UNIVERSITÀ DEGLI STUDI DI PADOVA

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THE INTERACTION BETWEEN DEPRESSION AND AUTONOMIC DYSREGULATION IN PATIENTS UNDERGOING CARDIAC SURGERY

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CONTENTS

OVERVIEW

The studies reported in this thesis are part of a wide longitudinal collaborative project of the Department of General Psychology (University of Padova), the Ca' Foncello Treviso Hospital and the Highly Specialized Rehabilitative Hospital (ORAS, Motta di Livenza). The project involved a multimodal assessment in patients eligible for first time cardiac surgery, aimed at evaluating cognitive and affective deficits, which in turn are well known risk factors for postoperative adverse outcomes. Preliminary findings showed that preoperative depression significantly predicted depression three months after cardiac surgery; furthermore, preoperative depression was associated with postoperative cognitive decline at 18 months follow-up. These findings have been particularly relevant for the present project, that focused on autonomic factors which mediate the relationship between depression and increased cardiac risk.

Altered autonomic control on the heart [as indexed by reduced heart rate variability (HRV)] has been suggested as the most plausible mechanism by which depression is associated to increase cardiac risk. Four studies have been carried out: in the first study, the relationship between depression and impaired autonomic modulation on heart was investigated, in patients who underwent first time cardiac surgery. The findings displayed reduced vagal cardiac control in depressed patients, compared to nondepressed patients.

In the second study, the relationship between depression, emotion regulation strategies and cardiac autonomic control was examined. The findings yielded that disproportionate suppression of emotion partially mediate the relationship between depression and reduced vagal control on the heart.

Not only depression has been associated to reduced vagal control at rest, but also with abnormalities in vagal modulation during emotional stressors. Therefore, the third study

aimed at examining parasympathetic cardiac control during three emotional imagery tasks in depressed and non-depressed patients, after cardiac surgery. A direct association between postoperative depression and exaggerated vagal withdrawal during the imaging of the unpleasant script was found.

Finally, the research was focused on possible non pharmacological treatment of depression in patients after cardiac surgery. The fourth study aimed at evaluating the effectiveness of a short cardiorespiratory biofeedback training in increasing vagal control on the heart and reducing depressive symptoms in patients after first time cardiac surgery. The rehabilitative protocol included the administration of a respiratory sinus arrhythmia (RSA) biofeedback training, in addition to the standard rehabilitation protocol, compared to the standard rehabilitation protocol only. RSA-biofeedback resulted effective in increasing vagal control on the heart, thus lowering an important cardiac risk factor. Moreover, the training resulted in a reduction of depressive symptoms, with a positive influence on mood.

In conclusion, the present thesis confirms and extends the association between depression and reduced vagal control also in patients after first time cardiac surgery, thus supporting the role of depression as a potential risk factor for morbidity and mortality after cardiac surgery. In addition, it highlights the role of suppression of emotion as an affective trait and that of emotional reactivity to stressors in mediating the relationship between depression and increased cardiac risk. Finally, it provides evidence in support of the usefulness of an RSA-biofeedback training in patients after cardiac surgery. These findings provide suggestions for improving well-being and health care interventions in patients after cardiac surgery.

Keywords: Depression; Emotion regulation; Cardiac surgery; Autonomic nervous system; Heart rate variability; Vagal tone; Biofeedback

CHAPTER 1

GENERAL INTRODUCTION

1.1 Depression and cardiovascular diseases

Depression and cardiovascular diseases are listed as two of the most detrimental diseases in developed countries by the Statistics from The Global Burden of Disease project (Mathers & Loncar, 2006; Murray & Lopez, 1997).

Depression is a underdiagnosed and undertreated mood disorder, characterized by depressed mood, anhedonia, loss of interest, decreased energy, sense of futility, low self-esteem and feelings of hopelessness. According to the Diagnostic and Statistical Manual (American Psychiatric Association, 2013) major depression is characterized by depressed mood, loss of interest or pleasure in daily activities that has also a relapse on social and work activity, concentration, and may affect appetite and sleep habits. In addition, depressive conditions include subclinical symptoms that are milder or briefer compared to diagnoses of major depression. Usually, mild and brief symptoms have small impact on a person's life, on the contrary, mild and persistent symptoms may be detrimental to a person's adjustment. In fact, subclinical depression has been reported to predict development of major depression and other emotional problems, and may result in significant impairment in affective and social functioning (Gotlib, Lewinsohn, & Seeley, 1995; Horwath, Johnson, Klerman, & Weissman, 1992; Wells et al., 1989; Zonderman, Herbst, Schmidt, Costa, & McCrae, 1993)

Depression disorders (including major depression, moderate depressive symptoms and mild subclinical depressive symptoms) are highly prevalent, with a lifetime prevalence

reported between 8% and 17% (Andrade et al., 2003; Blazer, Kessler, McGonagle, & Swartz, 1994; Kessler et al., 1994), and, by the year 2020, is likely to become the second most important cause of disease burden, right after cardiovascular diseases (Murray & Lopez, 1997).

Depression disorders are psychological disorders that can be said to be fatal. In fact, depression disorders are associated to high rates of disability and mortality due to suicide (Clark & Fawcett, 1992) and, importantly, depression disorders are strongly associated to cardiovascular diseases. Evidence from both experimental and epidemiological studies support the hypothesis of a bidirectional relationship between depression disorders and cardiovascular diseases.

Cardiovascular diseases (CVD) are a wide group of disorders affecting the heart and blood vessels, and the most commonly associated with depression are hypertension, unstable and stable coronary heart disease (CHD) and congestive heart failure (CHF) therefore, these CVDs will be principally consider in this following sections. The major cause of artery disease is atherosclerosis, that occurs as an inflammatory response to chronic damages of the vessel wall. When the atherosclerotic plaque undergoes events like erosion, rupture, thrombosis, or spasm a major cardiac event occurs. Valve diseases may affect each heart valve and the most common diseases are valve stenosis and valve prolapse. Valve stenosis is characterized by commissural fusion, most frequently caused by rheumatic disease, while valve prolapse consists in an abnormal movement of the valve beyond its normal position, causing reversed blood flow and blood regurgitation.

Currently CVDs are the primary cause of morbidity, disability and mortality worldwide, showing a continue increasing trend, and this incidence is predicted to increase to approximately 25 million deaths by 2020 (Dahlöf, 2010).

More importantly, patients who survive acute cardiovascular events are likely to become chronic patients, and, in turn, CVDs heavily compromise quality of life. Indeed, CVDs represent an important economic burden to the national health system. In 1999, the total sum of direct (e.g., treatment) and indirect cost (e.g., lost days of work) of CVDs in the United States were estimated as $ 180 billion (Keyes & Lopez, 2012). Recently, it has been assessed that in Italy cardiovascular drugs account for more than 25% of the pharmaceutical costs (Agenzia Italiana del Farmaco, 2012).

Depression is strongly associated with CVDs, in fact, while the prevalence of depression in the general population is approximately 2–9% (American Psychiatric Association, 2000), its prevalence in patients after myocardial infarction is approximately 45% (Schleifer et al., 1989), and might be even higher in patients with chronic cardiovascular conditions such as congestive heart failure (CHF) (Freedland et al., 2003). Recently, a large study on 1167 elders compared the prevalence of depression among cardiac patients (heart failure, post myocardial infarction and post CABG patients) with a reference group of healthy individuals. Patients in each of the cardiac groups showed a higher prevalence of anxiety, depression and hostility compared to that in the group of healthy individuals. Specifically, 63% of heart failure patients exceeded the threshold for depression compared to 56% of post-myocardial infarction patients, 53% of post-coronary artery bypass graft patients and only 33% of healthy individuals (Moser et al., 2011). Almost three-quarters of patients with heart failure reported experiencing symptoms of depression and the heart failure group had the greatest percentage of patients with depressive symptoms.

Given the high prevalence of both depression and cardiovascular diseases and the thigh association between them, in the next sections this relationship will be described, and the need for understanding the mechanisms responsible for this link will be underscored.

1.1.1 Depression: consequence or predictor of cardiovascular diseases?

Converging evidence from a large body of research highlight a strong, bidirectional, relationship between depression and CVDs. The role of CVDs as a relevant risk factor for mood disorders, particularly depression, is well known and recognized (Freedland et al, 2003; Schleifer et al., 1989). The presence of cardiovascular disease can directly and indirectly influence mood disorder, including both depression and anxiety symptoms. Depression induced by CVDs can result from cognitive-behavioral processes (e.g., dealing with significant changes in lifestyle, poor health habits, worries about physical health, anxiety feelings, or fear for the future and contemplation of one's mortality) or physiological processes (e.g., autonomic nervous system dysregulations, neurotransmitters and hormonal modifications). Both psychological and physiological mediators might contribute to the relationship between cardiovascular disease and mood changes.

On the other side, in the last two decades many studies have highlighted the role of depression as an important and independent risk factor for the onset, maintenance and exacerbation of cardiovascular diseases (Barth, Schumacher, & Herrmann-Lingen, 2004; Ford et al., 1998; Glassman & Shapiro, 1998; Hemingway & Marmot, 1999). As shown in Figure 1.1, several lines of evidence indicate that depression predicts incidence of cardiovascular disease, as well as cardiac-related morbidity and mortality, in individuals with no prior history of cardiac pathophysiology (Anda et al., 1993; Barefoot & Schroll, 1996; Everson et al., 1996; Penninx et al., 2001).

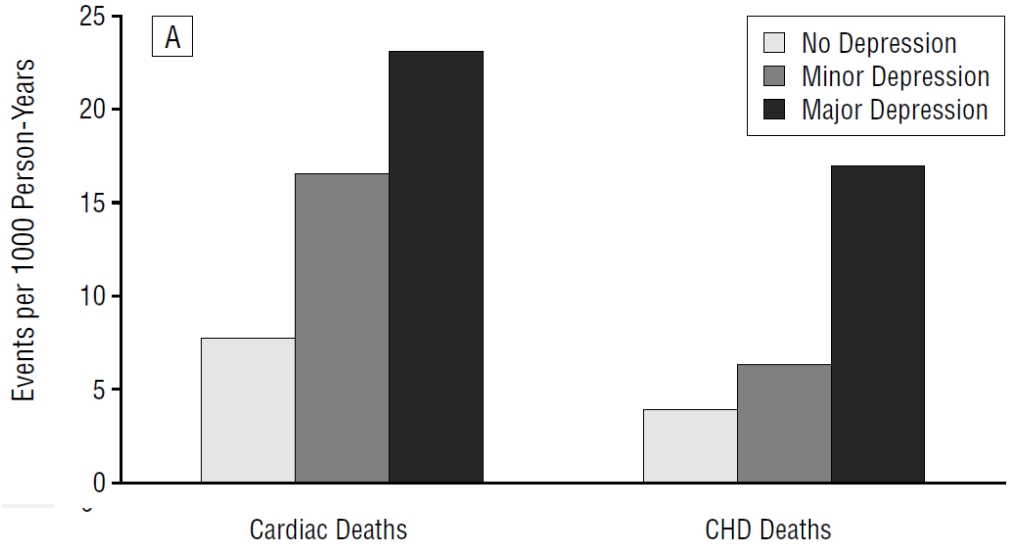


Figure 1.1. Cardiac death and CHD death rates per 1000 person-years by depression status in individuals without cardiac disease (N=2397) (Penninx et al., 2001)**.**

For instance, Carney and colleagues, 1995 estimated that about 50% of patients who were depressed at the time cardiovascular disease was initially diagnosed have had at least one more previous depressive episodes. Wulsin and Singal (2003) reviewed studies that reported the association between depression and coronary heart disease (CHD), the authors reported that depressive symptoms were associated with roughly a 60% higher likelihood of developing CHD. Also, in a large cohort study of 2847 individuals, Penninx and coworkers (2001), found that depression increases the risk for cardiac mortality in both individuals with and without cardiac diseases at baseline. The relationship remained significant even after adjusting for demographic factors (such as age and sex), smoking, alcohol use, blood pressure, body mass index, and comorbidity.

Moreover, a large body of literature have displayed that depression in patients with existent CVD increases the risk for morbidity and adverse cardiac events associated with

heart disease (Barefoot & Schroll, 1996; Carney & Freedland, 2003; Carney et al., 2005; Everson et al., 1996; Frasure-Smith, Lespérance, & Talajic, 1995; Frasure-Smith & Lespérance, 2003). A large meta-analysis on the mortality linked to depression in patients with coronary heart disease found that depression was associated with two times higher mortality risk in the two years after the initial assessment. Also, this negative prognostic effect persisted in the long-term (Barth et al., 2004). More recently, Lichtman and coworkers (2008) showed a dose-response relationship between the increasing of depression severity and subsequent cardiac events, with more severe depression being associated with higher risk of earlier and more severe cardiac events.

The association between mood disorders and CVDs has been shown to be independent of traditional cardiovascular risk factors such as reduced physical activity, smoking, hypertension, high cholesterol, increased body mass index and diabetes (Anda et al., 1993; Barefoot & Schroll, 1996; Barth et al., 2004; Carney et al., 1988; Frasure-Smith & Lespérance, 2003; Penninx et al., 2001).

Therefore, the majority of the studies reported data in support of depression as a risk factor for both the development of and the worsening of CVD. More importantly, given the growing evidence on depression as a risk factor for CVD, recently the American Heart Association (AHA) reported an advisory in which depression have been introduced as an officially recognized cardiac risk factor for coronary heart disease (CHD).

1.2 Depression after cardiac surgery

Cardiac surgery is frequently performed to treat complications of cardiovascular diseases, and/or to remove or reduce cardiac symptoms, like angina and pressure over the chest. The most common operated surgical intervention for ischemic diseases is coronary

artery bypass graft (CABG). Cardiac valve replacement and repair is used as a therapy for degenerative, infectious and congenital lesions of aortic and mitral valve. In general the benefits, positive outcomes of both CABG and cardiac valve surgery are well established and include reduction of cardiac symptoms angina and stenosis, the stabilization of ventricular function, increased survival rate (Eagle et al., 1999) and improvements in the quality of life and functional activity of daily living (Shan, Saxena, McMahon, Wilson, & Newcomb, 2013). CABG and cardiac valve surgery differ for many factors, including patients related characteristics (usually patients undergoing cardiac valve surgery are older), technical differences and postoperative complication. Especially, CABG surgery is often associated with heart failure, myocardial infarction, arrhythmia, thrombosis and stroke (Hannan et al., 2003), while cardiac valve surgery is associated with atrial fibrillation, and less frequently, renal failure and stroke (Mathew et al., 2004).

Even though many CVD patients may be relieved after cardiac surgery, due to better physical function and overall wellbeing, undergoing cardiac surgery is a significant life event, with a relevant impact on the patients' affective states. In fact, many studies have disclosed that a modest, still consistent, number of patients report cognitive and emotional disorders, such as a decline in cognitive domains, anxiety and mood disorders after CABG (Arrowsmith, Grocott, Reves, & Newman, 2000; Ho et al., 2004; McKenzie, Simpson, & Stewart, 2010). Similarly, valve surgery has been associated with increased anxiety and mood disorder postoperatively (Ho et al., 2005; Székely et al., 2007).

Langosch and Schmoll-Flockerzie (1992) highlight that both patients who underwent CABG or valve surgery could report increased levels of global psychopathology, especially higher anxiety and depression symptoms. Depressive symptoms occur both immediately after the surgery and all over the first 3 to 6 months after hospital discharge (Gallagher, McKinley, & Dracup, 2004) and may persist in the long term. More importantly,

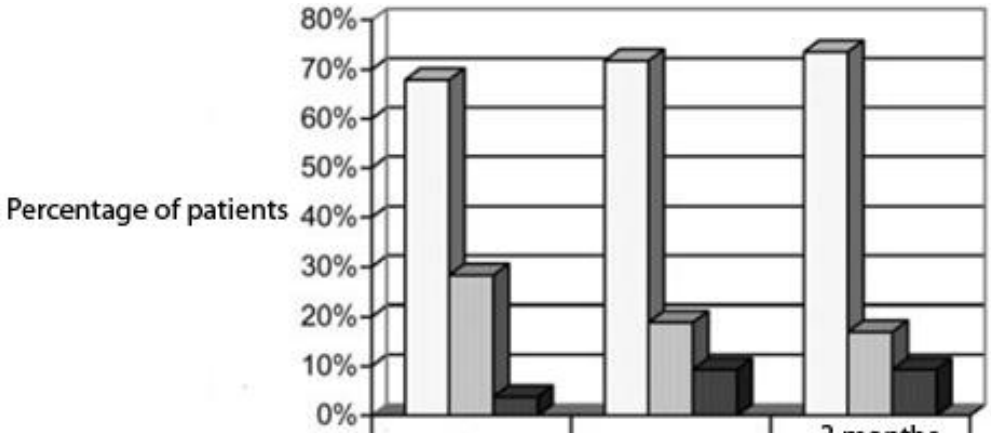
postoperative depression has a negative impact on recovery after cardiac surgery, resulting in reduced postoperative quality of life (Dickens, Cherrington, & McGowan, 2012), increased rehospitalization rate (Burg, 2003b), morbidity (Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001) and even increased mortality risk (Scheier, 1999).

Given the growing relevance of depression in the cardiac surgery context, incidence and consequences of postoperative depression will be described.

High rates of depression are commonly reported in patients undergoing cardiac surgery. Specifically, the prevalence of major depression among these patients is reported at around 20% (Connerney et al., 2001; Fráguas, Ramadan, Pereira, & Wajngarten, 2000) while depressive symptoms are commonly reported by 20% to 36% of patients before cardiac surgery (Figure 1.2) (Langeluddecke, Fulcher, Baird, Hughes, & Tennant, 1989; McKhann, Borowicz, Goldsborough, Enger, & Selnes, 1997; Pirraglia, Peterson, William-Russo, Gorkin, & Charlson, 1999; Rymaszewska, Kiejna, & Hadryś, 2003). McKhann and colleagues (1997) reported that 27% of patients had clinically significant scores on the Center for Epidemiological Study-Depression (CES-D) questionnaire prior to CABG surgery. Similarly, Ho and colleagues (2005) reported a prevalence of depressive symptoms of 29% before cardiac valve surgery (including aortic valve replacement, mitral valve replacement, and valve replacement without CABG).

Even though cardiac surgery is usually effective in improving physical function and overall wellbeing, depression often persist from pre- to postoperative period. Timberlake and coworkers (1997) examined the modifications in depression from preoperative to postoperative periods in patients who underwent cardiac surgery. They found a temporary increase in the incidence of clinical depression immediately after the surgical procedure (50% of the patients showed clinical depression eight days after the surgery), with a long-term reduction to levels below that found prior to surgery. The increased depression

incidence in the short period following surgery is probably associated with the great discomfort and pain due to the main surgery, as well as isolation from family, friends, and home. Nevertheless, eight weeks after the operation, 24% of patients were still significantly depressed, and, one year after the surgical procedure, 22% of the patients were still depressed.



	Preoperative	Postoperative	3 months follow-up
Without depression	67,90%	71,70%	73,60%
Mild depression	28,30%	18,90%	17%
Moderate depression	3,80%	9,40%	9,40%

Figure 1.2. Percentage of patients without depression and with mild or moderate depression as measured by the Beck Depression Inventory (BDI) preoperatively, postoperatively and at follow up (Rymaszewska et al., 2003).

Preoperative major depression has been found to persist after cardiac surgery in up to 22% of patients (Vingerhoets, 1998), while, the incidence of depressive symptoms in the

postoperative period is 32% (Burg, 2003a; Magni et al., 1987; McKhann et al., 1997). Magni and colleagues (1987), reported poor postoperative psychological outcome prevalence in 25% of patients after cardiac surgery, with depression and anxiety being particularly prominent. Several other studies have described similar incidence of depression and anxiety disorders following CABG (Cay & O'Rourke, 1992; Pimm, Foole, & Feist, 1986).

Even though depressive symptoms may show an improvement after cardiac surgery, at least in some patients, the majority of patients who were depressed preoperatively continued to display depression after cardiac surgery. More importantly, it has been shown that a small number of patients, without depression preoperatively, may develop depression after cardiac surgery (reactive depression). Pirraglia and coworkers (1999) evaluated the incidence of depression from preoperative period to three months follow-up after cardiac surgery.

As shown in Figure 1.3, the authors reported that the majority (91%) of patients without preoperative depression were not depressed in the postoperative period (i.e., absent depression), nevertheless, a small group of patients (9%) who were not depressed prior to surgery developed depression after cardiac surgery (i.e., reactive depression).

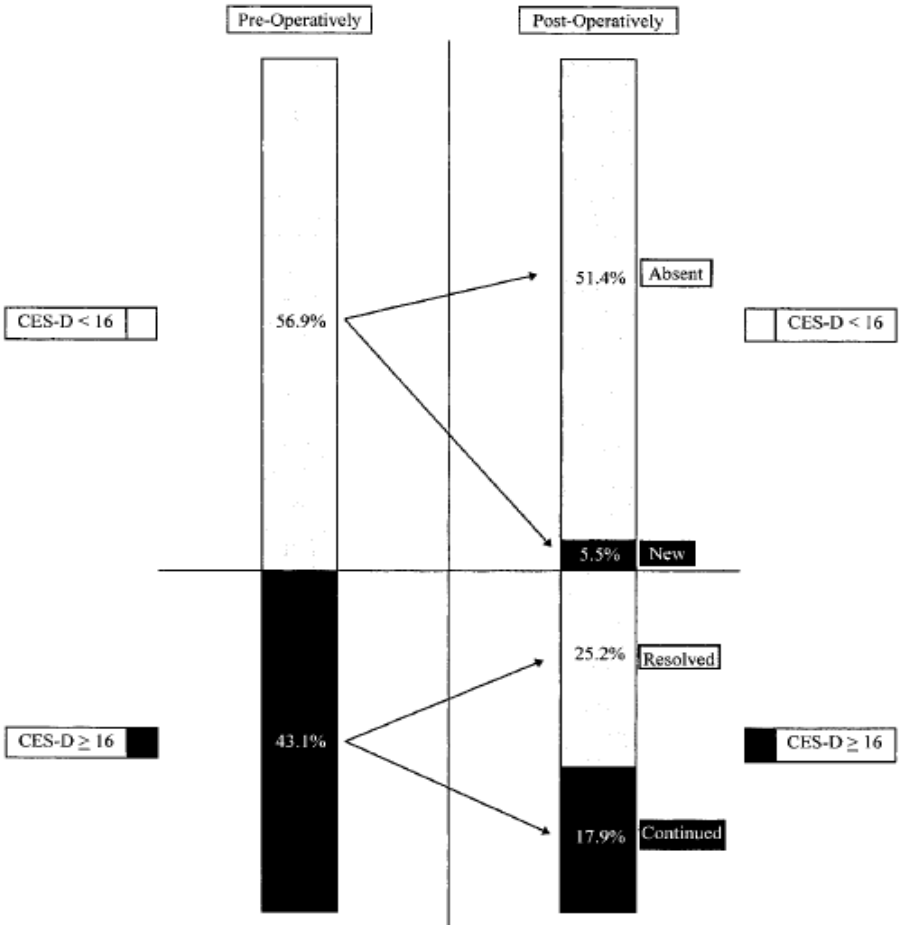


Figure 1.3. Proportion of patients with and without depressive symptoms as measured by the Center for Epidemiological Study-Depression (CES-D) preoperatively and at 6 months follow-up. The white bars show the proportion of patients without depressive symptoms (CES-D score < 16); the black bars show the proportion of patients with depressive symptoms (CES-D score ≥ 16). Labels are reported next to the segment of the 6 months follow-up bar that they represent. "Absent" means no depression preoperatively and at follow-up; "New" correspond to reactive depression (patients without depression preoperatively who showed depression at follow-up); "Resolved" correspond to improved depression (patients with depression preoperatively and without depression at follow-up) and "Continued" means persistent depression at both the evaluations (Pirraglia et al., 1999).

