However, due to discrepancies among results, there is still some controversy regarding the existence, nature and magnitude of their relationship. In this context, Schulman and Stromberg, 2007, (Schulman and Stromberg 2007) conducted a review of the meta-analyses and systematic reviews on this subject. As inclusion criteria, the authors used the Database of Abstracts of Reviews of Effects (DARE) criteria and they chose to include only those reviews and meta-analyses which had measured the magnitude of the effect of anger, hostility and TABP on the cardiovascular outcomes. The final analysis included five systematic reviews (Hemingway and Marmot 1999; Rozanski, Blumenthal et al. 1999; Kuper, Marmot et al. 2002; Suls and Bunde 2005). As a common result, they showed positive results between TABP, hostility, anger and CHD in healthy populations. For individuals with heart disease the review showed conflicting results. The authors concluded that TABP, hostility, anger and anger expression may not constitute a risk factor for worse prognosis in all patient samples, and their effects would be more significant in a previously healthy population. In such patients negative affect could harm the cardiovascular system directly or indirectly by increasing cardiovascular risk factors such as hypertension and atherosclerosis (Matthews, Owens et al. 1998; Pollitt, Daniel et al. 2005).

In a more recent review and meta-analysis, Chida and Steptoe (2009) (Chida and Steptoe 2009) selected only prospective cohort studies, exploring the causal association of measures of anger and hostility and heart disease. A total of 21 cohorts with healthy patients at baseline with 71 606 individuals, and 18 cohorts of patients with existing CHD with 8120 individuals were included. These studies were published between 1983 and 2006 and performed in a wide range of countries (Europe, America and Australia). This meta-analysis found that 28% of studies with healthy individuals and 26.3% of studies with CHD patients showed significant harmful effects. The overall combined hazard ratio (HR) was 1.19 (95% CI 1.05 to 1.35) for the healthy population and 1.23 (95% CI 1.08 to 1.42) for the disease population, indicating a positive association. In subgroup analysis, it was found that cohorts with longer follow-up periods showed higher HR than the overall effect both in studies with healthy and with CHD individuals. Also, in studies with CHD patients, the HR was sustained even after controlling for baseline disease status and treatment (1.20 95% CI 1.0 to 1.44). Focusing on mortality analyses, a positive association was also found between anger

and hostility and cardiovascular mortality. Thus, this review emphasizes the increased risk of negative affect for those with established CHD, in contrast to the results of Schulman and Stromberg.

The development of a validated gold standard for the assessment of negative affect is necessary to allow the comparison between studies. Moreover, the concepts of anger and hostility do not include a clear cutoff for its morbidity and consequently data about their prevalence, course, comorbidity and treatment response are lacking. Besides this difference in instruments, there is also a disagreement concerning the results of clinical studies focused on the relationship between psychological traits and cardiovascular disease.

Undeniably, a consistent body of evidence links negative affect with heart disease. In addition, the efficacy of psychotherapeutic interventions in cardiac patients was recently demonstrated (Linden, Phillips et al. 2007). While the clinical use of screening instruments for anger and hostility is not yet a reality, in the future the multi-disciplinary approach involving psychological techniques, possibly specifically focused on these traits, might become an important strategy in the management of patients with CHD. Moreover, recent advances in our understanding of pathophysiology involving physical and emotional changes will potentially allow specific case definitions and possible targeted drug therapies for certain forms of negative affect.

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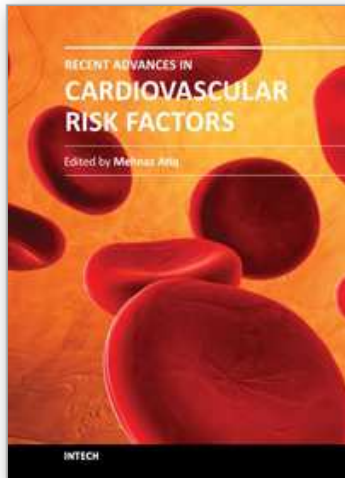
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## **Recent Advances in Cardiovascular Risk Factors**

Edited by Prof. Mehnaz Atiq

ISBN 978-953-51-0321-9

Hard cover, 522 pages

**Publisher** InTech

**Published online** 21, March, 2012

**Published in print edition** March, 2012

Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Marco A.A. Torquato Jr., Bruno P.F. de Souza, Dan V. Iosifescu and Renerio Fraguas (2012). Anger, Hostility and Other Forms of Negative Affect: Relation to Cardiovascular Disease, Recent Advances in Cardiovascular Risk Factors, Prof. Mehnaz Atiq (Ed.), ISBN: 978-953-51-0321-9, InTech, Available from:  
<http://www.intechopen.com/books/recent-advances-in-cardiovascular-risk-factors/negative-affects-and-cardiovascular-disease>

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