Moreover, among patients who were depressed before surgery, roughly 50% were still depressed afterwards (i.e., persistent depression), whereas depression improved from the preoperative to postoperative period in the remaining 50% of patients (i.e., improved depression) (Pirraglia et al., 1999).

Similarly, Patron and coworkers (in press) recently found that depression three months after cardiac surgery, as evaluated with the CES-D, was predicted by preexisting depression, state anxiety and higher score on the European System for Cardiac Operative Risk Evaluation (EuroSCORE; Nashef et al., 1999).

More importantly, the authors reported that patients who developed postoperative depression (i.e., reactive depressed patients) were characterized by higher biomedical risk factors (i.e., greater EuroSCORE) than those without depression both in the preoperative and postoperative periods. More severe biomedical risk factors are very likely to interact with cardiac surgery effects, causing poor physical conditions and quality of life after cardiac surgery, that, in turn, may lead to reactive depression. More importantly, the finding that patients with reactive depression have higher risk of mortality than those without depression may be implicated as one possible mechanism underlying the relationship between postoperative depression and cardiac morbidity and/or mortality after surgery. Conversely, patients with preoperative and postoperative depression (i.e., persistent depressed patients) were characterized by more severe depression (i.e., greater CES-D scores) before surgery compared to those whose depression improved from the preoperative to postoperative period. the severity of preoperative depressive symptoms may account for postoperative depression and represent a plausible marker of depression-related postoperative risk in patients after surgery.

In conclusion, depression disorder prior to cardiac surgery significantly increased the likelihood of being depressed after surgery.

1.2.1 Depression as a risk factor for adverse events after cardiac surgery

Depression has been shown to be an independent risk factor for the development and persistence of CVDs, and more importantly, both pre- and postoperative depression has been associated with negative outcomes after cardiac surgery. First evidence that preoperative depressive symptoms and anxiety symptoms, were associated with adverse outcomes after cardiac surgery were reported in clinical works during the late 1960s (Blachly & Blachly, 1968; Kimball, 1969) More recently, results from different studies have suggested that preoperative symptoms of depression significantly predict postoperative cardiac events such as unstable angina, myocardial infarction, repeat CABG and death (Baker, Andrew, Schrader, & Knight, 2001; Frasure-Smith et al., 1995; Scheier, 1999). In a longitudinal study, preoperative emotional distress (including symptoms of depression, asthenia and anxiety) was associated with increased rate of cardiac events during three years follow-up after CABG. In addition, higher emotional distress symptoms were significantly correlated with poorer quality of life one year after cardiac surgery (Perski et al., 1998). Connerney and coworkers (2001) evaluated the impact of both major depression and depressive symptoms in 309 patients who underwent CABG surgery. The results displayed evidence that women had a higher risk of nonfatal and fatal cardiac events compared to men (see Figure 1.4). More importantly, major depression significantly increases the incidence of nonfatal cardiac events, independently from classic risk factors (such as age, left ventricular function, diabetes).

A prospective cohort study on 648 patients undergoing valve surgery found that preoperative depression was associated to increase six-month all-cause mortality, with a 1.9-fold increased odds of death, even after adjusting for other clinical risk variables (Ho et al., 2005). The findings were consistent across subgroups of patients who underwent aortic valve replacement, mitral valve replacement, and valve replacement without CABG.

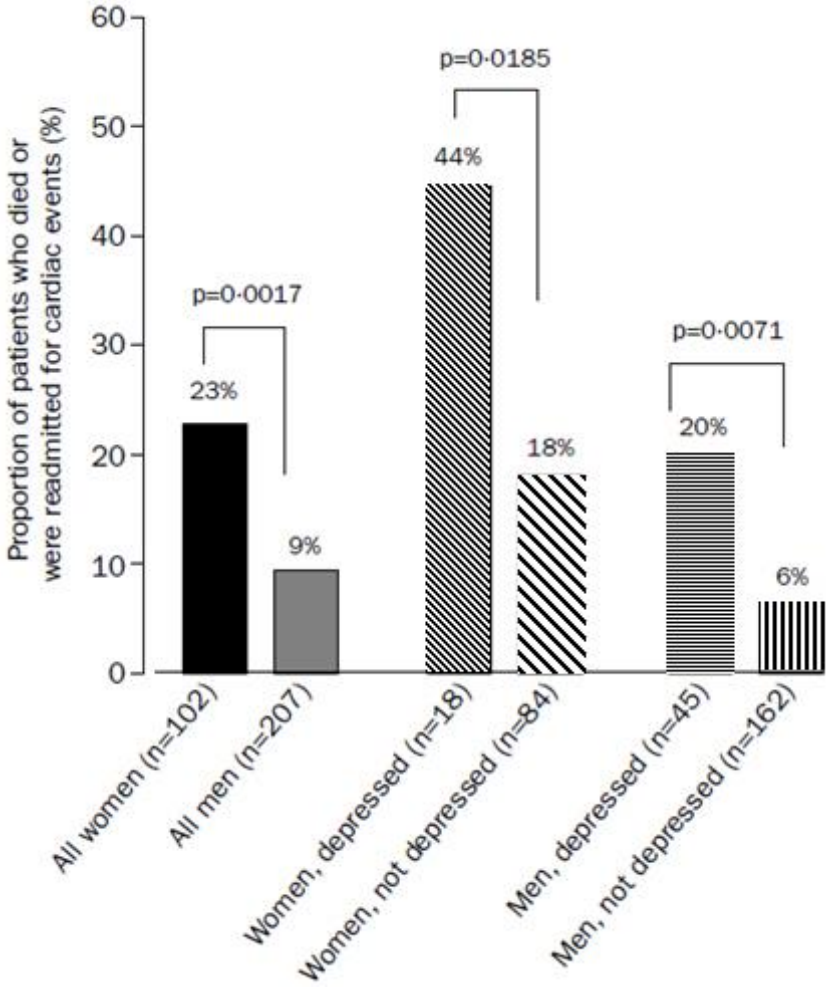


Figure 1.4. Frequency of cardiac events after CABG surgery (defined as readmission to the hospital for a cardiac event or death by cardiac event) by sex and presence or absence of major depressive disorder (Connerney et al., 2001).

As mentioned previously, preoperative depression frequently persists after cardiac surgery. Therefore, postoperative depression is associated with a higher risk of cardiac morbidity and fatal cardiac events (Burg, 2003a; Connerney et al., 2001; Scheier, 1999). Indeed, several studies reported the association between postoperative depression and a higher rate of cardiovascular morbidity or mortality (Ariyo et al., 2000; Blumenthal et al., 2003a; Lespérance & Frasure-Smith, 2000; Penninx et al., 2001). Saur and coworkers (2001) studied depressive symptoms and medical outcomes in 416 patients scheduled for CABG. The authors reported that the presence of depressive symptoms both before or after surgery was associated to higher readmission rate for cardiac problems within 6 months after surgery. Blumenthal and colleagues (2003) in the largest study of depression as a risk factor for mortality in patients after cardiac surgery, showed that patients with persistent (i.e., before as well as six months after CABG) mild or moderate to severe depression had a greater likelihood (i.e., more than twice) of death than those who were never depressed. Goyal and colleagues (2005) studied the role of both preoperative and postoperative depressive symptoms on quality of life six months after cardiac surgery. The findings showed that both preoperative depressive symptoms and postoperative increases in depressive symptoms were associated with poor quality of life six months after cardiac surgery.

Given this evidence, it is of particular relevance to identify those patients at higher risk of persistent depression or to develop reactive depression, given that either pre and postoperative depression are risk for cardiac morbidity and/or mortality after surgery (Ariyo et al., 2000; Blumenthal et al., 2003b; Lespérance & Frasure-Smith, 2000)

1.2.2 Depression treatments in cardiac patients

Given that depression is an independent and important cardiac risk factor, particular attention must be paid to depression treatment selection, especially in depressed cardiac patients. Depression treatments comprehend different interventions that can be categorized in three main groups: pharmacological medications, psychological therapies, and biobehavioral trainings. In addition, in this context, cardiac rehabilitation programs are of particular relevance.

Among pharmacological treatments, tricyclic antidepressants are the oldest antidepressant agents. Tricyclics act by elevating levels of serotonin, dopamine, and mostly norepinephrine (NE) in the brain and antagonizing histamine, muscarinic, and alpha-adrenergic receptors (Stern, Rosenbaum, & Fava, 2008). Although this class of medications is effective in reducing depressive symptoms, tricyclics are not recommended in cardiac patients because they may cause vagal inhibition, conduction disturbances, and arrhythmias, and compared with selective serotonin reuptake inhibitors (SSRIs), tricyclics have been associated with more frequent adverse cardiac events (Carney, Freedland, Miller, & Jaffe, 2002).

Even less conventional antidepressant medication, such as monoamine oxidase inhibitors (MAOIs), lithium, and barbiturates, have been associated with elevated cardiovascular risk (Cohen, Gibson, & Alderman, 2000; Pratt et al., 1996).

Another group of antidepressant agents is SSRIs, that act by blocking the neuronal reuptake of serotonin, resulting in a higher level of serotonin in the synapses. SSRIs have been reported to be safe and effective in patients with both unstable and stable CHD, (Lespérance et al., 2007; Roose et al., 1998) and they seem to increase safety profile in cardiac patients (Stern et al., 2008). In addition, the use of SSRIs was associated with improvement in depressive symptoms resulting in no risk of adverse cardiac events in

patients with cardiovascular diseases (CVDs) (Glassman et al., 2002; Strik et al., 2000) and in patients after myocardial infarction (MI) (Shapiro et al., 1999). Glassman and coworkers (2002) reported no significant differences between sertraline (SSRIs) and placebo on several cardiac outcomes (i.e., number of left premature ventricular contractions, ventricular ejection fraction, prolongation of QT interval, or major adverse cardiac events) in patients with CHD. More importantly, sertraline was associated with higher improvement in depression response rates. Further evidence came from the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) study, that evaluated the efficacy of citalopram (SSRIs) in 284 patients with stable CHD over 3 months (Lespérance et al., 2007). The findings showed that this medication was effective in reducing depressive symptoms, increasing functional status, and improving interpersonal relationships. In addition, patients treated with citalopram showed no difference in cardiac measures, compared with the control group, suggesting that citalopram was safe and tolerable for CHD patients (Lespérance et al., 2007). Overall, these findings suggest that SSRIs are both effective in reducing depressive symptoms and safe for administration in patients with CVDs. Moreover, the inhibitory effects of SSRIs on platelets have been implicated in a decreased risk of MI and mortality (Serebruany, Gurbel, & O'Connor, 2001).

Although many studies displayed the effectiveness of SSRIs in reducing depression, there are less data supporting the hypothesis that SSRIs may also improve cardiac outcomes in these patients. In fact, the studies investigating the cardiac outcomes in depressed patients treated with SSRIs found no significant reductions in recurrent cardiac events and mortality (Glassman et al., 2002; Shapiro et al., 1999; Strik et al., 2000). Therefore, SSRIs antidepressant treatment can be only partially recommended in patients with CVDs.

Regarding second-generation antidepressants, such as mirtazapine, bupropion, venlafaxine, and duloxetine, there are fewer data about the efficacy and safety in the

treatment of depression in patients with CVDs. Mirtazapine, broadly classified as a centrally acting alpha-2 adrenergic receptor antagonist, has been found to be effective in reducing depressive symptoms in patients after MI without side effects on the cardiovascular system (Honig et al., 2007; van Melle et al., 2007) although mirtazapine intake has been often associated with weight gain and hyperlipidemia, that are risk factors for cardiac patients.

The effects of venlafaxine and duloxetine, both members of the serotonin-norepinephrine reuptake inhibitor (SNRI) class, have not been studied in CVD patients yet, but given that venlafaxine tends to increase blood pressure, the administration is not recommended in these patients.

Therefore, a wide range of pharmacological medications, including tricyclic antidepressants, MAOIs, lithium, barbiturates, alpha-2 adrenergic receptor antagonists, and SNRIs, cannot be recommended in patients with CVDs because they can have cardiac side effects, that are to be avoided in these patients. Side effects may include anticholinergic effects (Feighner, 1999) and/or vagolytic effects (Agelink, Majewski, Andrich, & Mueck-Weymann, 2002), yielding to reduced heart rate variability (HRV) (Schroeder et al., 2002). Exception must be made for the class of SSRIs that does not show significant cardiac side effects. However, this class of medication exerts no effect in reducing cardiac risk; therefore, SSRIs cannot be recommended as the only treatment in CVD patients.

Based on these limitations, in recent years, more attention has been paid to nonpharmacological interventions for depression. Many studies have examined the effects of regimented psychotherapeutic interventions in cardiac patients with comorbid depression disorder. These treatments include interpersonal therapy (IPT) and cognitive behavioral therapy (CBT). The major focuses of IPT are improving interpersonal relationships, self-esteem, and, of course, depressive symptoms, whereas CBT emphasizes the patients' ability to recognize how their feelings, emotions, thoughts, and behaviors interact in maintaining

depressive symptoms (Elkin et al., 1989; Leichsenring, Hiller, Weissberg, & Leibing, 2006; Stern et al., 2008). In this context, both IPT and CBT are characterized by a limited duration (lasting typically for 12–16 sessions), and many studies have shown their effectiveness in reducing depressive symptoms in patients without CVDs (Elkin et al., 1989; Leichsenring et al., 2006; Lett et al., 2005; Stern et al., 2008).

Lespérance and colleagues (2007) compared the effectiveness of IPT, with medical management as a control, in patients with stable CHD and comorbid moderate to severe depression. While medical management resulted to be more effective in patients with reduced functional ability and lower social supports, both medical management and IPT were associated with significant improvements in depressive symptoms (Lespérance et al., 2007).

CBT effectiveness has been studied by Berkman and colleagues (2003) in the ENRICHD study. In this wide study, 2,481 patients with a diagnosis of minor or major depressive disorder and low perceived social support after MI were randomized to receive either the standard cardiac rehabilitation program or CBT for a maximum of 6 months. Patients who underwent CBT treatment and had low perceived social support and minor or major depression experienced statistically significant improvements in depressive symptoms and social support scores. Nevertheless, these reductions in depressive symptoms faded over time. No differences emerged comparing the 2 groups in terms of cardiac outcome, such as MI or death (Berkman et al., 2003).

More recently, a smaller study on 123 patients who underwent CABG surgery within the past year and had a diagnosis of minor or major depression explored the effectiveness of CBT in the treatment of depression. The patients were randomized to receive CBT, supportive stress management, or the standard cardiac rehabilitation program. After 3 months, the findings displayed that depressive symptoms improved in both the patients in CBT and in supportive stress management compared with the cardiac rehabilitation group.

No difference emerged between patients with minor and major depression. In addition, CBT treatment was associated with greater improvement in anxiety symptoms, hopelessness, perceived stress, and mental health–related quality of life (HRQoL) compared with usual care. More importantly, after 9 months, only patients in the CBT group maintained the results (Freedland et al., 2009). Interestingly, Carney and coworkers (2000) reported that CBT can also reduce resting heart rate in severely depressed patients. Since studies evaluating the effectiveness of psychotherapeutic interventions in reducing cardiac risk factor are controversial, these interventions in depressed cardiac patients should be accompanied by specific intervention for the reduction of cardiac risk (Lett et al., 2005).

Furthermore, the collaborative care literature adds more evidence suggesting the effectiveness of psychotherapy in CVD patients. Specifically, collaborative care is a population-based approach in which multidisciplinary primary care teams, such as a nurse or social work case manager and a psychiatrist, assist the primary care provider in delivering the treatment. Collaborative care and care management programs should help to improve depression identification and treatment in patients with cardiac disease. Interventions that include collaborative care have been reported to be effective in reducing depressive and anxiety symptoms and in improving mental health–related quality of life and functional status (Davidson, Rieckmann, Clemow, Schwartz, & Shimbo, 2010; Huffman et al., 2011; Rollman & Belnap, 2011). In particular, collaborative care programs focused on depression treatment have been found to be effective in different primary care patients (Katon et al., 1999), the elderly (Chang-Quan et al., 2009), and those with diabetes mellitus (Katon et al., 2004), arthritis (Chang-Quan et al., 2009), or cancer (Ell et al., 2008). Recently, a telephone-based study evaluated the effectiveness of collaborative care therapy in patients after an acute cardiac event (such as MI, unstable angina, coronary heart failure exacerbation, or arrhythmia). Depressed patients were contacted by a social work care manager who, together

with the patients, considered the symptoms and treatment options. Results showed reductions in depressive and anxiety symptoms, improvements in mental health–related quality of life, and further decreases in depression symptoms at 6 and 12 months of follow-up (Huffman et al., 2011).

Most of the interventions mentioned above are commonly included in cardiac rehabilitation programs. Cardiac rehabilitation programs consist of interventions designed to improve the physical, the psychological, and the social functioning of the patients with CVDs and of the patients who underwent cardiac surgery. Usually, these programs include an assessment of the patient's baseline status, counseling on the appropriate use of cardioprotective drugs, nutritional counseling, interventions aimed at reducing classic risk factors such as smoking cessation and weight management, physical activity and exercise training, psychosocial counseling, and stress reduction intervention. Cardiac rehabilitation programs have been consistently reported to reduce depressive symptoms in CVD patients following major cardiac events (Blumenthal et al., 2005; Lavie & Milani, 2006, 2004). A recent study showed that the cardiac rehabilitation program was associated with a marked reduction in the prevalence of depressive symptoms, that, in turn, resulted in a significant improvement in survival rate after a major coronary event (Milani & Lavie, 2007). Stress reduction intervention or relaxation training are usually part of cardiac rehabilitation programs. Relaxation training allows to teach the individual to reduce his or her tension or stress, accumulated due to acute or chronic stressful experiences, without using external means (van Dixhoorn & Duivenvoorden, 1999).

Relaxation training usually focuses on attention, mental representations such as images and words (meditation/mindfulness, autogenic training, and hypnosis), muscle contraction and relaxation (progressive muscle relaxation), and breathing instructions.

Relaxation techniques have been consistently reported to be effective in depressive symptoms reduction (Gonzales, 2001) and in lowering distress, blood pressure, and cholesterol levels, that, in turn, leads to reduced mortality and cardiac adverse events (Linden, Stossel, & Maurice, 1996). Recently, a review reported that a wide group of relaxation therapies—such as stress management, progressive muscle relaxation, hypnosis, autogenic training, meditation, and biofeedback—were effective in enhancing recovery after a cardiac ischemic event when added to standard cardiac rehabilitation. More importantly, relaxation therapies were associated with improved mood and decreased anxiety, with a reduction in resting heart rate and in the frequency of angina pectoris, and with increased return to work and a higher survival rate (van Dixhoorn & White, 2005).

Among relaxation techniques, there has been growing interest in the application of cardio-respiratory biofeedback, which stimulate differential systems involved in cardioregulatory phenomenon.

Depression treatment in cardiac patients is a challenge; antidepressant medications are often contraindicated in these patients because of vagolytic effects and cardiac side effects. Among pharmacological medications, only SSRIs have been shown to be safe in cardiac patients. Nevertheless, they cannot be recommended as the only treatment in depressed patients with CVDs because SSRIs are not associated with reduced cardiac risk. Psychotherapeutic intervention (IPT and CBT) and collaborative care management have been reported to be effective in improving mood and reducing depressive symptoms in cardiac patients. However, they cannot be recommended as the only intervention because there is no proof of their effectiveness in reducing cardiac risk. Finally, cardiac rehabilitation programs, including psychosocial intervention such as relaxation training, have been reported to influence depression symptoms, stress feelings, and classic biomedical risk factors.

More importantly, a few studies have displayed the efficacy of cardio-respiratory biofeedback in increasing vagal control on the heart (thus reducing cardiac risk) (Cowan, Kogan, Burr, Hendershot, & Buchanan, 1990; Del Pozo, Gevirtz, Scher, & Guarneri, 2004) and improving perceived stress and depressive symptoms in CVD patients (Nolan et al., 2005). Therefore cardio-respiratory biofeedback may be a useful interventions aimed at reducing depressive symptoms and their psychophysiological correlates, which, in turn, are considered risk factors for cardiac morbidity and mortality in patients with cardiovascular diseases. Cardio-respiratory biofeedback training details will be further described in the next sections.

1.3 Psychophysiological factors linking depression to increased cardiac risk

Despite the evidence that depression is strongly associated with CVDs, the pathophysiological mechanisms underlying this relationship remains unclear. Stressful events and, most importantly, prolonged or excessive in amplitude responses to stress are thought to influence the pathogenesis of both depression (Griffiths, Ravindran, Merali, & Anisman, 2000) and CVDs (Schwartz et al., 2003) by exerting negative effects on behavioral and biological processes that influence disease risk.

A stress response occurs when an individual perceives that environmental demands exceed his or her ability to face the situation and can be associated with dysphoria and emotional disease.

The acute stress response to sudden stress, also known as the fight-or-flight response, is characterized by modifications that help the body to mobilize the necessary resources to deal with the stressor. Usually, stress response results in increased cognitive alertness,

cardiovascular modifications such as rapid increases in heart rate and blood pressure, respiration rate, and muscle tension and in decreased gastrointestinal activity (Cacioppo, 1994).

The stress response is controlled centrally by the hypothalamus and the brain stem. Acute and chronic stress responses are characterized by the activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system. Initially, the hypothalamic neurons increase the synthesis of corticotropin-releasing factor (CRF), that, in turn, leads to the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. Then the ACTH hormone induces the release of glucocorticoids (mainly cortisol) from the adrenal cortex (Figure 1.5). Glucocorticoids are involved in the control of both body homeostasis and stress response, and more importantly, they produce an inhibitory feedback on the hypothalamus neurons involved in ACTH secretion to limit the duration of the exposure to glucocorticoids, thus minimizing the negative effects (i.e., immunosuppression) of these hormones.

The activation of the sympathetic branch of the autonomic nervous system (ANS) not only provides rapid responses of the cardiovascular, respiratory, gastrointestinal, and renal systems but also increases in epinephrine and NE circulation from the adrenal medulla. In addition, the HPA axis and sympathetic nervous system activation lead to an increase in the aldosterone level (Kubzansky & Adler, 2010).

Usually, stress response is limited to the duration of the stressor, but when the stressor or the individual perception of a stressful situation persists, it produces a chronic hyperactivation and the continuous release of neurotransmitters and hormones, increasing the risk for depression disorders and cardiac diseases (Björntorp, Holm, & Rosmond, 1999).

Stress response affects a number of behavioral mechanisms, that, in turn, have been reported to be involved in the relationship between depression and CVDs. Several studies

reported that depressed patients are less likely to engage in health-promoting behaviors, such as initiating and maintaining a healthy diet (Everson-Rose et al., 2004; Ziegelstein, 2000) and regular physical exercise (Mendes de Leon, 1998; Whooley et al., 2008; Ziegelstein, 2000), reducing or avoiding smoking and alcohol consumption (Everson-Rose et al., 2004; Fenton & Stover, 2006), adhering to medical treatments and regimens (Bollini, Pampallona, Kupelnick, Tibaldi, & Munizza, 2006; Fenton & Stover, 2006; May et al., 2010; Rieckmann et al., 2006; Ziegelstein, 2000), adhering to cardiac rehabilitation protocols (Casey, Hughes, Waechter, Josephson, & Rosneck, 2008; McGrady, McGinnis, Badenhop, Bentle, & Rajput, 2009) and engaging in stress reduction behaviors (Ziegelstein, 2000). Therefore, depressed patients may show higher cardiac risk because they are less likely to adhere to lifestyle changes and medical treatments and regimens that are required to improve cardiovascular health and to reduce cardiac risk.

Among lifestyle-related risk factors, environmental stressors, stress at work and in family life (including work overload and high psychological demands at work), lack of social support, marital conflicts, health problems, or long-term stressful conditions in the family have all been strongly associated with mood disorder onset. More importantly, stress at work and within the family have been found to increase CVD risk 2.7- to 4.0-fold (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2007; Orth-gome, Wamala, Horsten, Schneiderman, & Mittleman, 2000), while social isolation and low social support result in 1.5- to 3.0-fold increased risk of CVDs (Lett et al., 2005; Mookadam & Arthur, 2004). In addition, mood disorders and depressive symptoms have been frequently associated with excessive fatigue and vital exhaustion (including loss of vitality and libido, listlessness, tiredness, and increased irritability), that, in turn, have been shown to be a risk factor for MI and sudden cardiac death (Appels & Mulder, 1988; Kop, 1999). Moreover, exhaustion results are

predictive of future myocardial infarction independent of age, cholesterol, blood pressure, antihypertensive medications, and smoking (Appels & Mulder, 1988).

Among emotional risk factors, anxiety disorders have been found to be frequently comorbid with depression disorder. Hence, anxiety has been investigated as a mechanism involved in the relationship between depression and cardiovascular diseases. Some studies have reported the effect of anxiety disorders—such as panic attack, generalized anxiety, and phobic anxiety—in increasing risk for CVDs by 1.01- to 4.2-fold (Chen, Tsai, Lee, & Lin, 2009; Shibeshi, Young-Xu, & Blatt, 2007). Conversely, many studies have been inconclusive, finding little or no influence of anxiety on CVD risk (Meyer, Buss, & Herrmann-Lingen, 2010; Roest, Martens, de Jonge, & Denollet, 2010; Roest, Martens, Denollet, & de Jonge, 2010). Therefore, anxiety is unlikely to be a major contributor to the relationship between depression and CVDs.

In conclusion, despite the reported relationship between behavioral, lifestyle-related, and psychological mechanisms linking depression to increased cardiac risk, current findings on these mechanisms are still far from being conclusive.

Inflammatory response

As mentioned above, the stress response may lead to an inflammatory response, and this association is supported by the fact that some neuropeptides, such as CRF, mediate both the responses. In addition, several lines of evidence suggest that depression is associated with the dysregulation of the immune system and activation of the inflammatory response (Dantzer, 2006; Dunn, Swiergiel, & de Beaurepaire, 2005; Hawkley, Bosch, & Engeland, 2007). The inflammatory response in depressed patients has been demonstrated by the increased secretion of proinflammatory cytokines such as interleukin (IL-1, IL-2, and IL-6), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α (Empana et al., 2005; Miller, Stetler,

Carney, Freedland, & Banks, 2002; Penninx et al., 2003; Zorrilla et al., 2001). More importantly, inflammation response may contribute to the development of depressive symptoms. In fact, the high secretion of proinflammatory cytokines has been shown to induce neurohormonal modifications (resulting in HPA hyperactivation) and changes in the activity of monoamines, such as serotonin, dopamine, and NE, that are believed to contribute to depression (Anisman, Hayley, Turrin, & Merali, 2002).

Recent studies have reported that depressed individuals, both with and without a history of CVD, have increased levels of proinflammatory cytokines, particularly C-reactive protein (CRP), IL-1, and IL-6 (Howren, Lamkin, & Suls, 2009; Kop et al., 2010; Miller, Maletic, & Raison, 2009). Immune system activation and inflammation response have been directly associated with cardiovascular disorders. Specifically, proinflammatory cytokine activity has been linked to atherosclerotic plaque formation, progression, and rupture (Moyer, Sajuthi, Tulli, & Williams, 1991; Ross, 1999). Furthermore, it has been found that during acute myocardial infarction, some proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 are released into the systemic circulation (Das, 2000).

A study on 559 women examined the relationship between depression, cardiac ischemia, and inflammatory response. Interestingly, the findings showed a predictive role of depression on cardiac ischemia, and even after controlling for proinflammatory factors such as CRP and IL-6, depression continued to be the most predictive factor. Inflammatory factors reduced the association between depression and cardiovascular events by 20%, suggesting a small yet still significant contribution of proinflammatory factors (Vaccarino et al., 2007).

Inflammatory response seems to play a role, although small, in the relationship between depression and cardiac outcomes.

Renin-angiotensin aldosterone system activation

Stress response is associated with renin-angiotensin-aldosterone system (RAAS) activation; in fact, both HPA axis and sympathetic adrenomedullary system activation lead to an increase in the aldosterone level (Kubzansky & Adler, 2010). Some studies have reported a hyperactivation of the RAAS in individuals exposed to high stress, in patients suffering from mood disorders (Connor & Leonard, 1998; Pollak & Yirmiya, 2002) and in CVD patients (Felder et al., 2001). Emanuele and colleagues (2005) found high levels of circulating aldosterone and a high trend in plasma renin levels in a sample of depressed patients who met the criteria for major or minor depression (Association American Psychiatric, 1994), compared with controls matched for age and gender (Emanuele et al., 2005). More importantly, a higher level of circulating aldosterone may be involved in depression disorder development by promoting inflammation response and by stimulating catecholamine release (Murck, Schüssler, & Steiger, 2012). In addition, hyperaldosteronism is associated with cardiac arrhythmias, vascular injury, myocardial necrosis, and heart failure (Felder et al., 2001; Stier, Chander, & Rocha, 2002).

Hence, it is feasible that hyperaldosteronism is involved in the relationship between depression and cardiac risk.

Endothelial dysfunctions

There are evidences that endothelial dysfunctions play a role in the relationship between depression and cardiac risk. Endothelial dysfunctions have been found to be linked to depression disorder (Cooper et al., 2010; Pizzi, Manzoli, Mancini, & Costa, 2008). One of the mechanisms that have been proposed to link endothelial dysfunction to depression postulates that inflammation reactivity may play a role in the endothelial damage of the cerebral vasculature and thus contribute to the development of depression disorder.

Mainly, endothelial dysfunctions are involved in the process leading to coronary thrombosis (Miyata et al., 2000) and in the development of ischemic coronary heart disease (Skop & Brown, 1996). Furthermore, endothelial dysfunctions have been reported in depressed patients with established CVDs (Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005). Recently, Pizzi and colleagues (2009) found that the treatment of depression with SSRIs improved endothelial function in patients with coexisting depression and established CHD.

Therefore, there is some evidence, although far from conclusive, that endothelial dysfunctions may be involved in the relationship between depression and cardiac outcomes.

Platelets Activation

Platelets may be activated through several pathways mediated by platelet surface receptors. In particular, serotonin can activate the platelets by binding to specific serotoninergic receptors on their surface. When the platelets are activated, they release substances that induce irreversible platelets aggregation and thrombus formation. Serotonin is not only involved in platelets aggregation, but it is well recognized that serotonin is implicated in depression pathogenesis. Both serotoninergic dysfunction (Shrestha et al., 2012) and increased platelet reactivity to serotonin (Shimbo et al., 2002) have been found in patients with minor or major depression. More importantly, increased platelet reactivity to serotonin may lead to increase the risk for thrombus formation (Shimbo et al., 2002). Furthermore, SSRIs have been shown to decrease platelet reactivity both in vitro and in patients with CHD. Specifically, SSRIs act by inhibiting serotonin reuptake by the serotoninergic receptors, blocking the process of platelet activation (Serebruany et al., 2001; Serebruany et al., 2005). Excessive platelet reactivity possibly mediates the increased cardiac risk in patients with depressive disorder.

Autonomic nervous system disorders

Most of the above-mentioned factors are associated with ANS dysregulation, which has been consistently reported to mediate the relationship between depression and cardiac disorders.

The ANS mediates completely, or in part, the cardiac reflex mechanisms, that are essential in regulating the cardiovascular function. The ANS consists of 2 branches that regulate the function of the heart, namely, the sympathetic and the parasympathetic systems. The interplay between the sympathetic and the parasympathetic activity causes constant modifications in the heart activity. These regular modifications allow to maintain a dynamic homeostasis and to respond to stressors and situational factors. Hence, disturbances of cardiac reflexes may be crucial in the relationship between depression and CVDs. The normal cardiac rhythm is controlled by the electrical activity of the cardiac sinoatrial node, innervated from both the branches (sympathetic and parasympathetic) of the ANS. (Randall, 1994). Specifically, postganglionic parasympathetic terminals release acetylcholine on the sinoatrial node, resulting in a reduction in the rate of depolarization and in a lower heart rate. In contrast, sympathetic terminals on the sinoatrial node release NE, that increases the sinoatrial node rhythm by means of a cascade of second messenger intracellular signals that mediate beta1 receptors. In addition, HR can be modulated by the effect of different neuropeptides (e.g., neuropeptide Y) (Hill, Wallick, Martin, & Levy, 1995). Thus, ANS modifications have a high impact on the heart rate at rest. In fact, resting heart rate is heightened as a result of sympathetic nervous system activation combined to vagal withdrawal.

Many studies have reported the association between depression and autonomic cardiac dysregulation, such as vagal control withdrawal, hyperactivation of the sympathetic nervous system, and as a consequence, elevations in heart rate, decrease in HRV, and

alteration of the baroreceptor reflexes (Barton et al., 2007; Carney et al., 1995; Murray Esler, 1982; Hausberg, Hillebrand, & Kisters, 2007; Krittayaphong et al., 1997; Pitzalis et al., 2001; Rechlin, Claus, & Weis, 1994; Rechlin, 1994; Watkins, Grossman, Krishnan, & Blumenthal, 1999).

During the past decades, advances in psychobiology and biological psychiatry have contributed to the discoveries of numerous neurochemical, neuroendocrine, and neuroanatomical alterations associated with ANS dysregulation in depression. Many studies have reported the hyperactivation of the HPA axis in nonmedicated depressed patients. Specifically, heightened CRF concentration, blunting of the ACTH response to CRF administration, hypercortisolemia, pituitary and adrenal gland enlargement, and evidence of increased numbers of hypothalamic CRF neurons in the postmortem tissue were reported in patients with major depression (Asnis et al., 1987; Barton et al., 2007; Maes, De Ruyter, Claes, & Suy, 1998; Weber, Lewicka, Deuschle, Colla, & Heuser, 2000).

The hypersecretion of NE has also been displayed in unipolar depression. Peripheral plasma NE concentrations are produced by the rate of release from sympathetic nervous system nerve terminals. Therefore, increased sympathetic activity leads to elevated plasma NE concentration.

Some studies showed that depressed patients, compared with nondepressed subjects, displayed higher plasma NE concentration at rest and greater elevation in plasma NE in response to the orthostatic challenge test (Gold et al., 2005). This means that the sympathetic activity is both tonically elevated and more reactive to stress in depressed patients. Furthermore, depressed patients who show no response to a dexamethasone test reveal a higher basal level of plasmatic NE compared with depressed patients who show a suppressor response to dexamethasone. These results suggest an elevated sympathetic activity in depressed patients resistant to dexamethasone (Barnes et al., 1983). Interestingly, Gold and

colleagues (2005) found no differences in the concentration level of plasma catecholamines between patients with mild, moderate, or severe depression, although only unmedicated patients with severe depression displayed an association between high levels of plasma NE and increased cardiac mortality.

Many studies have shown a relationship between depression, CVDs, and heightened basal heart rate. In fact, a high heart rate at rest has been reported in depressed patients both with and without CVDs (Carney et al., 1988; Forbes & Chaney, 1980). Similarly, depressed patients with (Carney et al., 1988) or without CVDs (Lechin et al., 1995) have been found to display higher heart rates compared with individuals without depression. In addition, depressed patients with comorbid CVDs exhibit higher heart rates than nondepressed patients with CVDs (Carney, Freedland, Rich, Smith, & Jaffe, 1993). The mechanism resulting in heightened basal heart rate in depressed patients may involve the effect of NE and epinephrine on cardiac β-adrenergic receptors at the sinoatrial node level or imply an increased sensitivity of myocardial β-adrenergic receptors (Kannel, Anderson, McGee, Degatano, & Stampfer, 1987). However, a few studies failed to find an association between depression and a higher heart rate at rest (Barton et al., 2007; Dawood et al., 2007), although it is acknowledged that a fast heart rate at rest is a prognostic factor for morbidity and mortality related to heart disease (Ferrari, Censi, Mestrorilli, & Boraso, 2003).

Furthermore, the literature on disrupted autonomic balance suggests that increased sympathetic and/or decreased parasympathetic tone may predispose both patients with (Podrid, 1990; Pruvot et al., 2000) and without CVDs to ventricular fibrillation, ventricular tachycardia, and sudden cardiac death (Kleiger, Miller, Bigger, & Moss, 1987; Lown & Verrier, 1976). Alterations of the ANS activity have been found to be associated with cardiovascular risk factors such as increased body mass index, heightened blood glucose, and hypertension; in addition, similar autonomic changes are noticed in acute and chronic CVDs,

including arrhythmias, atherosclerosis, heart failure, and myocardial ischemia (Billman, Schwartz, & Stone, 1982; Carney et al., 1993; Dyer et al., 1980; Esler & Kaye, 2000; Kannel et al., 1987; Kristal-Boneh, Raifel, Froom, & Ribak, 1995; La Rovere, Bigger, Marcus, Mortara, & Schwartz, 1998; Palatini & Julius, 1997; Schwartz et al., 1988).

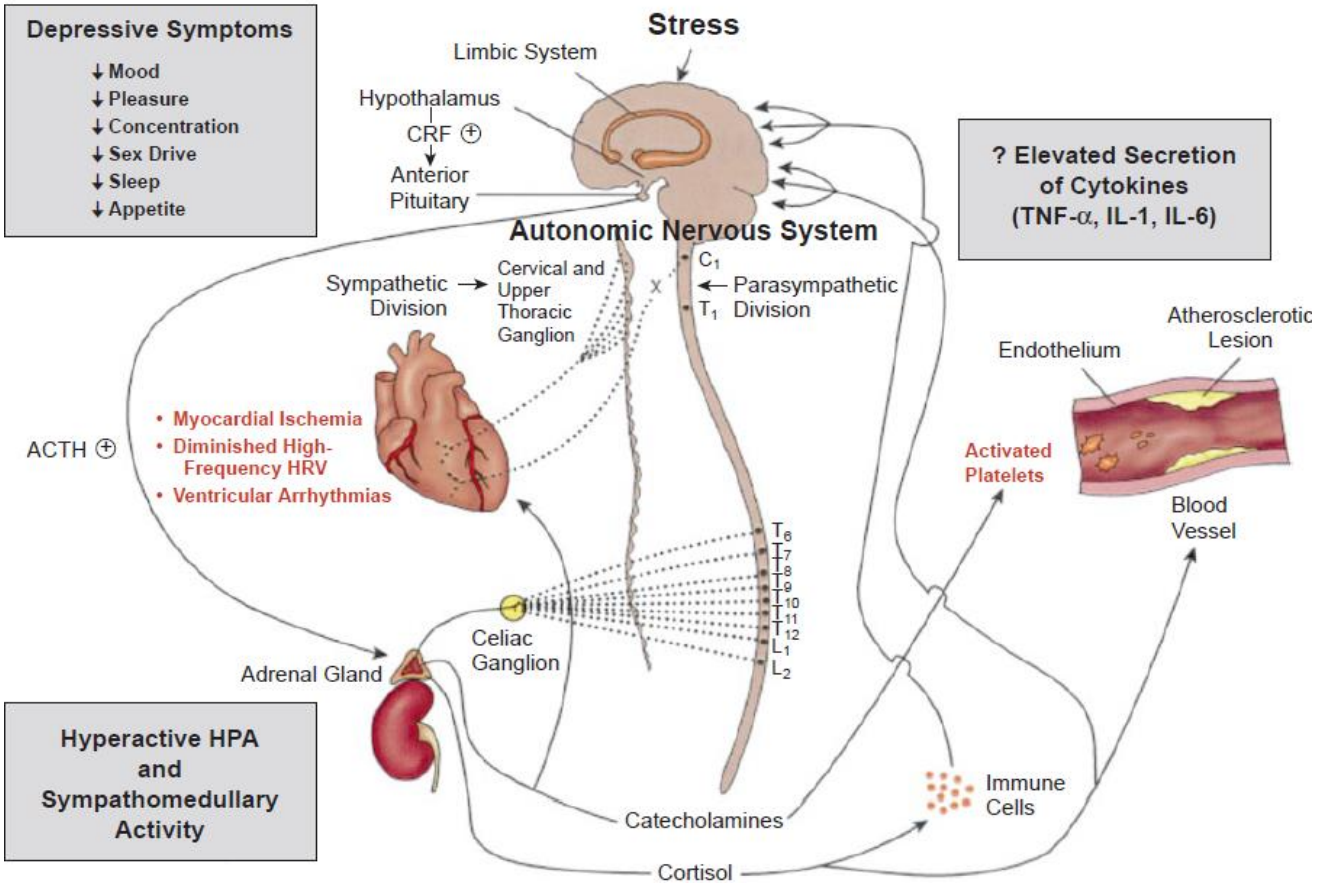


Figure 1.5. Diagram of the psychobiological and neuroendocrine mechanisms involved in the stress response. Autonomic nervous system innervation of the heart via parasympathetic vagus (X) and sympathetic nerves (postganglionic efferent from cervical and upper thoracic paravertebral ganglia) are shown. CRF = corticotropin-releasing factor; ACTH = corticotropin; TNF-alpha = tumor necrosis factor; IL-1 = interleukin 1; IL-6 = interleukin 6; HRV = heart rate variability; HPA = hypotalamic-pituitary-adrennocortical axis (Musselman, Evans, & Nemeroff, 1998)

In summary, a large body of literature supports the hypothesis of altered ANS activity as a mechanism underlying the link between depression and increased cardiac risk. ANS activity, and specifically the balance between sympathetic and parasympathetic activity on the heart, can be easily detected by means of HRV. Therefore, in the next sections, HRV and its measures will be described.

1.3.1 Heart rate variability (HRV) as a measure of autonomic nervous system activity

Cardiac rhythm is easily determined by means of electrocardiogram (ECG). Heart rate (HR) is controlled by reciprocal influences of acceleratory sympathetic nervous system activity and decelerator parasympathetic nervous system activity. The constant interplay between the two systems results in a rhythmic oscillation, also known as heart rate variability (HRV). Specifically, HRV is the physiological phenomenon of oscillation in the interval between consecutive heartbeats or the fluctuation between consecutive instantaneous heart rates (see Figure 1.6).

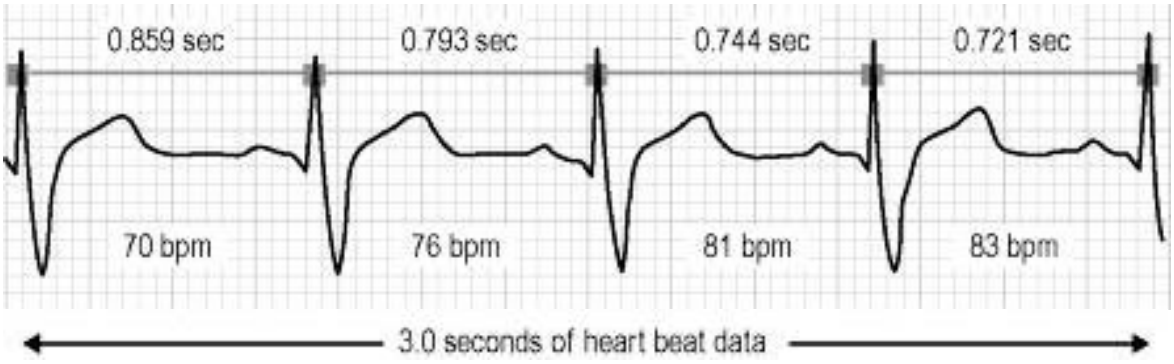


Figure 1.6. Variations in the interval between consecutive heartbeats (Watkins, 2011).

Analysis of HRV is an accurate method of measuring neural autonomic nervous system influences on cardiac function.

As mentioned above, the cardiac neural control is mediated mainly via the interaction between sympathetic and parasympathetic branches, that are strongly interconnected from central nervous system to postganglionic endings. Given the opposite effect of sympathetic or parasympathetic branches on heart function, the activation of either sympathetic or parasympathetic system is commonly associated with the inhibition of the other one, suggesting the presence of balance between the two systems, namely, the sympathovagal balance (Malliani, 2000). Yet, sympathetic and parasympathetic activity on heart can be simultaneously activated or inhibited.

Commonly, the autonomic sympathovagal balance swings from rest, characterized by a predominance of homeostatic negative feedback reflexes, that allow to maintain a slow heart rate and reduced metabolic rate, to excitatory states (i.e., physical or emotional stress), characterized by central mechanisms activation (i.e., the perception of a threatening stimulus), that through positive feedback enhance cardiac performance (Malliani, Pagani, Lombardi, & Cerutti, 1991). This continual excitatory-inhibitory interaction leads to dynamic heart rate oscillations, namely heart rate variability. Thus, HRV reflects complex processes of cardiac neural chronotropic control (Calkovska and Javorka, 2008).

HRV analysis represents a noninvasive method to obtain information about cardiac autonomic regulation and provides important indications on central-peripheral interaction (Carney et al., 2001; Carney et al., 2002; Krittayaphong et al., 1997; Task Forcey, 1996).

In general, it is assumed that high variability is an index of better system functioning and is associated to better health and adaptability. According to assumptions based on

complexity theories, to maintain stability and flexibility of the organism a dynamic relationship among system elements is needed (Thayer & Lane, 2000). In fact, stable and adaptable biological systems are characterized by complex patterns of oscillation, which represent the self-regulatory reflexes of the body (Giardino, Lehrer, & Feldman, 2000). Complex oscillation patterns in the human body include slow circadian rhythms such as the sleep-wake cycle, and temperature modifications, and faster oscillation patterns, such as the baroreflex activity and HRV. A well regulated and healthy flexible body is characterized by complex and relatively high amplitude oscillations patterns. Therefore, reduction in amplitude or complexity is an index that body self-regulatory systems are not functional and unable to deal with obstacles such as stress, diseases or injuries. Patterns of variability that are organized (not random variability), rather than static levels, reflect better adaptability and the ability to face the environmental demands that are constantly changing. Thus, higher variability in the oscillation patterns of the system leads to optimal system functioning, whereas scarce variability, or rigid regularity, causes morbidity, diseases and mortality (Ellis & Thayer, 2010).

As HRV reflects general health and adaptability, it correlates negatively with age (Liao et al., 1995) and positively with aerobic capacity in the adult population (Hedelin, Wiklund, Bjerle, & Henriksson-Larsén, 2000; Pardo et al., 2000). Diminished HRV, on the contrary, is a sign of vulnerability to stress, whether the decrease arises from psychological or physical stress. More importantly, decreased HRV has been recognized as an important marker of impaired cardiovascular regulation. In fact, low HRV has been associated with excessive sympathetic modulation and/or inadequate vagal control (Task Force, 1996).

1.3.2 Measurement and components of HRV

To obtain heart rate variability (HRV) inter beat intervals (IBIs) must be measured from time series of electrocardiography (ECG). In addition, photoplethysmography (PPG) has been recently used as a noninvasive yet reliable method to obtain HR and IBIs. ECG produces waveforms that peak due to the ventricular depolarization phase of the cardiac cycle, namely, the R wave. Conversely, PPG is mainly used to monitors arterial oxygen saturation on a continuous basis. Arterial oxygen saturation is directly associated to arterial blood flow, that reflect the mechanical pump function of the heart. Given that mechanical heart activity is coupled to its electrical activity, arterial blood flood, recorded by means of PPG, reflects the cardiac rhythm. This characteristic forms the basis for comparison of ECG-derived HRV and PPG-derived HRV. Recently, some studies have demonstrated that parameters of HRV calculated from PPG are highly correlated with the parameters of HRV obtained from ECG (see Figure 1.7). Thus, HRV obtained from PPG could be reliably used as an alternative measurement of HRV (Bolanos, Nazeran, & Haltiwanger, 2006; Lu et al., 2008; Selvaraj, Jaryal, Santhosh, Deepak, & Anand, 2008).

After ECG or PPG is obtained, the signal is digitalized by a computer and a series of R-R (distance in time between two consecutive R waves) or a series of P-P (peak to peak interval on the PPG waves) intervals is derived.

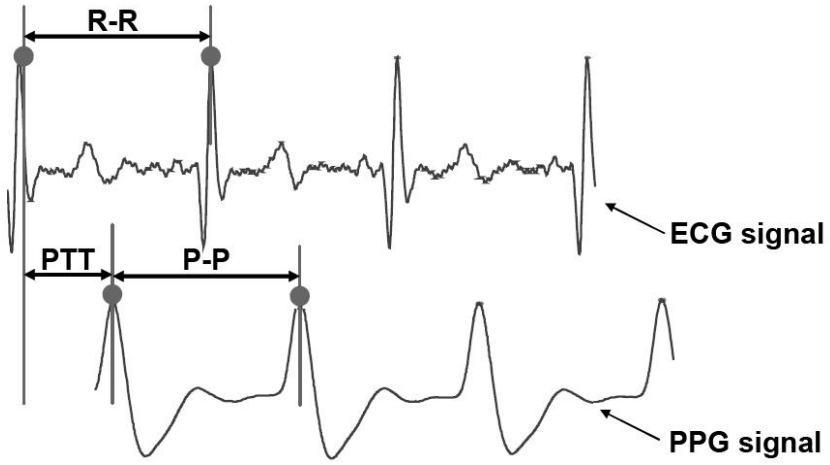


Figure 1.7. Simultaneous recording of photoplethysmographyc signal and electrocardiographyc signals. R-R = R to R interval; PTT = Pulse Transit Time; P-P = Pulse to Pulse interval; ECG = electrocardiography; PPG = photoplethysmography (modified from Liu et al., 2010).

Methods for quantifying HRV are categorized as: (a) time domain which are global descriptive statistics to characterize the distribution of heart periods (e.g., standard deviation, and variance) (see Table 1.1) and (b) frequency domain which consist of power spectral analysis of the IBIs series, in order to extract specific frequency components of variance that have been related to functional processes or physiological mechanisms (see Table 1.2).

Among time domain HRV indexes, standard deviation of the normal IBIs, or NN intervals (SDNN) is the simplest variable to calculate (Formula 1).

$$\sqrt{\frac{1}{N}\sum_{i=1}^{N}(RR_i - \overline{RR})} \quad (1)$$

Specifically, SDNN reflects the whole cyclic components responsible for variability in the period of recording. Some other statistical variables are calculated from specific

segments of the total period, among which, rMSSD, NN50 and pNN50. rMSSD consist in the square root of the mean squared differences of successive NN intervals (Formula 2).

$$\sqrt{\frac{1}{N-1}(\sum_{i-1}^{N-1}(RR_{i+1} - RR_1)^2)} \quad (2)$$

NN50, correspond to the number of successive NN intervals differences greater than 50 ms (Formula 3).

$$\sum_{i=1}^{N}\{|RR_{i+1} - RR_i| > 50ms\} \quad (3)$$

pNN50 correspond to the proportion of NN50 on the total number of NN intervals (Formula 4).

$$\frac{NN50}{N} \times 100 \quad (4)$$

All three rMSSD, NN50 and pNN50 are strongly correlated index of short-term variation, and, are estimate of high frequency variations in heart rate. Thus all of these indexes highly correlate with indexes of vagal activity on heart.

Table 1.1. *Time domain indexes of HRV*

Time domain indexes	Units	Description
SDNN	ms	Standard deviation of the inter beat intervals. Estimate of overall HRV.
rMSSD	ms	Square root of the mean squared differences of successive inter beat intervals. Cardiac vagal control on the heart.
NN50		Number of successive NN intervals differences greater than 50 ms
pNN50		proportion of NN50 on the total number of NN intervals

Regarding spectral or frequency domain indexes, the power spectrum of the whole IBIs series is conventionally divided in three bands, each corresponding to different physiological processes: very low frequency (VLF), low frequency (LF), and high frequency (HF) components (see Figure 1.8).

The VLF component (range 0.005–0.05 Hz) can be influenced by several different systems, such as the renin-angiotensin, thermoregulatory, and peripheral vasomotor systems (Akselrod et al., 1981; Kamath et al., 1987; Taylor, Carr, Myers, & Eckberg, 1998). Thus, the attribution of a specific physiological process to these heart period changes might be questioned.

The attribution of an autonomic processes to LF component (range 0.05–0.15 Hz) is controversial. Some studies proposed that the LF range reflect mainly sympathetic outflow (Malliani, Lombardi, & Pagani, 1994; Malliani et al., 1991) while most investigators report that LF range seems to be influenced by both the sympathetic and parasympathetic systems and is specifically associated with baroreflex function (Kamath et al., 1987). Moreover, this component is influenced by body position, in particular, there is evidence that in supine

position, the sympathetic system contributes only minimally to LF (Myers, Cohen, Eckberg, & Taylor, 2001; Eckberg, 2000).

There is more agreement on HF range (0.15-0.40 Hz) interpretation, that is mainly reported as an index of parasympathetic activity (Task Force, 1996). Specifically, during normal breathing (9-24 breath per minute) HF is reported as an index of vagal control on the heart and respiratory sinus arrhythmia (Berntson et al., 1997; Paul Grossman & Taylor, 2007).

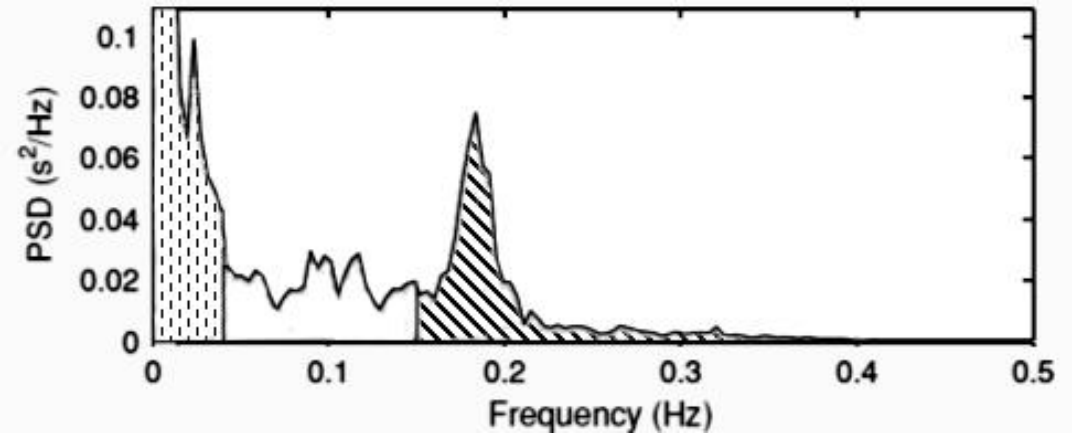


Figure 1.8. Power spectrum of one hour recording IBIs series divided in three bands, red (range 0.005–0.05 Hz) correspond to very low frequency (VLF); blue (range 0.05–0.15 Hz) correspond to low frequency(LF); yellow (range 0.15-0.40 Hz) correspond to high frequency (HF) components.

While the measurement of VLF, LF and HF power components is usually reported in absolute values of power (ms^2), LF (Formula 5) and HF (Formula 6) can also be transformed in normalized units (n.u.), which is calculated dividing the relative value of each power component by the total power minus the VLF component.

$$\frac{LF}{(Total\ Power - VLF)} \times 100 \tag{5}$$

$$\frac{HF}{(Total\ Power - VLF)} \times 100 \tag{6}$$

LF and HF transformation in n.u. specifically emphasizes the influence and balance of the two branches of the autonomic nervous system (Task Force, 1996). In addition, the normalization process reduce the effect of the changes in total power on the values of LF and HF bands. Nevertheless, absolute values of the LF and HF power should always be reported together with the normalized units in order to describe the whole distribution of power in spectral components. Finally, LF/HF ratio (Formula 7) is widely used as a measure of autonomic balance (Task Force, 1996).

$$LF[ms^2] \Big/ HF[ms^2] \tag{7}$$

Higher LF/HF ratio reflect higher influence of the sympathetic activity and/or reduced influence of the parasympathetic control on the heart.

Table 1.2. *Frequency domain indexes of HRV*

Frequency domain indexes	Units	Description	Frequency Range
VLF	ms^2	Very low frequency. VLF reflect many systems activities, among which renin-angiotensin, thermoregulatory, and peripheral vasomotor systems.	0.005-0.05 Hz
LF	ms^2	Low frequency. LF reflect sympatethic and parasympatethic control of the heart, and baroreflex influences.	0.05-0.15 Hz
HF	ms^2	High frequency. HF reflect cardiac vagal control and respiratory sinus arrhythmia.	0.15-0.40 Hz
LF n.u.		LF power in normalized units.	
HF n.u.		HF power in normalized units.	
LF/HF		Sympathovagal balance.	

Respiratory sinus arrhythmia

Respiratory sinus arrhythmia is an additional cardiorespiratory index that is strongly associated with HRV indexes. Specifically, RSA is a physiological cardiorespiratory phenomenon characterized by rhythmical fluctuation in heart periods, or R-R interval, that are in phase relationship with respiration. In fact, normally, HR accelerates during inspiration and slows down during expiration (Figure 1.9).

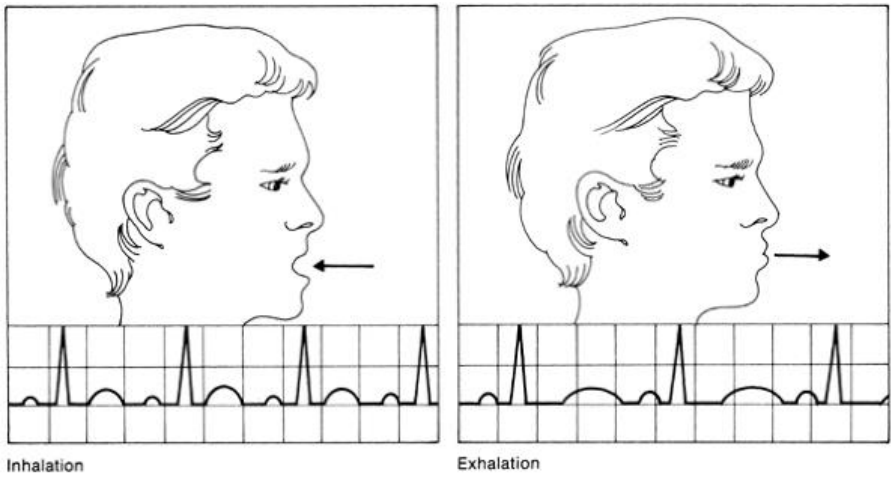


Figure 1.9. Schematic representation of electrocardiogram during respiration. The RR intervals decreases during inhalation and increases during exhalation reflecting respiratory sinus arrhythmia (Thaler, 2010).

Over the last decades, several studies have supported the hypothesis that RSA is mainly mediated by the vagal nerve, at least within the normal physiological range of respiration rate (9-24 breath per minute). RSA is the result of the effects of both peripheral afferent and central respiratory mechanisms (Berntson, Cacioppo, & Quigley, 1993). During inhalation, a reflex inhibition on vagal nerve outflow is produced by thoracic stretch receptors, resulting in an increase in HR. During exhalation the absence of thoracic stretch receptors inhibitory effect result in vagal nerve excitation that cause a reduction in HR (see Figure 1.10).

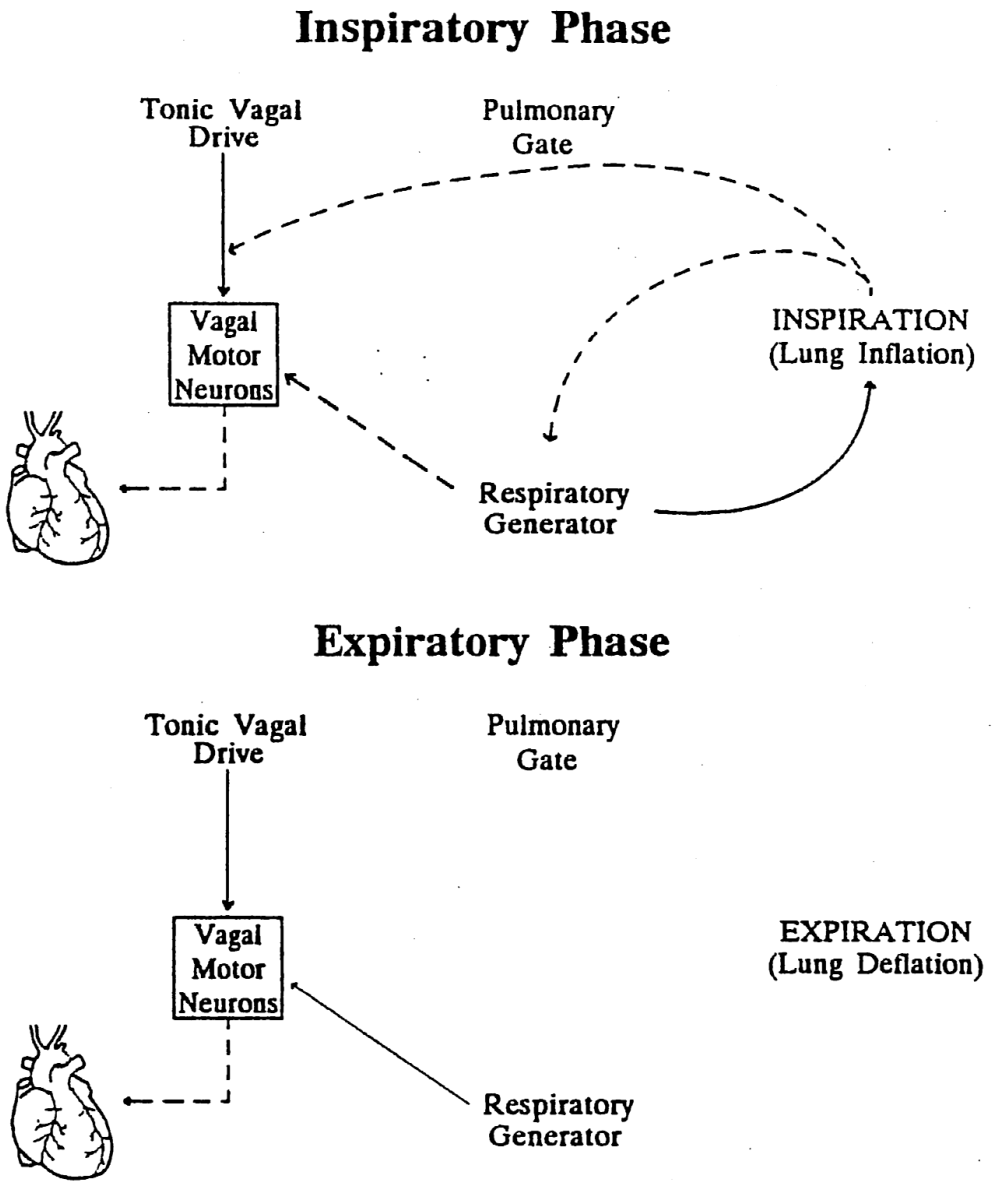


Figure 1.10. Schematic illustration of the interaction between primary determinants of RSA, either central and peripheral, as a function of respiration phase. Solid lines illustrate excitatory influence; dashed lines illustrate inhibitory influences (Berntson et al., 1993).

Therefore, cardiac acceleration during inspiration reflect parasimpathetic inhibitory influences upon the sinoatrial node. On the contrary, cardiac deceleration during expiration mirrors vagal excitatory influences upon the heart via the sinoatrial node.

Since the respiratory frequency band range in the human adult from about 9 to 24 breath per minute (corresponding to 0.15 - 0.4 Hz), RSA is often matched with HF component. Thus, RSA is thought to be mediated predominately by fluctuations of vagal-cardiac nerve activity and can provide a reliable index of vagal activity (Eckberg, 2003; Hedman, Tahvanainen, Hartikainen, & Hakumäki, 1995; Berntson et al., 1997; Grossman & Taylor, 2007). In addition, some studies have reported that RSA reflect rhythmic waxing and waning of the parasympathetic efferent on the sinoatrial node (Eckberg, 2003; Hedman et al., 1995).

More specifically, RSA arises from a complex interaction of central and peripheral factors. In fact, several factors possibly contribute to RSA, including , cardiac and pulmonary stretch reflexes, central cardiorespiratory rhythm generators and tonic and phasic baroreceptor (Saul, 1990; Spyer, 1990). In particular, the two predominant sources of the respiratory modulation of vagal outflow are a) the phasic modulation (both excitatory and inhibitory) of vagal motor neurons operated by the central respiratory nuclei and b) the influence of pulmonary stretch receptors which determines phasic excitatory inputs on the vagal nerve. These two mechanisms are functionally linked via the diaphragmatic control of respiration, and, the balance between these two mechanisms may be altered by specific respiratory maneuvers and chemoreceptor actions on the respiratory generator. Anrep and coworkers (1936) suggested that both central and peripheral mechanisms contribute approximately equivalently to RSA.

Respiratory and cardiovascular system react to a wide variety of environmental demand that requires elevated metabolic responses, but also to psychological and behavioral variations, as well as physiological state, including modification in the levels of alertness, different types of emotion, mental activity and arousal.

Given that different processes may interfere and modify the relationship between respiration process and vagal control, the RSA-vagal control association is not always direct, thus, desuming vagal regulation from RSA is complicated. In fact, the exact phase relationship between respiratory oscillation and HR fluctuation depend on the respiration rate (Eckberg, 1983). Furthermore, even when autonomic tone is stable, the amplitude of HR fluctuations depend upon both respiratory frequency and depth of ventilation (i.e. tidal volume; Hirsch & Bishop, 1981). In addition, people breathe at different frequencies and RSA sometimes is decoupled from the vagal influence on HR (Sargunaraj et al., 1996; Yasuma, 2004). Furthermore, even acetylcholine metabolism may affect RSA. In fact, the vagal nerve determine the releasing of acetylcholine during exhalation (resulting in HR increases), nevertheless acetylcholine may be metabolized more completely during slow respiration, compared to fast respiration, thus causing a reduction in the effect of the vagal nerve activity on HRV (Eckberg & Eckberg, 1982) and thus decouple amplitude of RSA from quantity of vagus nerve traffic. In addition, sympathetic activity may affect HF of HRV under some circumstances (Taylor, Myers, Halliwill, Seidel, & Eckberg, 2001).

Hence, it is important to consider respiration rate while evaluating HRV indexes, both HF and/or RSA as a measure of autonomic parasympathetic function.

1.3.3 HRV alterations and cardiovascular diseases

Reduced HRV is associated with a wide variety of cardiovascular disorders including hypertension, particularly when accompanied by left ventricular hypertrophy (Mancia, Ludbrook, Ferrari, Gregorini, & Zanchetti, 1978), sudden cardiac death (Goldberger, Rigney, Mietus, Antman, & Greenwald, 1988; Goldberger, 1991), mainly from arrhythmic events

after myocardial infarction (Bigger, Fleiss, Rolnitzky, & Steinman, 1993; Farrell et al., 1991), ventricular arrhythmia (Matveev & Prokopova, 2002), presence and severity of ischemic heart disease (Huikuri & Mäkikallio, 2001); and risk of rejection after heart transplant (Izrailtyan et al., 2000).

Several lines of evidence have documented that reduced RSA may represent an index of poor vagal control, that, in turn, is a marker of cardiovascular risk both in patients with and without CVDs (Bigger et al., 1992; Hayano et al., 1990).

The unbalance of the autonomic nervous system plays an important role in a wide range of visceral-somatic and mental diseases. As mentioned before, the balance between sympathetic and parasympathetic branches is associated to healthy, adaptable and flexible physiological system. Reduced parasympathetic activity and/or excessive sympathetic reactivity is frequently reported as associated with several maladaptive conditions, and with the increased risk of cardiovascular adverse outcomes (Friedman, 2007; Porges, 2007; Thayer & Sternberg, 2006). Specifically, a constant reduced parasympathetic activity on the heart may lead to accelerated heart rate at rest, reduced HRV and longer recovery time after a stressor occurs. Moreover, elevated sympathetic reactivity may cause disproportionate increment of heart rate in response to a stressor. Therefore, the correct functioning of the ANS and a dynamic balance between sympathetic and parasympathetic systems both during rest and in response to different internal/external stressors is important in order to maintain flexibility, adaptability and health. Decreased HRV have been related to onset and exacerbation of CVDs, such as hypertension, coronary heart disease, and congestive heart failure. In fact, CVD patients display a reduced HRV (Kristal-Boneh et al., 1995), and diminished variability in heart rate have been shown to be a risk factor negative outcomes in myocardial infarction and CHF (Kleiger et al., 1987; Tapanainen et al., 2002; Wolk,

Kulakowski, & Ceremuzynski, 1996). Many studies reported that a reduced HRV represents an independent risk factor for cardiovascular mortality in patients with stable CHD (Rich et al., 1988) and after a myocardial infarction (Glassman, Roose, & Bigger, 1993; Kleiger et al., 1987).

Furthermore, although few negative findings have been reported on the relationship between depression and HRV in CHD patients (Gehi, Mangano, Pipkin, Browner, & Whooley, 2005), there is abundant evidence that depressed patients with CHD or acute myocardial infarction are characterized by a reduced HRV compared to individuals without depression (Carney et al., 2001, 2002; Krittayaphong et al., 1997; Stein, Domitrovich, Kleiger, Schechtman, & Rottman, 2000).

1.3.4 HRV alterations and depression

Reduced amplitude and complexity of HRV is associated with a wide range of psychological dysfunctions, including anxiety and depression (Agelink, Boz, Ullrich, & Andrich, 2002; Gorman & Sloan, 2000; Kawachi, Sparrow, Vokonas, & Weiss, 1995; Yeragani, Balon, Pohl, & Ramesh, 1995). Reduced HRV has been found in depressed patients with and without CVDs, compared to individuals without depression (Carney et al., 1995; Pitzalis et al., 2001; Rechlin et al., 1994; Rechlin, 1994). Some studies reported reduced cardiac vagal control in adult patients with depression (Kikuchi et al., 2009; Udupa et al., 2007). Krittayaphong and colleagues (1997) found that patients with higher depressive symptoms on the Minnesota Multiphasic Personality Inventory-Depression (MMPI-D; Hathaway & McKinley, 1967) compared to patients with lower scores had significantly lower HRV. In addition, cross-sectional and longitudinal studies have displayed that reduced levels of RSA are linked to depression and/or depressive symptoms in nonsurgical

populations (Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Carney, Freedland, Rich, & Jaffe, 1995). In addition, a few studies have demonstrated that baroreceptor reflex (baroreflex) sensitivity may be reduced in patients with depression (Watkins et al., 1999). A reduction in baroreflex sensitivity has been reported to differentiate high- from low-risk patients recovering from myocardial infarction and CHF (Mortara et al., 1997).

However, discrepant findings have also been reported regarding the relationship between RSA and depression (Carney et al., 1988; Khaykin et al., 1998) and between reduced HRV and depression (Yeragani et al., 1991; Dawood et al., 2007). Possible reasons for these inconsistent findings involve the heterogeneity of individuals diagnosed with depression (Gotlib & Hammen, 1992), small sample sizes, and the quantification of RSA without controlling for possible confounds such as respiratory rate and depth (Grossman & Taylor, 2007).

Pharmacological data suggest that one possible mechanism underlying the relationship between depression and reduced HRV may involve central serotonergic regulation (Khaykin et al., 1998). In fact, recently, Barton and colleagues (2007) showed the efficacy of pharmacological treatment with selective serotoninergic reuptake inhibitors (SSRIs) in depressed patients in reducing sympathetic activation, as shown by a norepinephrine spillover reduction. However, a few studies have reported adverse effects in patients with depression treated with SSRIs (Dawood et al., 2007), while some studies have reported no significant cardiovascular changes (neither positive nor negative) (Nemeroff, Musselman, & Evans, 1998; Roose & Miyazaki, 1998; Roose et al., 1998).

In conclusion, reduced ANS control of the heart, characterized by imbalance between sympathetic and parasympathetic modulation, is likely a central mechanism contributing to the increased cardiac risk associated with depression disorder (for reviews, Brown, Barton, & Lambert, 2009; Carney & Freedland, 2009).

1.4 Aims of the research project and outline of the studies

With the goal of increasing our understanding of depression as a cardiac risk factor, this thesis investigates the psychophysiological mechanisms underlying the relationship between depression and increased cardiac risk in patients after first time cardiac surgery, and, secondarily, it explores the effectiveness of a biofeedback training in reducing cardiac risk in these patients.

Accordingly, the primary aim of the first study was to investigate whether the association between depression symptoms and reduced heart rate variability can be extended to patients after first time cardiac surgery, independently of anxiety symptoms, and specifically if depression would be related to reduced vagal control after cardiac surgery. The experiment reported in chapter two examined the relationship between postoperative depressive symptoms and reduced vagal control on the heart, as measured by HRV indexes, controlling for anxiety symptoms. It is hoped that this will lead to a better understanding of the psychophysiological mechanism linking depression to increased cardiac risk.

The current thesis also aims to examine the role of emotion regulation in the relationship between depression and HRV. The experiment in chapter three aimed to investigate whether patients with depressive symptoms after first time cardiac surgery use altered emotion regulation strategies when compared to nondepressed patients. Moreover, it was examined whether excessive use of expressive suppression strategy would mediate the relationship between depression and reduced HRV. Excessive use of expressive suppression was hypothesized to increase cardiac risk, further decreasing HRV. The understanding of the role of altered emotion regulation strategies can lead researchers to better comprehension of the emotional factors in the relationship between depression and the sympathovagal imbalance.

The current thesis also aims to observe vagal modulation during a stressful emotional situation in depressed patients after cardiac surgery. The experiment reported in chapter four examined vagal activity, as measured by HF index of HRV, during three emotional stressors in depressed and non-depressed patients after cardiac surgery. It was hypothesized that depression would be associated with greater stress response, characterized by vagal withdrawal during unpleasant situation rather than neutral and pleasant ones. The understanding of the relationship between postoperative depressive symptoms and sympathovagal balance during emotional stressors can lead researchers to develop easy-to-use protocols in order to improve the diagnosis and treatment of depressed patients.

Given the relevant role played by depression as a risk factor for postoperative adverse outcomes, and the lack of completely effective and reliable treatment for depressive symptoms in cardiac patients the research was finally focused on possible non pharmacological treatment of depression in patients after cardiac surgery. The experiment in chapter five was designed to examine the effectiveness of a short training with RSA-biofeedback. Specifically, the current experiment was carried out to investigate whether the biofeedback intervention would be effective in increasing vagal control of heart rate (as measured by RSA) at rest. Secondarily, it examined whether the RSA-biofeedback training would also be associated with a reduction in depressive symptoms, thus contributing to lowering risk factors linked to depressive symptoms after cardiac surgery, which may influence clinical outcomes in these patients.

CHAPTER 2

Postoperative depression and reduced heart rate variability [1]

2.1 Abstract

Objective: Depression is a risk factor for cardiovascular diseases. Reduced heart rate variability (HRV), which reflects altered autonomic nervous system activity, has been suggested as one of the mechanisms linking depression to cardiovascular diseases. However, the relationship between depression and HRV has not yet been investigated in patients undergone cardiac surgery. Therefore, the main aim of this study was to examine whether postoperative depression could be related to reduced HRV.

Methods: Eleven patients with depression and 22 patients without depression, who had undergone cardiac surgery, were enrolled postoperatively. In all patients, HRV was derived from a four-minute blood volume pulse recording at rest. Analyses of covariance and partial correlations, while controlling for anxiety, were used to examine the associations between postoperative depression and each HRV parameter.

Results: Compared to non-depressed patients, patients with depression showed significantly lower standard deviation of N-to-N intervals (SDNN) (p = .02), root mean square successive difference of N-to-N intervals (rMSSD) (p = .001), and high frequency power (p = .002). Partial correlation analyses showed that depression was inversely related to SDNN (r = -.49, p = .005), rMSSD (r = -.58, p = .001), and high frequency power (r = -.41, p = .02), whereas it was unrelated to other HRV parameters (p's > .09).

1 Results from this study have been partially published in: Patron, E., Messerotti Benvenuti, S., Favretto, G., Valfrè, C., Bonfà, C., & Palomba, D. (2012). Association between Depression and Heart Rate Variability in Patients after Cardiac Surgery: A Pilot Study. Journal of Psychosomatic Research, 73, 42-6.

Conclusions: The current findings extend the depression-reduced HRV relationship to the patients after cardiac surgery. Also, our study suggests that postoperative depression is more likely to be associated with reduced vagal modulation on the heart than with excessive sympathetic activity.

Keywords: autonomic nervous system; cardiac surgery; depression; heart rate variability

2.2 Introduction

Several lines of evidence suggest that depression is a relevant and independent risk factor for cardiovascular diseases onset (Carney et al., 2005). Specifically, Wulsin and Singal (2003) reported that depressive symptoms were associated with roughly a 60% greater likelihood of developing coronary heart disease (CHD). Also, Lichtman and coworkers (2008) found a dose-response relationship between the increasing of depression severity and subsequent cardiac events, with more severe depression being associated with greater risk of earlier and more severe cardiac events. The physiological mechanisms underlying depression as risk factor for developing cardiovascular diseases are still debated (Carney et al., 2005, 2002). The strongest evidence implicates an altered autonomic tone as a possible link between depression and cardiovascular morbidity or even mortality (Carney et al., 2005, 2002). Indeed, it is well-established that depression is associated to dysregulation of the hypothalamic pituitary-adrenal axis, as well as increased sympathetic nervous system activity (Siever & Davis, 1985; Veith, 1994). Decreased parasympathetic and/or increased sympathetic nervous system activity, in turn, may predispose patients with cardiovascular diseases to ventricular fibrillation, ventricular tachycardia, and sudden cardiac death (Podrid, Fuchs, & Candinas, 1990; Pruvot et al., 2000).

Heart rate variability (HRV) has been widely used to assess cardiac autonomic modulation since it reflects the influence of both sympathetic and parasympathetic nervous system effects on the heart (Carney et al., 2001; Carney et al., 2002; Krittayaphong et al., 1997; Task Force, 1996). A reduced HRV is associated with sympathovagal imbalance, in particular, excessive sympathetic modulation and/or inadequate vagal control (Task Force, 1996). Specifically, it has been reported that a reduced HRV is an independent risk factor for cardiac mortality after a myocardial infarction (Bigger et al., 1993; Kleiger et al., 1987) and in patients with stable CHD (Rich et al., 1988). Moreover, although few negative findings have been reported on the relationship between depression and HRV in CHD patients (Gehi et al., 2005), there is large evidence that depressed patients with CHD or acute myocardial infarction have a reduced HRV compared to individuals without depression (Carney et al., 2001; Carney et al., 2002; Krittayaphong et al., 1997; Task Force, 1996).

Cardiovascular diseases such as heart valve diseases, coronary heart disease, or aneurysms of the ascending aorta can be surgically treated. Nevertheless, high rates of depression are commonly reported in 25% to 30% of patients undergoing cardiac surgery (Langeluddecke et al., 1989; McKhann et al., 1997; Pirraglia et al., 1999). Langeluddecke and coworkers (1989) found that 36% of patients had clinically significant scores on the Center for Epidemiological Study of Depression scale (CES-D) prior to coronary artery bypass graft (CABG) surgery. Similarly, McKhann and colleagues (1997) using the same scale (i.e., CES-D) reported that the incidence of preoperative depression in patients undergoing a CABG was 27%. Preoperative depression may persist after cardiac surgery in up to 20% of the patients (Vingerhoets, 1998) and 32% of the patients had clinically significant depression at least once in their postoperative period (Burg, 2003b; McKhann et al., 1997). More importantly, patients with postoperative depression are at higher risk of cardiac morbidity and fatal cardiac events (Burg, 2003a; Connerney et al., 2001; Scheier,

1999). Indeed, several studies reported the association between postoperative depression and a higher incidence of cardiovascular morbidity or mortality (Ariyo et al., 2000; Blumenthal et al., 2003b; Penninx et al., 2001).

Despite several studies on the association between depression and a reduced HRV in patients with cardiovascular diseases, to our knowledge, this potential relationship has not yet been investigated in patients after cardiac surgery. Accordingly, the main aim of the current pilot study was to examine whether depression would be related to reduced HRV in patients who had undergone first-time cardiac surgery. Specifically, it was hypothesized that patients with depression had a reduced HRV at rest compared to those without depression after cardiac surgery.

2.3 Methods

Participants

After receiving the local ethics committee's approval, 33 patients (mean age = 60.7, *SD* = 8.1) who underwent first-time cardiac surgery were sequentially enrolled in this study after their written informed consent was obtained. All patients underwent cardiac surgery at a regional specialized hospital and were admitted for rehabilitation in a highly specialized hospital between November 2010 and July 2011. Patients underwent heart valve surgery (*N* = 8), coronary artery bypass graft surgery (CABG) (*N* = 15), and combined surgery (heart valve plus CABG surgery) (*N* = 10). Each patient had the same protocol of cardioplegia and a mild hypothermic cardiopulmonary bypass. Ages greater than 75, inability to read or understand Italian, visual or auditory impairments, use of psychotropic drugs, other life-threatening medical illness, and prior cerebrovascular and/or neurological diseases were the

exclusion criteria. All patients were treated in the hospital with beta-blockers and/or angiotensin-converting enzyme inhibitors. Based on the presence of clinically significant depression (i.e., scoring greater than 16 on the Center for Epidemiological Study-Depression, CES-D) (Fava, 1982; Radloff, 1977), the patients were classified into one of two groups: with depression (N = 11) or without depression (N = 22). The descriptive statistics for each group are reported in Table 2.1.

Psychological evaluation

The psychological evaluation included a short clinical interview and three self-reporting questionnaires aimed at assessing depression and anxiety symptoms. The anxiety and depression questionnaires were selected according to their sensitivity, specificity and reliability and consisted of:

Center for Epidemiological Study-Depression (CES-D; Fava, 1982; Radloff, 1977); that is a 20-item, self-reporting questionnaire designed to measure the presence of common symptoms of depression over the previous week. It includes six components: depressed mood; feelings of guilt and worthlessness; feelings of helplessness and hopelessness; psychomotor retardation; loss of appetite; and sleep disturbance. Respondents indicate how often within the last week they experienced the symptoms on a four-point Likert scale and scores range from 0 to 60, with the higher scores indicating greater depressive symptoms. Scores equal or greater than 16 are indicative of clinically significant depression. Reliability and validity of the scale have been tested in either general and clinical populations (Radloff, 1977), yielding very good internal consistency with an alpha of 0.85 for the general population and 0.90 for a psychiatric population. Moreover, construct validity was supported by differences between the psychiatric in- patients and the general population.

Table 2.1. *Demographic, Biomedical, and Surgical Characteristics of Patients with Depression and without Depression*

Variable	Group with Depression (*N* = 11)	Group without Depression (*N* = 22)	*p*
Age (years)	62.5 (10.2)	59.8 (6.7)	.36
Education (years)	8.7 (3.8)	11.0 (3.1)	.08
Male Sex (*N*, %)	8 (73)	20 (91)	.30
Surgical Procedure			.90
CABG (*N*, %)	5 (46)	10 (46)	
Heart Valve (*N*, %)	2 (18)	6 (27)	
Combined (*N*, %)	4 (36)	6 (27)	
Diabetes (*N*, %)	3 (27)	3 (14)	.39
Hypertension (*N*, %)	7 (64)	10 (46)	.47
Myocardial Infarction (*N*, %)	3 (27)	1 (5)	.11
Dyslipidemia (*N*, %)	4 (36)	11 (50)	.47
PTCA (*N*, %)	0 (0)	4 (18)	.27
Smoking			.48
Actual (*N*, %)	1 (9)	6 (27)	
Past (*N*, %)	4 (36)	4 (18)	
No (*N*, %)	6 (55)	12 (55)	
HR (bpm)	75.3 (7.4)	74.1 (9.6)	.72
STAI Y1	39.9 (6.3)	31.4 (8.7)	.007
STAI Y2	37.4 (7.0)	31.3 (6.6)	.02

Notes: Data are *M* (*SD*) of continuous and *N* (%) of categorical variables. CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; HR = heart rate; STAI Y1, STAI Y2 = state-trait anxiety inventory form Y1 and Y2.

Self-reported anxiety symptoms were assessed by means of the two subscales of the State-Trait Anxiety Inventory (STAI-Y1 and STAI-Y2; Spielberger, Gorsuch, & Lushene,

1970; Spielberger, 1996). The STAI-Y form 1 and 2 is a 40-item questionnaire rated by patients and divided into two equal and separate parts; the first part measures the state anxiety presented by the subject in the exact moment of compilation (STAI-Y1) while the second part concerns the usual tendency for the subject to be anxious (STAI-Y2). Each item is rated from 1 to 4 depending on the intensity of the symptoms. This scale has been frequently used in psychiatric research and in the evaluation of emotional modifications in a surgical context.

Physiological recordings

Blood volume pulse (BVP) was recorded by means of a photoplethysmographic detection sensor attached to the left ring finger, and heart rate (HR) was obtained. Photoplethysmography is a simple, non-invasive technique used to detect blood volume changes. As electrical and mechanical activities of heart are coupled, photoplethysmography can be used for determining the normal-to-normal (NN) intervals (or inter-beat intervals), and HR corresponds to the reciprocal of the N-to-N intervals. The HR signal derived from the analog output of the BVP amplifier was processed via a 12-bit analog-to-digital converter, with a sampling rate of 256 Hz and stored sequentially for spectral analysis. All HR data were exported in Kubios-HRV 2.0 software (University of Kuopio, Kuopio, Finland) and artifacts were corrected with a piecewise cubic spline interpolation method that generates missing or corrupted values into the normal-to-normal (NN) intervals. Time domain indexes are measures of the total variation of heart rate and were calculated as follows:

1) Standard deviation of NN intervals (SDNN) expressed in ms;

2) Root mean square successive difference of N-to-N intervals (rMSSD) expressed in ms.

Fast Fourier spectral analysis was then applied on the N-N series to compute frequency domain indexes, that, in turn, were calculated as follows:

1) Very low frequency (VLF) power (0 to 0.04 Hz) in ms^2.
2) Low frequency (LF) power (0.04 to 0,15 Hz) in ms^2.
3) High frequency (HF) power (0.15 to 0.40 Hz) in ms^2.

All frequency domain indexes were logarithmically transformed to normalize their distribution. In addition, the LF/HF ratio was computed as the ratio of LF(ms^2)/HF(ms^2) as a measure of sympathovagal balance (Malliani, Lombardi, & Pagani, 1994; Task Force, 1996).

Procedure

After their admission for rehabilitation, all patients underwent the assessment protocol, about two weeks (range 10-14 days) after cardiac surgery. The assessment protocol consisted of psychological evaluation aimed at assessing depression and anxiety symptoms, and a physiological recording in resting conditions. All self-reporting questionnaires assessing depression and anxiety were administered individually by a trained psychologist blind to the physiological assessment. After the psychological evaluation HR was recorded at rest over a four-minute period for each patient. NN intervals were then used to compute HRV. Given that photoplethysmography is subject to movement artifacts, each patient was instructed to stay still and not to talk during the HRV recordings. All physiological recordings were taken with the patients seated on a semireclined armchair after adaptation to the laboratory. In order to avoid possible confounder effect of circadian variations on cardiac activity, each physiological measurement was taken in a quiet and isolated laboratory during morning hours (from 10:00 to 12:00).

Statistical analysis

Analysis of variance (ANOVA), with Group (patients with depression, patients without depression) as the between-subjects factor, was used to compare age, education, STAI Y1 and Y2 scores, and HR, in the two groups. Fisher's exact test or chi-square analyses were conducted to compare the two groups in terms of demographic, biomedical, and behavioral variables.

These preliminary analyses showed greater state and trait anxiety scores on STAI Y1 and Y2, respectively, in patients with depression than those without depression (see Results). Given that anxiety may influence HRV (Watkins, Grossman, Krishnan, & Sherwood, 1998) and is strongly related to depressive symptoms (Gorman, 1997), STAI Y1 and STAI Y2 scores were used as covariates in the subsequent analyses to control for state and trait anxiety. Separate analyses of covariance (ANCOVAs), with Group (patients with depression, patients without depression) as the between-subjects factor, and STAI Y1 and Y2 scores as covariates, were conducted on SDNN, rMSSD (i.e., time domain measures of HRV) as well as logVLF, logLF, logHF, and LF/HF (i.e., frequency domain measures of HRV). Partial eta-squared (η_p^2) was reported as a measure of the effect size. The η_p^2 values considered to represent small, medium, and large effects are .01, .06, and .14, respectively (Cohen, 1988).

To evaluate the relationship between CES-D scores and each HRV parameter, partial correlations were calculated, adjusting for possible effects of state and trait anxiety (i.e., scores on STAI Y1 and Y2, respectively). A p value of $< .05$ was considered statistically significant. All statistical analyses were performed using STATISTICA 6.1 (StatSoft Inc., Tulsa, OK, USA).

2.4 Results

Characteristics of Patients with Depression and without Depression

Fisher's exact test or chi-square analysis revealed no group differences for gender (p = .30), surgical procedures (p = .90), hypertension (p = .47), diabetes (p = .39), dyslipidemia (p = .47), previous myocardial infarction (p = .11), previous percutaneous transluminal coronary angioplasty (p = .27), and smoking (p = .48). Similarly, ANOVA yielded no group differences for age ($F_{(1, 31)}$ = 0.86, p = .36, η_p^2 = .03), or education ($F_{(1, 31)}$ = 3.27, p = .08, η_p^2 = .10), HR ($F_{(1, 31)}$ = 0.13, p = .72, η_p^2 = .004). In contrast, ANOVA showed group differences for STAI Y1 ($F_{(1, 31)}$ = 8.29, p = .007, η_p^2 = .21), and STAI Y2 ($F_{(1, 31)}$ = 5.88, p = .02, η_p^2 = .16). STAI Y1 and Y2 scores were significantly greater in patients with depression than those without depression.

Relationship between Depression and Heart Rate Variability

ANCOVA yielded a significant main effect for Group on both time domain measures, i.e., SDNN ($F_{(1, 29)}$ = 6.08, p = .02, η_p^2 = .17), and rMSSD ($F_{(1, 29)}$ = 13.48, p = .001, η_p^2 = .32). SDNN and rMSSD values were significantly lower in patients with depression than those without depression. Also, ANCOVA yielded a significant main effect for Group on logHF ($F_{(1, 29)}$ = 12.09, p = .002, η_p^2 = .29), and LF/HF ratio ($F_{(1, 29)}$ = 8.25, p = .008, η_p^2 = .22). LogHF values were significantly lower in patients with depression that those without depression and vice versa for LF/HF ratio. In contrast, no significant main effects for Group were found on logVLF ($F_{(1, 29)}$ = 2.77, p = .11, η_p^2 = .09), and logLF ($F_{(1, 29)}$ = 0.06, p = .81, η_p^2 = .002). All means (*SD*) of each HRV parameter are reported in Table 2.2.

Partial correlation analyses, adjusting for STAI Y1 and Y2 scores, revealed significant inverse associations between CES-D scores and SDNN (r = -.49, p = .005),

rMSSD (r = -.58, p = .001), and logHF (r = -.41, p = .02), whereas CES-D scores were unrelated to logVLF (r = .30, p = .10), logLF (r = -.04, p = .82), and LF/HF (r = .31, p = .09).

Table 2.2. *Relationship between Depression and Heart Rate Variability Parameters*

HRV Index	Group with Depression (*N* = 11)	Group without Depression (*N* = 22)	*p*	η_p^2
SDNN (ms)	17.5 (9.8)	36.7 (25.2)	.02	.17
rMSSD (ms)	8.1 (3.2)	43.3 (32.9)	.001	.32
logVLF (ms²)	2.0 (0.6)	1.7 (0.7)	.11	.09
logLF (ms²)	1.6 (0.5)	1.7 (0.6)	.81	.002
logHF (ms²)	1.2 (0.4)	2.2 (0.7)	.002	.29
LF/HF	3.6 (4.2)	0.9 (1.5)	.008	.22

Notes: Results are reported as *M* (*SD*). HRV = heart rate variability; SDNN = standard deviation of all NN intervals in ms; rMSSD = the square root of the mean of the sum of the squares of differences between adjacent NN intervals in ms; logVLF = logarithm transformation of very-low-frequency power (0.0033 to 0.04 Hz) in ms²; logLF = logarithm transformation of low-frequency power (0.04 to 0.15 Hz) in ms²; logHF = logarithm transformation of high-frequency power (0.15 to 0.40 Hz) in ms²; LF/HF = the Ratio LF [ms²]/HF [ms²].

2.5 Discussion

The current study examined the association between depression and HRV in patients who underwent cardiac surgery. Patients with depression showed a more reduced HRV, as measured by SDNN, than those without depression. Also, compared to non-depressed patients, depressed patients were characterized by lower rMSSD and HF power (i.e., time

and frequency domain HRV measures, respectively), indicative of reduced cardiac vagal modulation. A sympathovagal imbalance, as indexed by the increased LF/HF ratio, was also observed in patients with depression compared to those without depression. Moreover, correlation analyses yielded that CES-D scores were inversely related to SDNN, rMSSD, and HF power. More importantly, the associations between depression and time and frequency HRV domains were independent of state or trait anxiety, as assessed by STAI Y1 and Y2. In contrast, CES-D scores were unrelated to VLF and LF powers, that reflect both sympathetic and parasympathetic activities, and LF/HF ratio, that reflects also a sympathetic influence on the heart (Malliani et al., 1994; Task Force, 1996).

These novel findings add to the literature on physiological mechanisms underlying the association between depression and cardiovascular disease by showing that a depression-reduced HRV relationship extends to patients after cardiac surgery. These preliminary findings complement a large body of studies that have documented reduced HRV in depressed individuals with cardiovascular diseases (Carney et al., 2002) as well as after a myocardial infarction (Carney et al., 2001; Stein et al., 2000).

Although it is well-established that increased sympathetic and/or reduced parasympathetic cardiac control can represent the physiological mechanisms linking depression to cardiovascular diseases, the relative contribution of the sympathetic and parasympathetic nervous systems to depression as a risk factor for cardiovascular diseases is still debated (Carney et al., 2001; Carney et al., 2005). The current pilot study provides the evidence for the relationship between depression and reduced vagal cardiac modulation rather than increased sympathetic cardiac modulation. Indeed, a selective association was found between CES-D scores and reduced rMSSD and HF power, that, in turn, are considered to be largely influenced by parasympathetic activity of the heart (Taylor et al., 1998). In contrast, VLF and LF powers, that mostly reflect sympathetic and parasympathetic

effects on the heart, were unrelated to CES-D scores. Therefore, our findings suggest that postoperative depression is more likely to be associated with reduced vagal rather than excessive sympathetic modulation of the heart.

Along with depression, anxiety has been frequently linked to reduced HRV. Specifically, low HRV has been reported in patients with high levels of anxiety after a myocardial infarction (Martens, Nyklícek, Szabó, & Kupper, 2008; Watkins, Blumenthal, & Carney, 2002). Therefore, it is noteworthy that our pilot study showed an association between depression and reduced HRV, even after controlling for anxiety as measured by STAI Y1 and Y2.

It is important to consider the clinical benefits of the current findings. Several lines of evidence indicate that postoperative depression represents a relevant and independent risk factor for adverse patient outcomes after cardiac surgery (Blumenthal et al., 2003; Connerney et al., 2001; Scheier, 1999). Specifically, Scheier (1999) observed a two-fold increase in the odds of having a cardiac event within six months after surgery in patients with depressive symptoms. Moreover, Connerney and coworkers (2001) reported that a major depressive disorder was an independent predictor of cardiac events in the 12 months after a CABG, even after controlling for other biomedical risk factors. Blumenthal and colleagues (2003b) showed that depressed patients after cardiac surgery with persistent (i.e., before as well as six months after a CABG) mild or moderate to severe depression had more than twice the risk of cardiac death compared to patients without depression. Our findings suggest that reduced HRV, especially a reduced vagal control, is a potential mechanism underlying the relationship between postoperative depression and subsequent cardiac events or mortality after surgery.

The current findings should be interpreted in light of a number of possible methodological limitations. First, this study used a relatively small sample size and,

therefore, should be considered as a pilot study. Nonetheless, the effect size, which indicates the proportion of the variance in the dependent variable that is related to the independent variable(s), showed a large main effect for the group on SDNN, rMSSD and log HF (η_p^2 > .17). Second, all patients were treated in a hospital with beta-blocker and/or angiotensin-converting enzyme inhibitor medication, that, in turn, influenced cardiovascular physiology and, therefore, blood pressure, HR, and HRV values. Nevertheless, the pharmacological treatment was part of these cardiac patients' standard clinical care in this post-surgical context and was the same between individuals with depression and those without depression. Third, the current pilot study did not take into account respiration rate and respiratory sinus arrhythmia, even though HRV indexes may be confounded and exaggerated by respiration without reflecting completely the influence of vagal regulation on the HR (Soares, Moreno, Cravo, & Nóbrega, 2005). Fourth, we employed photoplethysmography, an easier-to-use technique than electrocardiography, that, in turn, is the gold-standard method to measure HR and to determine HRV. Nonetheless, several studies have reported that photoplethysmographic variability highly correlates with a HRV extracted from an electrocardiogram (Association American Psychiatric, 1994; Demirel, Akkaya, Oflaz, Tükek, & Erk, 2002). Finally, we did not conduct follow-up evaluations and, therefore, we do not know whether the current results can predict long-term clinical outcomes in patients who underwent cardiac surgery. Clearly, future research is warranted to replicate and extend the present preliminary findings by conducting short- and long-term clinical follow-ups.

In conclusion, the current study investigate the relationship between depression and time and frequency domain measures of HRV in patients who underwent cardiac surgery. HRV indexes, that are known to be associated with cardiac morbidity and mortality, were significantly lower in patients with depression than those without depression. Moreover, our

findings suggest that depression may be selectively related to impaired parasympathetic activity as revealed by reduced rMSSD and HF power.

CHAPTER 3

The mediating role of emotion regulation on the relationship between depression and reduced heart rate variability [2]

3.1 Depression and emotion regulation

Depression is progressively being conceptualized as a disorder of emotion (Gross & Muñoz, 1995). In fact, the core symptoms of depression disorder include persistent and excessive negative mood and emotions and loss of interest or pleasure in daily activities, suggesting that impaired regulation of emotion may play an important role in their development or maintenance (Campbell-Sills, Barlow, Brown, & Hofmann, 2006b).

Emotions mirror the individual perception of relevant environmental stimuli, including not only the perception of challenges and threats, but also the perceived ability to deal with them (Frijda, 1988). Affective system, including emotion regulation processes, is efficient when it promotes flexible adaptation to changing environmental demands.

More importantly, both altered emotion regulation as a trait and altered emotion regulation in response to stressors have been proposed as pathophysiological mechanisms involved in the development of depression disorders. For example, many studies reported that higher HRV levels are associated with the ability to produce emotional responses appropriate to the context, specifically, during emotion modulated startle responses, fear-potentiated startle responses, and phasic heart rate responses, in addition to behavioral and

2 Results from this study have been partially published in: Patron, E., Messerotti Benvenuti, S., Favretto, G., Gasparotto, R., & Palomba, D. (2014). Depression and reduced heart rate variability after cardiac surgery: The mediating role of emotion regulation. Autonomic Neuroscience: Basic and Clinical, 180:53-58.

self reported emotional responses (Melzig, Weike, Hamm, & Thayer, 2009; Ruiz-Padial, Sollers, Vila, & Thayer, 2003; Julian F Thayer & Brosschot, 2005). Thus, emotion regulation strategies are involved in the process of selection of the optimal response, from a large behavioral repertoire. In addition, emotion regulation strategies help the inhibition of responses that are dysfunctional. In this context, HRV may be considered a useful resource that modulate and support this regulatory function (Julian F Thayer & Lane, 2009). Recently, Butler and coworkers (2006) found that, during situations requiring emotional regulation, phasic increases of HRV can facilitate effective emotional regulation processes and are associated with flexible and efficient use of emotional regulation strategies.

Literature has mainly focused on two strategies of emotion regulation, that is, cognitive reappraisal and suppression of emotion-expressive behavior (Gross, 2002). The former, cognitive reappraisal, which comes early in the emotion-generative process, is described as construing a potentially emotion-provoking situation in a neutral, nonemotional one and therefore is a type of cognitive change. The latter, suppression of emotion-expressive behavior, which appears later in the emotion-generative process, is defined as inhibiting ongoing emotion-expressive behavior and therefore is a type of response modulation. There is evidence that whereas cognitive reappraisal is effective for reducing both expression and experience of emotion without side effects on memory or physiology, emotion suppression reduces emotion expression, but fails to reduce the feeling of emotion and is associated with memory and physiological responding impairment (Gross & Levenson, 1997; Gross, 1998). It has been shown, indeed, that cognitive reappraisal is associated with greater positive emotion experience and expression, and reduced negative emotion experience and expression. The habitual use of emotion suppression strategy, by contrast, has been related to a wide range of negative outcomes, including, higher levels of psychopathology, negative mood, worse social adjustment, and reduced well-being (Gross &

John, 2003; Moore, Zoellner, & Mollenholt, 2008). More interestingly, there is consistent evidence that suppression of emotion-expressive behavior, but not cognitive reappraisal, increases sympathetic cardiovascular activity, as indexed by decreases in finger temperature, finger pulse, and pulse transit times to the finger and ear (Gross & Levenson, 1997; Harris, 2001), and electrodermal system activity (Gross, 1998).

Therefore, depression disorder is characterized by altered emotion regulation strategies, which, in turn, may increase cardiac risk in these patients.

3.2 Abstract

Background: Heart rate variability (HRV), as an index of autonomic nervous system (ANS) functioning, is reduced by depression after cardiac surgery, but the underlying mechanisms of this relationship are poorly understood. Poor emotion regulation as a core symptom of depression has also been associated with altered ANS functioning. The present study aimed to examine whether emotion dysregulation could be a mediator of the depression-reduced HRV relationship observed after cardiac surgery.

Methods: Self-reported emotion regulation and four-minute HRV were measured in 25 depressed and 43 nondepressed patients after cardiac surgery. Mediation analysis was conducted to evaluate emotion regulation as a mediator of the depression-reduced HRV relationship.

Results: Compared to nondepressed patients, those with depression showed lower standard deviation of normal-to-normal (NN) intervals ($p < .05$), root mean square successive difference of NN intervals ($p < .004$), and number of interval differences of successive NN intervals greater than 50 ms (NN50) ($p < .05$). Increased low frequency (LF) in normalized units (n.u.) and reduced high frequency (HF) n.u. were also found in depressed compared to nondepressed patients (p's $< .01$). Mediation analysis revealed that suppression of emotion-expressive behavior partially mediated the effect of depression on LF n.u. and HF n.u.

Conclusions: Results confirmed previous findings showing that depression is associated with reduced HRV, especially a reduced vagal control and a sympathovagal imbalance, after cardiac surgery. This study also provides preliminary evidence that increased trait levels of suppression of emotion-expressive behavior may mediate the depression-related sympathovagal imbalance after cardiac surgery.

Keywords: Cardiac surgery; Cognitive reappraisal; Depression; Emotion regulation; Emotion suppression; Heart rate variability

3.3 Introduction

There is consistent evidence that depression is an important and independent risk factor for the onset, the adverse course and outcomes in patients with coronary heart disease (CHD) (Carney et al., 2005; Wulsin & Singal, 2003). Specifically, it has been reported that depressive symptoms are associated with roughly a 60% greater likelihood of exhibiting CHD (Wulsin & Singal, 2003). Moreover, patients with depression are at greater risk to have a major cardiac event within 12 months of the diagnosis of CHD (Carney et al., 1988), and they are significantly more likely to die in the years following the diagnosis (Barefoot & Schroll, 1996). It has also been documented that depression is a risk factor for cardiac morbidity and/or mortality in patients who had undergone cardiac surgery (Blumenthal et al., 2003; Lespérance & Frasure-Smith, 2000).

It has been recently shown that depression is associated with reduced heart rate variability (HRV), a measure that reflects both sympathetic and parasympathetic activity (Task Force, 1996), in patients who underwent cardiac surgery (Patron et al., 2012). As mentioned above (see Chapter 2) patients with depression had significantly lower HRV, especially a reduced cardiac vagal control, at discharge from the hospital compared to nondepressed patients. This depression-related cardiac autonomic dysfunction is likely to increase the risk for adverse clinical outcomes in patients after surgery because it may lead to direct electrical instability of myocytes and increase the occurrence of ischemic events (Soares et al., 2005). Reduced HRV has been therefore suggested as one of the pathophysiological mechanisms underlying the strong role of postoperative depression as a

risk factor for subsequent cardiac events and/or mortality that has been reported in patients after cardiac surgery (Blumenthal et al., 2003; Lespérance & Frasure-Smith, 2000).

In recent years, depression has been directly associated with poor emotion regulation (Gross & Muñoz, 1995), especially excessive emotion suppression(Ehring, Tuschen-Caffier, Schnülle, Fischer, & Gross, 2010), and type D personality, that, in turn, have been linked to increased risk of cardiac morbidity and/or mortality (Mols, Martens, & Denollet, 2010). However, research has yet to investigate the relationship between depression and emotion regulation strategies in patients after cardiac surgery. More importantly, whether emotion regulation strategies could mediate the association between depression and ANS abnormalities after cardiac surgery has yet to be examined. In light of these considerations, the primary purpose of this study was to formally evaluate whether emotion dysregulation would mediate the effects of depression on HRV in patients who underwent cardiac surgery. Specifically, emotion suppression strategy was expected to mediate the effects of depression on HRV, especially on HRV indices reflecting increased sympathovagal imbalance. It was also hypothesized that, compared to nondepressed patients, those with depression would have significant lower HRV, greater emotion suppression and/or reduced cognitive reappraisal postoperatively.

3.4. Methods

Participants

After receiving the local ethics committee's approval, 68 patients (mean age = 58.5, *SD* = 8.5) who had undergone first-time cardiac surgery were enrolled in this study after their written informed consent was obtained. Given the difficulty of recruiting patients in the early postoperative period after cardiac surgery and in order to increase the sample size,

maintaining the homogeneity of the sample, 33 patients from a previous report (see Patron et al., 2012) were included in the present study. All patients had undergone cardiac surgery at the same regional hospital and were admitted for rehabilitation in the same specialized hospital between November 2010 and December 2012. The same surgical techniques, surgical team and α-stat moderately hypothermic cardiopulmonary bypass strategy were used for each patient. Ages greater than 75, use of psychotropic drugs, other life-threatening medical illness, and prior cerebrovascular and/or neurological diseases were the exclusion criteria. Patients were treated in the hospital with beta-blockers, angiotensin-converting enzyme inhibitors, anticoagulants, and/or antiarrhythmics. Based on the presence of clinically significant depression [i.e., scoring equal or greater than 16 on the Center for Epidemiological Studies of Depression scale (CES-D)] (Fava, 1982; Radloff, 1977), the patients were classified into one of two groups: with depression (N = 43) or without depression (N = 25). The descriptive statistics for each group are reported in Table 3.1.

Psychological evaluation

The psychological evaluation included a short clinical interview and two self-reporting questionnaires aimed at assessing depression and emotion regulation. The questionnaire to assess depression consisted of CES-D (Fava, 1982; Radloff, 1977), and Emotion regulation was assessed using the Emotion Regulation Questionnaire (ERQ) (Balzarotti, John, & Gross, 2010; Gross & John, 2003), which is composed by a 10-item scale that measures individual differences in habitual use of the emotion regulation strategies of cognitive reappraisal (i.e., ERQ-Reappraisal) and suppression of emotion-expressive behavior (i.e., ERQ-Suppression). The questionnaire includes six items for cognitive reappraisal and four items for emotion suppression. Scores range from 6 to 42 for reappraisal

scale and from 4 to 28 for suppression scale, with higher scores indicating higher reappraisal and suppression, respectively.

Table 3.1 *Demographic, Biomedical, Surgical, and Emotion Regulation Characteristics by Depression Status*

Variable	**Depressed (*N* = 25)**	**Not Depressed (*N* = 43)**	***p***
Age (years)	59.3 (9.5)	58.0 (8.0)	.55
Male Gender (%)	80	86	.51
Beta-blockers (%)	80	88	.35
ACE inhibitors (%)	56	54	.84
Anticoaugulant (%)	76	88	.18
Antiarrhythmics (%)	36	12	.02
Diabetes (%)	12	14	.99
Hypertension (%)	56	44	.35
Dyslipidemia (%)	48	44	.76
Myocardial Infarction (%)	12	9	.70
PTCA (%)	12	16	.74
Smoking			.43
Actual (%)	12	18	
Past (%)	48	33	
No (%)	40	49	
HR (bpm)	74.8 (10.9)	73.0 (10.5)	.50
Surgical Procedure			.06
CABG (%)	44	37	
Heart Valve Replacement (%)	20	47	
Combined (%)	36	16	
ERQ-Reappraisal	29.5 (6.2)	29.3 (7.2)	.93
ERQ-Suppression	17.0 (4.6)	13.8 (6.2)	.03

Notes: Data are *M* (*SD*) of continuous and percentage (%) of categorical variables. ACE = angiotensin-converting enzyme; PTCA = percutaneous transluminal coronary angioplasty; HR = heart rate; CABG = coronary artery bypass graft; ERQ = emotion regulation questionnaire.

Physiological recordings

Physiological measures were recorded in a standardized fashion using a computerized recording system (ProComp Infiniti, Thought Technology;Montreal, Canada). Photoplethysmography and electrocardiogram (ECG) were used to measure heart rate (HR) and HRV in 33 and 35 patients, respectively. A detailed description of photoplethysmographic method has been previously reported (see Chapter 2). Given that electrical and mechanical activities of the heart are coupled, there is large and consistent evidence that photoplethysmographic variability highly correlates with HRV extracted from an ECG (Lu et al., 2008; Selvaraj et al., 2008); photoplethysmography and ECG, therefore, can be used reliably and interchangeably to assess HRV. ECG signal was obtained from three disposable Ag/AgCl electrodes that were positioned on the patient's chest in a modified lead II configuration. Each ECG signal was amplified, band-pass filtered (1–100 Hz), and sampled at 256 Hz. A digital trigger detecting R-waves was applied to ECG signal to obtain inter-beat intervals. All ECG data were visually inspected and artifacts were corrected with a piecewise cubic spline interpolation method that generates missing or corrupted values into the normal-to-normal (NN) intervals (or inter-beat intervals). Then, time domain and frequency domain indices of HRV were calculated by Kubios HRV Analysis Software 2.0 (Matlab, Kuopio, Finland). Time domain indices, which are measures of the total variation of heart rate, were calculated as follows:

1) Standard deviation of NN intervals (SDNN) expressed in ms.
2) Root mean square successive difference of NN intervals (rMSSD) expressed in ms.
3) Number of interval differences of successive NN intervals greater than 50 ms in the entire recording (NN50), expressed in ms.

Among time domain HRV indices, SDNN, rMSSD, and NN50 were calculated as the most appropriate HRV measures for short-term recordings (Task Force, 1996) and as the most frequently used measures in literature (Kleiger et al., 1987).

Given that the correlation between time and frequency domain HRV indices is less consistent for short-term HRV recordings compared to those recorded over longer periods (i.e., traditionally 24 h) (Task Force, 1996), fast Fourier spectral analysis was then applied on the NN series to compute frequency domain indices, which, in turn, were calculated as follows:

1) Very low frequency (VLF) power (0 to 0.04 Hz) in ms^2.
2) Low frequency (LF) power (0.04 to 0.15 Hz) in ms^2.
3) High frequency (HF) power (0.15 to 0.40 Hz) in ms^2.

All frequency domain indices were logarithmically transformed to normalize their distribution. In addition, LF and HF components were expressed in normalized units (n.u.), which represent the relative value of each power component in proportion to the total power minus the VLF component and range from 0 to 100%. The relation between LF and HF components in n.u. emphasizes the controlled and balanced behavior of the two branches of the ANS, thus reflecting more accurately the sympathovagal balance (Malliani et al., 1994; Task Force, 1996). Moreover, the normalization has the advantage to minimize the effect of the changes in total power on the values of LF and HF components (Task Force, 1996).

Procedure

All patients completed the assessment protocol after their admission for rehabilitation, approximately two weeks (range 10-14 days) after cardiac surgery. The assessment protocol consisted of affective evaluation to assess depression and the habitual

use of emotion regulation strategies, and physiological recording to assess HRV in resting condition. All self-reporting questionnaires were administered individually by a trained psychologist blind to the physiological assessment. After the affective evaluation, ECG was recorded at rest over 4-min period for each patient. A 4-min period of ECG recording has been previously shown to be an adequate procedure to measure short-term time (i.e., SDNN, rMSSD, and NN50) and frequency (i.e., LF, HF, and VLF) domain HRV indices examined in the present study (Task Force, 1996). In order to avoid movement artifacts, each patient was instructed to stay still and not to talk during the ECG recordings. All ECG recordings were taken with the patients seated on a semireclined armchair after adaptation to the laboratory. Each physiological measurement was taken in a quiet and isolated laboratory during morning hours (from 10:00 to 12:00), in order to avoid possible confounder effect of circadian variations on cardiac activity.

Statistical analysis

As our first step, Fisher's exact test or chi-square analyses were conducted to compare the two groups in terms of gender, cardiac drugs, biomedical variables, smoking habits, and types of cardiac surgery. Then, separate analyses of variance (ANOVAs), with Group (patients with depression, patients without depression) as the between-subjects factor, were used to compare age, emotion regulation strategies, HR, and time and frequency domain indices of HRV in the two groups.

As our final step, we chose the analysis of covariance (ANCOVA) approach to assess mediation given that it is recommended for experimental designs where the sample size is low (Hoyle & Robinson, 2004). ANOVA and ANCOVA produce identical results to and are conceptually equivalent to regression analyses (Cohen, Cohen, West, & Aiken, 2003). Mediation analyses were used to examine whether suppression of emotion-expressive

behavior mediated postoperative cardiac autonomic dysfunctions, indicated by lower values of HRV indices in patients with depression compared to those without depression. Mediation is established when four criteria are satisfied. First, the independent variable must affect the dependent variable. The main effect of depression on HRV indices, that is, SDNN, rMSSD, NN50, LF n.u, and HF n.u. satisfied this criterion (see Results). Second, the independent variable must affect the mediator. This was established by the significant effect of depression on ERQ-Suppression scores (see Results). Third, the mediator must affect the dependent variable, and, fourth, the effect of the independent variable on the dependent variable must be reduced in the presence of the mediator. The amount of change of partial eta-squared (η^2_p), a measure of the effect size, associated with depression when emotion suppression is used as covariate reflects the importance of emotion suppression in explaining the effects of depression on HRV indices. Thus, the greater the change in the effect size for the depression condition factor, when ERQ-Suppression scores are used as a covariate, the greater the importance of emotion suppression in explaining these effects. Separate ANCOVAs, with ERQ-Suppression as the covariate, and depression as a between-subjects factor were conducted to simultaneously test whether the third and the fourth criteria were met.

The η^2_p values considered to represent small, medium, and large effects are .01, .06, and .14, respectively (Cohen, 1977). All statistical analyses were performed using STATISTICA 6.1 (StatSoft Inc., Tulsa, OK, USA). A p value of $< .05$ was considered statistically significant.

3.5 Results

Characteristics of patients with depression and without depression

Fisher's exact test or chi-square analysis revealed no group differences for gender $\chi^2(1) = 0.43$, $p = .51$, beta-blockers $\chi^2(1) = 0.88$, $p = .35$, angiotensin-converting enzyme inhibitors $\chi^2(1) = 0.04$, $p = .84$, anticoagulants $\chi^2(1) = 1.79$, $p = .18$, diabetes ($p = .99$), hypertension $\chi^2(1) = 0.88$, $p = .35$, dyslipidemia $\chi^2(1) = 0.09$, $p = .76$, previous myocardial infarction ($p = .70$), previous percutaneous transluminal coronary angioplasty ($p = .74$), smoking $\chi^2(2) = 1.68$, $p = .43$, and surgical procedures $\chi^2(2) = 5.82$, $p = .06$. A significant group difference for antiarrhythmics $\chi^2(1) = 5.74$, $p < .03$ was noted. Specifically, 36% of patients with depression were administered antiarrhythmics compared to 12% of nondepressed individuals. Similarly, separate ANOVAs yielded no group differences for age ($F(1,66) = 0.36$, $p = .55$, $\eta^2_p = .01$), and HR ($F(1,66) = 0.45$, $p = .50$, $\eta^2_p = .01$).

Depression, emotion regulation, and HRV

As far as emotion regulation strategies are concerned, while ERQ-Reappraisal scores did not differ between groups ($F(1,66) = 0.01$, $p = .93$, $\eta^2_p = .00$), ANOVA yielded significant group differences for ERQ-Suppression scores ($F(1,66) = 5.10$, $p < .04$, $\eta^2_p = .07$). Specifically, ERQ-Suppression scores were significantly greater in patients with depression than those without depression (see Table 3.1).

Separate ANOVAs yielded a significant main effect for Group on each time domain measure, i.e., SDNN ($F(1,66) = 4.54$, $p < .05$, $\eta^2_p = .06$), rMSSD ($F(1,66) = 9.56$, $p < .004$, $\eta^2_p = .13$), and NN50 ($F(1,66) = 4.12$, $p < .05$, $\eta^2_p = .06$). SDNN, rMSSD, and NN50 values were significantly lower in patients with depression than those without depression. Also, ANOVAs yielded a significant main effect for Group on LF n.u. ($F(1,66) = 7.36$, $p < .01$, η^2_p

= .10), and HF n.u. ($F(1,66) = 7.36$, $p < .01$, $\eta^2_p = .10$)[3]. LF n.u. values were significantly greater in patients with depression than those without depression and vice versa for HF n.u., as shown in Figure 1. In contrast, no significant main effects for Group were found on logVLF ($F(1,66) = 0.24$, $p = .62$, $\eta^2_p = .00$), logLF ($F(1,66) = 0.01$, $p = .91$, $\eta^2_p = .00$), and logHF ($F(1,66) = 2.58$, $p = .11$, $\eta^2_p = .04$). All means (SD) of each HRV index are reported in Table 3.2.

Emotion suppression as a mediator of sympathovagal imbalance

The original analyses indicated that 6% of the variance in SDNN, 13% in rMSSD, 6% in NN50, 10% in LF n.u. and 10% HF n.u. could be attributed to depression; these correspond to medium-size (i.e., rMSSD, LF n.u., and HF n.u.) or a small-to-medium (i.e., SDNN, and NN50) effect for depression on HRV indices. The effect of depression survived the covariate adjustment for emotion suppression on SDNN ($F(1,65) = 5.31$, $p < .03$, $\eta^2_p = .08$, $\Delta\eta^2_p = .02$), rMSSD ($F(1,65) = 8.08$, $p < .007$, $\eta^2_p = .11$, $\Delta\eta^2_p = -.02$), and NN50 ($F(1,65) = 4.71$, $p < .04$, $\eta^2_p = .07$, $\Delta\eta^2_p = .01$). In contrast, the covariate adjustment for emotion suppression partially mediated the effect of depression on LF n.u ($F(1,65) = 4.65$, $p < .04$, $\eta^2_p = .07$, $\Delta\eta^2_p = -.03$) and HF n.u. ($F(1,65) = 4.65$, $p < .04$, $\eta^2_p = .07$, $\Delta\eta^2_p = -.03$). This latter mediation was partial as a small-to-medium effect size remained.

[3] All significant effects on each HRV index survived the covariate adjustment for antiarrhythmics (p's $< .05$)

Table 3.2 *HRV in Patients With and Without Depression*

Variable	Depressed (*N* = 25)	Not Depressed (*N* = 43)	*p*	η_p^2
Time domain indices				
SDNN (ms)	20.4 (16.9)	33.8 (28.8)	.04	.06
rMSSD (ms)	14.8 (15.8)	32.9 (26.7)	.003	.13
NN50 count	3.5 (14.3)	23.4 (47.6)	.05	.06
Frequency domain indices				
logVLF (ms^2)	2.0 (0.7)	1.9 (1.0)	.62	.00
logLF (ms^2)	1.7 (0.8)	1.6 (1.0)	.91	.00
logHF (ms^2)	1.5 (0.7)	1.8 (0.9)	.11	.04
LF n.u. (%)	55.3 (20.3)	40.1 (23.3)	.009	.10
HF n.u. (%)	44.7 (20.3)	59.9 (23.3)	.009	.10

Notes: Results are reported as *M* (*SD*). HRV = heart rate variability; SDNN = standard deviation of all NN intervals in ms; rMSSD = the square root of the mean of the sum of the squares of differences between adjacent NN intervals in ms; NN50 = number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; logVLF = logarithm transformation of very-low-frequency power; logLF = logarithm transformation of low-frequency power; logHF = logarithm transformation of high-frequency power; LF n.u. = low frequency power expressed in normalized units [LF/(total power-VLF)*100]; HF n.u. = high frequency power expressed in normalized units [HF/(total power-VLF)*100].

3.6 Discussion

The current study examined the association between depression, emotion regulation strategies and HRV in patients who underwent first time cardiac surgery. The finding showed that, as expected, compared to nondepressed patients, those with postoperative depression were characterized by lower SDNN, rMSSD, and NN50 indices, indicative of reduced HRV and cardiac vagal control. A more pronounced sympathovagal imbalance, as reflected by increased LF n.u. and reduced HF n.u., was also observed in patients with depression as compared to those without depression after cardiac surgery. As far as the relationship between depression and emotion regulation strategies is concerned, we found that depressed patients reported using significantly more emotion suppression but not cognitive reappraisal strategies than nondepressed individuals. More interestingly, mediation analyses revealed that the increased trait levels of emotion suppression were in part responsible for the observed sympathovagal imbalance in patients who underwent cardiac surgery. Specifically, mediation analyses showed that one-third of the LF n.u. and HF n.u. variance explained by depression was accounted for by increased suppression of emotion-expressive behavior. On the contrary, the trait levels of emotion suppression strategy did not mediate the reduction in SDNN and in indices of HRV mediated by the vagal control on the heart, that is, the rMSSD, and NN50, observed in depressed patients as compared to those without depression.

Our main hypothesis that sympathovagal balance would be impaired by depression and that the trait level of suppression to down-regulate emotion-expressive behavior would mediate depression-related sympathovagal imbalance was supported. Our findings add to the literature showing that increased suppression of emotion-expressive behavior is selectively associated with increased sympathetic activation of the cardiovascular and electrodermal systems (Gross, 2002). Specifically, Gross, 1998 reported that, compared to participants in the cognitive reappraisal group, individuals who were instructed to suppress emotions

elicited by a disgust-inducing film showed increased sympathetic activation, as indexed by greater increases in skin conductance as well as greater decreases in finger temperature and in finger pulse amplitude. In a companion study, Gross and Levenson (1997) found that participants in the suppression group had increased sympathetic activation of the cardiovascular system, as reflected by decreases in finger temperature, finger pulse amplitude, and pulse transit times to the finger and ear, than those who were not instructed to suppress emotion elicited by negative and positive emotional films. Similarly, Harris (2001) has reported that, compared to non-suppression group, individuals who were told to suppress emotion elicited by an embarrassing video had pronounced effects on cardiovascular reactivity, that is, an increase of 67% and 38% in systolic and diastolic blood pressure, respectively, which continued even when the video had stopped.

As far as the association between depression and emotion dysregulation is concerned, our findings suggest that maladaptive emotion regulation could be a major symptom of depression (Gross & Muñoz, 1995). Specifically, our study showed that depressed individuals report using more frequently maladaptive emotion regulation strategies (i.e., suppression of emotion-expressive behavior), which have been found to be associated with dysfunctional outcomes (Gross & John, 2003). Our results are also in line with emerging evidence suggesting that emotion dysregulation is not confined to acute episode of depression but may be considered as a stable trait of depression (Ehring et al., 2010). Moreover, consistent with previous studies, no differences between depressed patients and healthy controls regarding cognitive reappraisal were noted (Campbell-Sills, Barlow, Brown, & Hofmann, 2006a; Ehring et al., 2010).

The present findings are in line with a large number of studies that have demonstrated cardiac autonomic dysfunction, as reflected by reduced HRV, in depressed patients with CHD (Carney et al., 1995; Stein et al., 2000) as well as in those after a

myocardial infarction (Carney et al., 2001) or after cardiac surgery (Patron et al., 2012). Our study also suggests that reduced HRV may be considered as a plausible marker for the depression-related increased risk of cardiac morbidity and/or mortality that has been documented in patients who underwent cardiac surgery (Carney et al., 2002; Lespérance & Frasure-Smith, 2000).

Although the relative contribution of the sympathetic and parasympathetic nervous systems to depression as a risk factor for cardiovascular diseases is still debated (Carney et al., 2005, 2002), the current findings suggest that depression is more likely to be associated with reduced cardiac vagal modulation and sympathovagal imbalance rather than excessive sympathetic activity on heart. Indeed, a selective association was found between depression and HRV indices that have been shown to be largely influenced by cardiac vagal control (i.e., rMSSD, and NN50) (Taylor et al., 1998) and by sympathovagal imbalance (i.e., LF n.u. and HF n.u.) (Malliani et al., 1994; Task Force, 1996). VLF and LF power components, by contrast, which are the mirror of both sympathetic *and* vagal influences on cardiac activity (Task Force, 1996), were unrelated to depression.

The current findings should be interpreted in light of a number of possible methodological limitations. First, although HRV, especially HF power, may be confounded and exaggerated by respiration without reflecting the influence of cardiac vagal control on the heart, we did not record respiration rate and respiratory sinus arrhythmia. However, there is consistent and abundant evidence that even uncontrolled HRV recordings have been found to predict adverse outcomes in patients with CHD (Bigger et al., 1993; Kleiger et al., 1987) or after myocardial infarction (Rich et al., 1988) and/or to show reduced HRV in depressed patients with CHD (Carney et al., 1995; Stein et al., 2000) or after myocardial infarction (Carney et al., 2001) compared to nondepressed individuals. Finally, given that it is well-established that HRV is reduced in patients who underwent recent cardiac surgery and then

gradually recovers over several months (Soares et al., 2005), HRV indices may not be stable in patients in the early postoperative periods. Clearly, future research is warranted to include long-term clinical follow-ups in order to examine the time course of depression and that of emotion dysregulation in relation to the alterations in temporal patterns of HRV after cardiac surgery.

The current study, examine the relationship among depression, emotion regulation, and HRV, as an index of cardiac autonomic functioning, in patients who had undergone cardiac surgery. In particular, the present findings add to the recent evidence that depression is associated with reduced HRV postoperatively (Patron et al., 2012) by showing that the increased trait levels of emotion suppression may partially and selectively mediate the effect of depression on sympathovagal imbalance in patients after cardiac surgery.

CHAPTER 4

Heart rate variability during emotional imagery in patients after cardiac surgery

4.1 Abstract

Objective: The main aim of the present study was to examine the influence of depression on heart rate and heart rate variability (HRV) reactivity during an emotional stressor task in patients after cardiac surgery.

Methods: Based on the scores of the Center for Epidemiological Studies of Depression (CES-D) scale, 28 patients after cardiac surgery were assigned either to the group with depression (CES-D scores ≥ 16; $N = 14$) or the one without depression (CES-D scores < 16; $N = 14$). Each patient completed a baseline and an emotional imagery task including pleasant, neutral and unpleasant scripts. Inter-beat intervals (IBIs) and HRV parameters were measured during the entire protocol.

Results: Compared to nondepressed patients, those with depression had greater reductions in HF expressed in normalized units (HF n.u.) during the imaging of the unpleasant script ($p < .01$, Cohen's d = 1.34). Moreover, HF n.u. were reduced during the imaging of unpleasant script than pleasant one in depressed patients only ($p < .03$, Cohen's d = 0.55). CES-D scores were also inversely correlated with changes in IBIs ($r = -.38$; $p < .05$) and HF n.u.($r = -.49$; $p < .01$) from baseline to imaging of unpleasant script.

Conclusions: These findings add to the literature of depression-related exaggerated cardiovascular reactivity by showing that a depression-increased vagal withdrawal relationship extends to patients after cardiac surgery. The present study suggests that

increased vagal withdrawal to unpleasant emotions in patients after cardiac surgery may mediate the conferral of cardiac risk by depression.

Keywords: cardiac surgery; cardiovascular reactivity; depression; heart rate variability; imagery; mood

4.2 Introduction

Depression is an important and independent risk factor for the onset, the adverse course and outcomes in patients with CHD (Carney et al., 2005; Wulsin & Singal, 2003). Specifically, there is evidence that depression is associated with a 60% greater likelihood of having CHD (Wulsin & Singal, 2003). Patients with depression are also more likely to have a major cardiac event within a year of the diagnosis of CHD (Carney et al., 2005) and/or to die in the years following the diagnosis (Barefoot & Schroll, 1996). Moreover, it has been consistently reported that depression is a risk factor for cardiac morbidity and/or mortality in patients who had undergone cardiac surgery (Blumenthal et al., 2003; Lespérance & Frasure-Smith, 2000).

The autonomic nervous system (ANS) has been identified as a pivotal site of dysregulation, with reduced parasympathetic and increased sympathetic nervous system activity leading to arrhythmias and sudden cardiac death (Musselman et al., 1998; Podrid et al., 1990). Given that depression itself is associated with reduced parasympathetic and/or increased sympathetic activity (Kemp et al., 2010), the presence of depression may potentiate the impaired parasympathetic control and increased sympathetic activity observed in patients with CHD. In turn, these depression-related ANS abnormalities, especially a reduced cardiac vagal control, may further predispose depressed patients with CHD to ventricular

tachycardia, ventricular fibrillation, myocardial ischemia, and sudden cardiac death (Carney et al., 2005, 2002).

In line with these findings, it has been reported that low heart rate variability (HRV), which reflects the balance between the sympathetic and parasympathetic nervous system effects on heart (Task Force, 1996), represents an independent risk factor for cardiovascular mortality in patients with recent myocardial infarction (Bigger et al., 1993; Kleiger et al., 1987) or stable CHD (Rich et al., 1988). More interestingly, there is abundant and converging evidence that, compared to nondepressed individuals, depressed patients with CHD have reduced HRV, which is associated with excessive sympathetic modulation and/or inadequate cardiac vagal control (Carney et al., 2001; Carney et al., 2005). In light of these findings, reduced HRV has been implicated as a plausible marker for the depression-related increased risk of cardiac morbidity and/or mortality in patients after myocardial infarction (Carney et al., 2001) or with CHD (Carney et al., 1995; Carney et al., 2005, 2002).

Intriguingly, it has been recently shown that a depression-reduced HRV association extends to patients who underwent cardiac surgery (Patron et al., 2012). In particular, Patron et al. (2012) observed that, compared to patients without depression, those with depression have reduced HRV, especially a lowered cardiac vagal control, at discharge from the hospital, thus suggesting an association between postoperative depression and cardiac vagal dysfunctions after cardiac surgery. Based on this finding, reduced HRV has been also suggested as one possible pathophysiological marker of depression-related ANS dysregulation that has been implicated as a risk factor for cardiac morbidity and/or mortality in patients after cardiac surgery (Blumenthal et al., 2003; Lespérance & Frasure-Smith, 2000).

In addition to the depression-ANS dysregulation relationship at rest, two studies have shown depression-related abnormalities in vagal reactivity during speech and cold pressor

tasks, indicating a reduced ability to regulate cardiac activity to meet the task demands (Appelhans & Luecken, 2006; Hughes & Stoney, 2000; Sheffield et al., 1998). Specifically, Sheffield et al. (1999) found that, compared to individuals without depression, depressed patients with CHD showed greater decreases in vagal activity, as reflected by reduced high frequency (HF) power of HRV, during speech task – a stressor that generally elicits reduction in HF power (Berntson et al., 1994). Hughes and Stoney (2000) extended this previous evidence by showing that depressed mood in healthy individuals elicited increased vagal withdrawal during speech task compared to individuals without depressed mood. In line with this finding, the same authors reported that depressed mood was associated with reduced increases in HF power during the forehead cold pressor task – a stressor that generally elicits increase in HF power (Durel et al., 1993; Khurana, Watabiki, Hebel, Toro, & Nelson, 1980). Consistent with these studies, a recent meta-analysis reported that depression is associated with increased heart rate reactivity, especially in those patients with cardiovascular diseases (Kibler & Ma, 2004). In particular, Kibler and Ma (2004) suggested that the depression-related autonomic imbalance may predispose depressed patients with cardiovascular diseases to exaggerated physiological stress reactions and therefore increase cardiac risk in these individuals. In other words, the autonomic dysregulation typically found in depressed patients with cardiovascular diseases is likely to be associated with exaggerated cardiac (i.e., heart rate and/or HRV) reactivity, which, in turn, increases the risk of cardiac morbidity and/or mortality.

However, it should be noted that the effect sizes of the relationship between depression and exaggerated cardiovascular reactivity in patients were only small to moderate (Kibler & Ma, 2004). This may be due to the fact that the vast majority of studies examining whether and how vagal reactivity could be modulated by depression used non-emotional tasks (e.g., mental arithmetic, cold pressor or Stroop tasks) (for a review, see Kibler & Ma,

2004). Conversely, the number of studies that investigated the influence of depression on vagal reactivity during *emotional* stressors is much more limited. This is particularly surprising given that it is well-established that depression is characterized by a bias toward negative affect or emotion, namely the *mood-congruent bias* (Eizenman et al., 2003; Erickson et al., 2005; Mogg & Bradley, 1998; Murphy et al., 1999), which, in turn, has been found to potentiate emotional and physiological reactivity to negative stimuli or context (Golin, Hartman, Klatt, Munz, & Wolfgang, 1977; Lewinsohn, Lobitz, & Wilson, 1973). In addition, despite the growing knowledge on the depression-related ANS dysregulation underlying exaggerated cardiovascular reactivity in patients with CHD, the influence of depression on vagal reactivity during stressors in patients who underwent cardiac surgery has yet to be investigated.

Based on these considerations, the present study was designed to examine whether postoperative depression would be associated with increased vagal withdrawal during an emotional imagery task in patients after cardiac surgery. It was hypothesized that, compared to patients without depression after surgery, those with postoperative depression would show greater vagal withdrawal, as reflected by lower HF power of HRV, during the imaging of unpleasant script rather than neutral and pleasant ones.

4.3. Methods

Participants

After receiving the local ethics committee's approval, 28 patients who had undergone first-time cardiac surgery were enrolled in this study after their written informed consent was obtained. Based on the presence of clinically significant depression [i.e., scoring greater than

16 on the Center for Epidemiologic Studies of Depression (CES-D) scale] (Fava, 1982; Radloff, 1977), the patients were classified into one of two groups: with depression (N = 14) or without depression (N = 14). All patients had undergone cardiac surgery at a regional specialized hospital and were admitted for rehabilitation in a highly specialized hospital between July 2012 and December 2012. Patients underwent heart valve surgery (N = 12), coronary artery bypass graft surgery (CABG) (N = 12), and combined surgery (heart valve plus CABG surgery) (N = 4). Each patient had the same protocol of cardioplegia and a mild hypothermic cardiopulmonary bypass. Ages greater than 75, use of psychotropic drugs, other life-threatening medical illness, and prior cerebrovascular and/or neurological diseases were the exclusion criteria. Patients were treated in the hospital with beta-blockers, angiotensin-converting enzyme inhibitors, antiarrhythmics, and/or anticoagulants. The descriptive statistics for each group are reported in Table 4.1.

Imagery task

Three narratives, selected from the Affective Norms of English Text (ANET) (34) based on standardized ratings of pleasure and arousal, were categorized as pleasant (narrative n. 8500: Pleasure, M = 8.5 SD = 1.5; Arousal, M = 8.2, SD = 1.7), neutral (narrative n. 2610: Pleasure, M = 5.4, SD = 1.3; Arousal, M = 3.1, SD = 1.7) or unpleasant (narrative n. 6020: Pleasure, M = 1.9, SD = 1.2; Arousal, M = 8.2, SD = 1.5). All patients were instructed to listen to the scripts read by the experimenter and upon offset vividly imagine the events described. The experimenter read the scripts slowly (for a total duration of 30-second each), in order for the patients to fully understand each script. Each imagery trial consisted of a 2 minutes of imagery followed by 2 minutes of rest. The order of the presentation of the three narratives was counterbalanced across participants. Afterwards, pleasantness and arousal of the current affective were rated using the Self-Assessment Manikin (Bradley & Lang, 2007).

Table 4.1. *Demographic and biomedical characteristics by depression status*

Variable	Group with depression (*N* = 14)	Group without depression (*N* = 14)	*p*
Age (years)	56.6 (8.4)	57.0 (8.4)	.89
Male Sex (*N*, %)	11 (79)	13 (93)	.60
Diabetes (*N*, %)	1 (7)	2 (14)	.99
Beta-blockers (*N*, %)	11 (79)	12 (86)	.99
ACE inhibitors (*N*, %)	7 (50)	5 (36)	.70
Antiarrhythmics (*N*, %)	4 (29)	2 (14)	.65
Anticoagulants (*N*, %)	13 (93)	14 (100)	.99
Hypertension (*N*, %)	8 (57)	5 (36)	.45
Myocardial infarction (*N*, %)	0 (0)	2 (14)	.48
Dyslipidemia (*N*, %)	7 (50)	5 (36)	.70
Smoking			.14
Actual (*N*, %)	2 (14)	0 (0)	
Past (*N*, %)	9 (64)	7 (50)	
No (*N*, %)	3 (22)	7 (50)	

Notes: Data are *M* (*SD*) of continuous and *N* (%) of categorical variables. ACE = angiotensinconverting enzyme.

Physiological recordings

HRV was recorded in a standardized fashion using a computerized recording system (ProComp Infiniti, Thought Technology; Montreal, Canada). ECG signal was obtained from three disposable Ag⁄AgCl electrodes that were positioned on the patient's chest in a modified lead II configuration. Each ECG signal was amplified, band-pass filtered (1–100 Hz), and sampled at 256 Hz. A digital trigger detecting R-waves was applied to ECG signal to obtain inter-beat intervals (IBIs). All ECG data were visually inspected and artifacts were corrected with a piecewise cubic spline interpolation method that generates missing or corrupted values into the normal-to-normal (NN) intervals (or inter-beat intervals). Fast Fourier spectral analysis was then applied on the NN series to compute frequency domain indices, which, in turn, were calculated by Kubios HRV Analysis Software 2.0 (Matlab, Kuopio, Finland) as follows:

1) Low frequency (LF) power (0.04 to 0.15 Hz) in ms^2.

2) High frequency (HF) power (0.15 to 0.40 Hz) in ms^2.

All frequency domain indices were logarithmically transformed to normalize their distribution. In addition, LF and HF components were expressed in normalized units (n.u.) (Task Force, 1996). Given that LF and HF n.u. are algebraically redundant we reported only the HF n.u. in the Results section.

Procedure

All patients completed the experimental protocol after their admission for rehabilitation, approximately two weeks (range 10-14 days) after cardiac surgery. Upon arrival for the session, the patients completed the Questionnaire upon Mental Imagery (QMI) (Sheehan, 1967), a 35-item self-report questionnaire that measures individual differences in imagery skills. QMI requires participants to indicate on 7-point scales how lively and vividly

they can imagine each item; scores range from 35 to 245, with lower scores reflecting better imagery ability. Then, after skin preparation, surface electrodes were placed over the right subclavicular space and a left intercostal space for measurement of ECG. After the electrodes were attached, patients rested for 5-min and then completed the imagery task. ECG was recorded during both the 5-min resting period (i.e., baseline) and the imagery task.

In order to avoid movement artifacts, each patient was instructed to stay still and not to talk during the ECG recordings. All ECG recordings were taken with the patients seated on a semireclined armchair after adaptation to the laboratory. Each physiological measurement was taken in a quiet and isolated laboratory during morning hours (from 10:00 to 12:00), in order to avoid possible confounder effect of circadian variations on cardiac activity. The light was dimmed to provide a relaxing atmosphere and the temperature in the room was approximately 21°C. After imagery task was completed, the sensors were removed and patients were debriefed and thanked for their participation.

Statistical analysis

As our first step, analysis of variance (ANOVA), with Group (with depression, without depression) as the between-subjects factor, was used to compare the age of the two groups. Chi-square or Fisher's exact test analysis was conducted to compare the two groups in terms of gender, smoking, biomedical risk factors (e.g., the presence of hypertension, diabetes, dyslipidemia, previous myocardial infarction), and cardiac drugs (i.e., beta-blockers, angiotensin-converting enzyme inhibitors, antiarrhythmics, and anticoagulants).

As our second step, mixed ANOVAs, with Group (with depression, without depression) as the between-subjects factor, and emotional Condition (Pleasant, Neutral, Unpleasant scripts) as a within-subjects factor, were conducted on self-reported evaluations of pleasantness and arousal.

As our third step, mixed analyses of covariance (ANCOVAs) with Group (with depression, without depression) as the between-subjects factor, emotional Condition (Baseline without script, Pleasant, Neutral, Unpleasant scripts) as a within-subjects factor, and QMI scores as covariate were conducted on HRV parameters (IBIs, ln LF, lnHF, and HF n.u.) collected during the imagery task. QMI score was entered as covariate given that depressed patients had higher QMI scores (i.e., worse imagery ability; M = 93.1; SD = 34.2) than those without depression (M = 72.9; SD = 42.6). Indeed, although we did not find an effect of group, when we considered the effect size of the mean difference between groups in QMI scores, we found a medium effect size (Cohen's d = 0.52). The significance of main effects and interactions was adjusted where appropriate using the Greenhouse–Geisser method to correct for violations of sphericity. In the results, the corrected p levels and epsilon (ε) are reported together with the uncorrected degrees of freedom. The Fisher's LSD test was used for post hoc analyses. Cohen's d was calculated as a measure of the effect size. The Cohen's d values considered to represent small, medium, and large effects are 0.20, 0.50, and 0.80 (Cohen, 1988).

Pearson's correlation coefficients were calculated between CES-D scores and residualized changes for IBIs and HRV parameters from baseline to pleasant, neutral and unpleasant imagery conditions. Residualized change scores were calculated by regressing IBIs and HRV parameters during baseline on their values during the imaging of pleasant, neutral and unpleasant scripts and calculating the residual of the resultant regression (40-43). Therefore, residualized change is an index of change that takes into account the patient's IBIs and HRV parameters during baseline. A p value of $< .05$ was considered to be statistically significant.

4.4 Results

Characteristics of patients with depression and without depression

Fisher's exact test or chi-square analysis revealed no group differences for gender (p = .60), smoking ($\chi^2[2] = 3.85$, p = .14), beta-blockers (p = .99), angiotensin-converting enzyme inhibitors ($\chi^2[1] = 0.58$, p = .70), antiarrhythmics (p = .65), and anticoagulants (p = .99), hypertension ($\chi^2[1] = 1.29$, p = .45), diabetes (p = .99), dyslipidemia ($\chi^2[1] = 0.58$, p = .70), and previous myocardial infarction (p = .48). Similarly, ANOVA yielded no group differences for age ($F[1, 26] = 0.02$, p = .89 , η^2_p = .00).

Emotional self-reports

Mixed ANOVAs on self-reported pleasantness of each script yielded a significant effect for Condition ($F[2, 52] = 36.9$, $p < .001$, ε = .92, η^2_p = .59). Greater scores (pleasantness) were found for pleasant and neutral scripts compared to unpleasant one (pleasant vs. unpleasant: $p < .001$, Cohen's d = 2.46; neutral vs. unpleasant: $p < .001$, Cohen's d = 1.88; pleasant vs. neutral: p = .33, Cohen's d = 0.27). Specifically, the mean (*SD*) pleasantness ratings for pleasant, neutral and unpleasant scripts were respectively 7.1 (2.3), 5.8 (2.7), 3.1 (2.4) in group with depression and 7.8 (1.5), 7.9 (1.8), 2.1 (1.3) in group without depression. No significant effect for Group ($F[1, 26] = 3.28$, p = .08, η^2_p = .11) or Group × Condition interaction ($F[2, 52] = 3.02$, p = .06, ε = .92, η^2_p = .10) was noted.

Similarly, in the case of arousal, a significant Condition main effect ($F[2, 52] = 15.46$, $p < .001$, ε = .84, η^2_p = .37) was noted. Greater scores were observed for pleasant and unpleasant scripts compared to neutral one (pleasant vs. unpleasant: p = .10, Cohen's d = 0.36; neutral vs. unpleasant: $p < .001$, Cohen's d = 1.24; pleasant vs. neutral: $p < .001$, Cohen's d = 0.91). Specifically, the mean (*SD*) arousal ratings for pleasant, neutral and

unpleasant scripts were respectively 5.6 (2.5), 3.0 (2.5), 6.1 (3.0) in group with depression and 4.4 (2.8), 2.4 (2.3), 5.9 (2.9) in group without depression. No significant effect for Group (F[1, 26] = 0.82, p = .37, η^2_p = .03) or Group × Condition interaction (F[2, 52] = 0.45, p = .60, ε = .84, η^2_p = .02) was noted.

Effects of depression on HRV parameters during the emotional imagery task

The Group × Condition ANCOVA on IBIs did not show a significant effect for Group (F[1, 25] = 0.40, p = .53 , η^2_p = .02), Condition (F[3, 75] = 0.46, p = .63, ε = .65, η^2_p = .02) or Group × Condition interaction (F[3, 75] = 1.27, p = .29, ε = .65, η^2_p = .05). In the case of HRV parameters, the Group × Condition ANCOVA on HF n.u. yielded a significant main effect for Group (F[1, 25] = 4.67, p < .05, η^2_p = .16), and a Group × Condition interaction effect (F[3, 75] = 3.49, p < .04, ε = .85, η^2_p = .12). Fisher's LSD post hoc test revealed that, compared to patients without depression, those with depression had significantly lower HF n.u. during unpleasant script (p < .01, Cohen's d = 1.34), but not during baseline (p = .12, Cohen's d = 0.56), pleasant (p = .59, Cohen's d = 0.20) and neutral (p = .08, Cohen's d = 0.67) scripts. Moreover, in patients with depression, a significantly lower HF n.u. for unpleasant script compared to pleasant one (p < .03, Cohen's d = 0.55), but not for other contrasts (ps > .21, Cohen's ds < .28), was noted. In patients without depression, no difference among conditions was found (ps > .09, Cohen's ds < 0.45). The main effect for Condition (F[3, 75] = 2.04, p = .13, ε = .85, η^2_p = .08) was not significant. Similarly, the Group × Condition ANCOVA on lnHF yielded a marginally significant Group × Condition interaction effect (F[3, 75] = 2.52, p = .08, ε = .82, η^2_p = .09), showing the same trend observed for HF component expressed in n.u. No significant main effect for Group (F[1, 25] = 1.78, p = .19 , η^2_p = .07) or Condition (F[3, 75] = 1.47, p = .24, ε = .82, η^2_p = .06) was

noted. Finally, the Group × Condition ANCOVA on lnLF did not show significant effect for Group (F[1, 25] = 0.00, p = .99 , η^2_p = .00), Condition (F[3, 75] = 1.59, p = .20, ε = .87, η^2_p = .06), or Group × Condition interaction (F[3, 75] = 0.72, p = .52, ε = .87, η^2_p = .03). The results of IBIs and HRV analyses are shown in Figure 4.1.

Correlation analyses revealed significant associations between CES-D scores and residualized changes in IBIs (r = -.38; p < .05) and HF n.u. (r = -.49; p < .01) from baseline to imaging of unpleasant scripts, as shown in Figure 4.2.[4] Specifically, greater CES-D scores were associated with greater reductions in IBIs (i.e., greater heart rate reactivity) and HF n.u. (i.e., greater vagal withdrawal) during the imaging of unpleasant script. By contrast, CES-D scores were unrelated to residualized changes in IBIs and HF n.u. from baseline to imaging of neutral and pleasant scripts (ps > .08). No significant correlations between CES-D scores and changes in lnLF and lnHF were noted (ps > .14).

[4] All significant correlation survived the adjustment for QMI score (p < .05). Moreover, the significant correlation between CES-D scores and residualized changes in HF n.u. from baseline to imaging of unpleasant script survived after the exclusion of two outliers (r = -.75, p < .001)

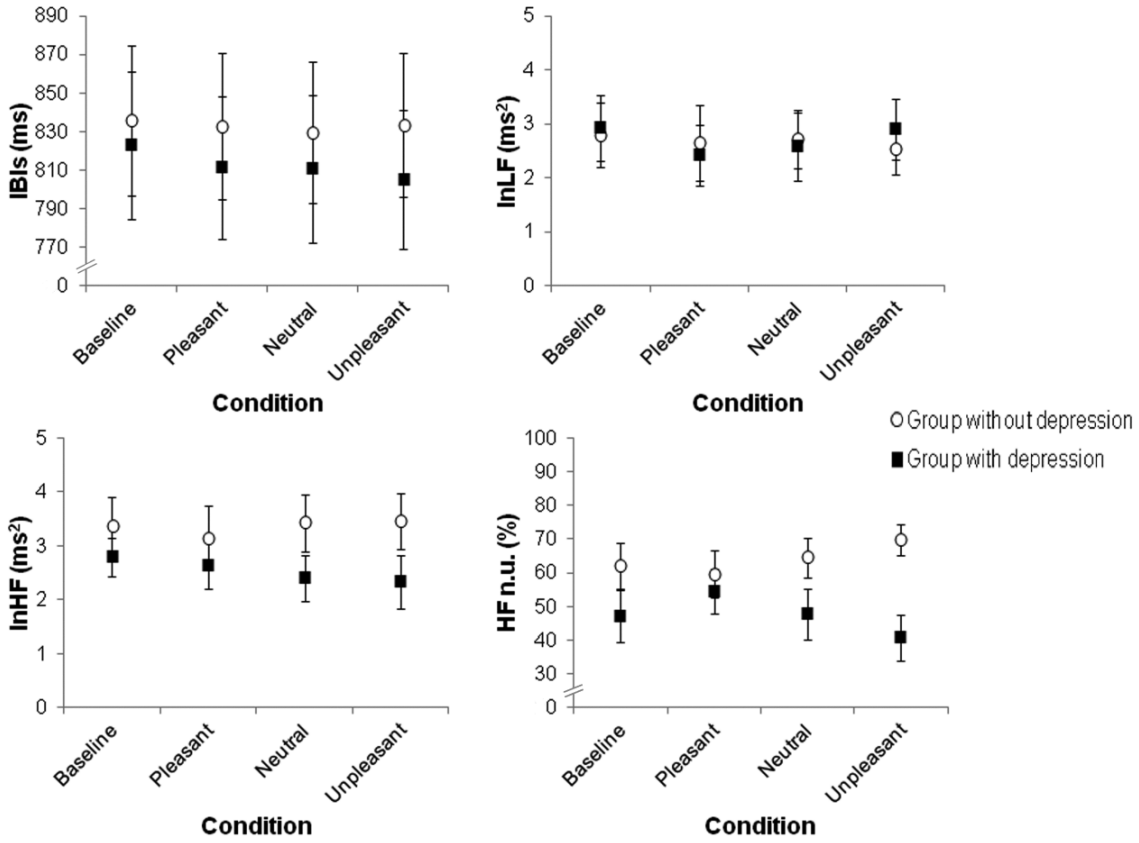


Figure 4.1. Mean (*SE*) IBIs, lnLF, lnHF, and HF n.u. reactivity as a function of emotional Condition (Baseline without script, Pleasant, Neutral and Unpleasant scripts) in the group with depression and without depression. Mixed ANCOVAs revealed a significant Group × Condition interaction effect ($p < .04$). Fisher's LSD post hoc test revealed that patients with depression had significantly lower HF n.u. during unpleasant script compared to patients without depression ($p < .01$, Cohen's d = 1.34). A significantly lower HF n.u. for unpleasant script compared to pleasant one ($p < .03$, Cohen's d = 0.55) in patients with depression was also noted. IBIs = inter-beat intervals in ms; lnLF = log of low frequency power (0.04 to 0.15 Hz) in ms^2; lnHF = log of high frequency power (0.15 to 0.40 Hz) in ms^2; HF n.u. = high frequency expressed in normalized units [HF/(total power-VLF)*100].

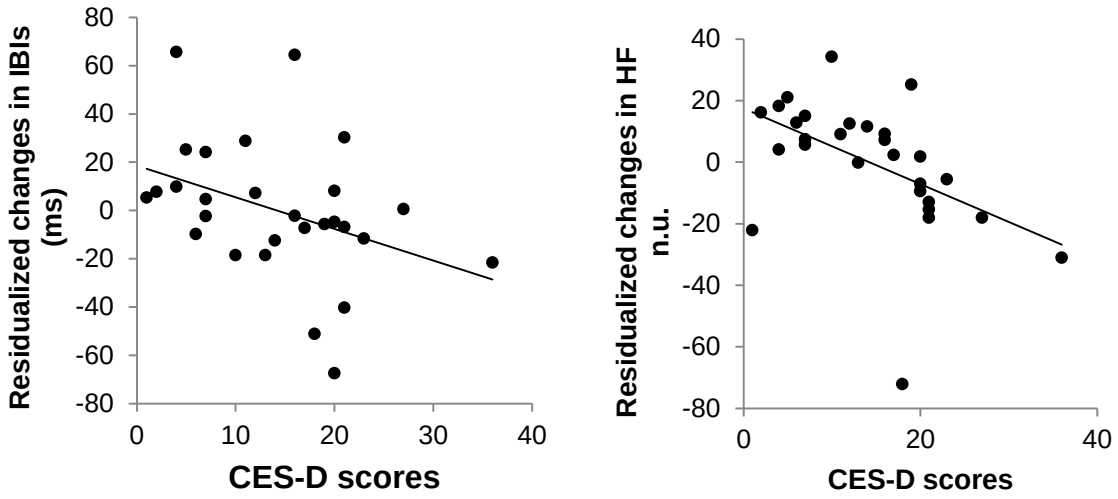


Figure 4.2. Correlation analyses between scores in the Center for Epidemiological Studies of Depression (CES-D) scale and residualized changes in inter-beat intervals (IBIs) (r = -.38; p < .05) and high frequency components expressed in normalized units (HF n.u.) (r = -.49; p < .01) from baseline to imaging of unpleasant script.

4.5 Discussion

The present study investigated the influence of depression on IBIs and HRV reactivity during an emotional imagery task in patients after cardiac surgery. We found that postoperative depression was directly associated with increased vagal withdrawal during the emotional imagery task. Specifically, our findings showed that patients with postoperative depression had significantly lower HF n.u., reflecting greater vagal withdrawal, during the imaging of unpleasant script compared to nondepressed patients after surgery. Consistent with this finding, CES-D scores were inversely associated with residualized changes in HF n.u. from baseline to unpleasant script, but not pleasant or neutral one. Moreover, unpleasant script elicited greater vagal withdrawal (i.e., reduced HF n.u.) in patients with depression

compared to neutral and pleasant scripts, whereas no difference among emotions in nondepressed patients was noted. Although not significantly, results obtained for lnHF resemble the same pattern of vagal reactivity found for HF n.u during emotional imagery task as a function of depression. By contrast, depression was unrelated to IBIs and lnLF reactivity during the imagery task. However, correlation analysis revealed that CES-D scores were significantly associated with greater reductions in IBIs (i.e., greater heart rate reactivity) from baseline to imaging of unpleasant script.

These novel findings add to the literature of depression-related exaggerated cardiovascular reactivity by showing that a depression-increased vagal withdrawal relationship extends to patients after cardiac surgery. In particular, these preliminary findings complement studies that have documented increased vagal withdrawal during non-emotional stressors (e.g., forehead cold pressor or mental arithmetic task) in healthy individuals with depressed mood (Hughes & Stoney, 2000) as well as in patients with cardiovascular diseases (Kibler & Ma, 2004). Most importantly, the present study suggests that increased vagal withdrawal to unpleasant emotions in patients who underwent cardiac surgery may mediate the conferral of cardiac risk by depression (Blumenthal et al., 2003; Lespérance & Frasure-Smith, 2000).

The main finding – the depression-related increased vagal withdrawal for unpleasant script – is in line with previous reports showing that depression is characterized by a mood-congruent bias toward negative valenced affects or stimuli (Eizenman et al., 2003; Erickson et al., 2005; Murphy et al., 1999). In turn, the mood-congruent bias toward negative information supports the maladaptive patterns of information that trigger and sustain depressed mood (Dalgleish & Watts, 1990; Mathews & MacLeod, 1994; Mogg & Bradley, 1998). Consistent with this finding, it has been proposed the negative potentiation view, which postulates that emotional and physiological reactivity to negative emotional stimuli is

potentiated by the pervasive negative mood states that are frequent in patients with depression (Golin et al., 1977; Lewinsohn et al., 1973).

Our results are at odds with a recent study in which depression was associated with blunted cardiovascular reactivity in patients with CHD (York et al., 2007). It should be noted, however, that the discrepancy between our findings and those of York and coworkers (2007) may be accounted for by methodological issues. Specifically, given that York and coworkers (2007) analyzed the correlation between depression and the change in cardiovascular parameters (i.e., heart rate, systolic and diastolic blood pressure) from the baseline (i.e., pre-stress) to recovery period (i.e., post-stress), they actually examined cardiovascular *recovery after* a stressor, but not cardiovascular *reactivity to* a stressor. Conversely, given that we were interested in examining the influence of depression on cardiovagal reactivity to emotional stimuli, reactivity of heart rate and HRV parameters was analyzed *during* different emotional conditions – resting baseline, pleasant, neutral and unpleasant scripts.

The relative contribution of the sympathetic and parasympathetic nervous systems to depression-related exaggerated cardiac reactivity as a risk factor for cardiovascular diseases is still debated (Carney et al., 2005). Nonetheless, the current findings suggest that depression is more likely to be associated with reduced cardiac vagal modulation rather than excessive sympathetic activity on heart. Indeed, a selective association was found between depression and HRV parameters that have been shown to be largely influenced by cardiac vagal control (i.e., lnHF and HF n.u.) (Berntson et al., 1997; Taylor et al., 1998). By contrast, reactivity of LF components, which are the mirror of both sympathetic *and* vagal influences on cardiac activity (Task Force, 1996), was unrelated to depression after cardiac surgery. A possible explanation for this finding is that cardiac sympathetic reactivity was at least partially blocked by beta-blockers, which also may explain null finding concerning IBIs

reactivity during the imagery task. However, it is important to note that CES-D scores were selectively associated with greater reductions in IBIs from baseline to imaging of unpleasant script, thus suggesting that depression does increase heart rate reactivity in negative context.

As far as baseline values are concerned, no significant group differences in cardiac vagal regulation (i.e., lnHF power and HF n.u.) between patients with depression and those without depression after surgery were noted. This finding is at odds with previous evidence that depression is associated with reduced HRV in patients with CHD as well as in those individuals who underwent cardiac surgery (Carney et al., 2001; Carney & Freedland, 2003; Patron et al., 2012). However, it should be noted that baseline lnHF power and HF n.u. were lower, although not significantly, in patients with depression than those without depression in the postoperative period. Given that the effect sizes between groups on resting vagally-mediated parameters were medium (lnHF: Cohen's d = 0.35; HF n.u.: Cohen's d = 0.56), the low statistical power due to a relatively small sample size may help to explain this null result.

The current findings should be interpreted in light of a number of possible methodological issues. First, this study used a relatively small sample size; therefore, the present results need to be replicated to fully understand the relationship between postoperative depression and cardiac reactivity during (emotional) stressors in patients after cardiac surgery. However, the effect sizes for HF n.u. were medium to large, with the largest effect sizes tending to occur between groups during the imaging of unpleasant script (Cohen's d = 1.34) as well as between pleasant and unpleasant scripts within individuals with depression (Cohen's d = 0.55). Second, the current study did not take into account respiration rate, even though the HRV may be confounded and exaggerated by respiration without reflecting the influence of vagal control on the HR (Grossman & Taylor, 2007). However, there is large evidence that even uncontrolled HRV recordings can be an independent predictor of adverse outcome in medically ill populations, especially in patients with

cardiovascular diseases (Bigger et al., 1993; Kleiger et al., 1987; Rich et al., 1988). Moreover, given that imagery task did not require patients to speak or read, it is likely that its influence on respiratory rate was minimal. Finally, depression was evaluated by means of CES-D questionnaire but not clinically evaluated in the patients enrolled in the study. Although CES-D has shown good psychometric properties, it has been validated in a large community population and cover the most symptomatic elements of depression such as sleep disturbance, poor appetite or fatigue, it cannot replace a psychiatric evaluation using structured criteria defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association, 2013). Clearly, future research is warranted to replicate and extend these findings by selectively studying patients with diagnosis of major depressive disorder.

In conclusion, the present study examine whether and how cardiac reactivity to emotional stimuli is modulated by depression in patients after cardiac surgery. Depression was associated with greater vagal withdrawal during the imaging of unpleasant emotion. This finding therefore suggests that depression-related vagal withdrawal during emotional stressors may be implicated as one plausible pathophysiological mechanism linking depression and cardiac risk in patients who underwent cardiac surgery.

CHAPTER 5

Depression treatments in patients with cardiovascular diseases[5]

5.1 Introduction to respiratory sinus arrhythmia biofeedback

Bio-behavioral techniques include a wide variety of relaxation training such as mindfulness, autogenic training, hypnosis, progressive muscle relaxation and biofeedback.

While in general, relaxation training has been reported to be effective in reducing stress and depressive symptoms, no consistent findings have been reported on relaxation training leading to reduced cardiac risk. Particularly, biofeedback Only biofeedback trainings, and specifically HRV biofeedback, has been reported to be effective in reducing cardiac risk.

Biofeedback train an individual to modify his bodily physiological activity in order to improve either health and/or performance (Gilbert & Moss, 2003; Schwartz & Andrasik, 2003; Shaffer, 2006). Therefore, the person should increase personal awareness of physiological processes and gain voluntary control over body and mind. In order to achieve these goals, biofeedback instruments are used to feed-back information about bodily physiological activity. Biofeedback instruments can be used to measure a wide range of physiological signals, such as, brain electrical activity (neurofeedback), muscle activity (EMG biofeedback), skin temperature (thermal feedback), electrodermal activity (SCL biofeedback), blood pressure, blood flow, respiration, heart rate, and heart rate variability.

[5] Results from this study have been partially published in: Patron, E., Messerotti Benvenuti, S., Favretto, G., Valfrè, C., Bonfà, C., Gasparotto, R., & Palomba, D (2013). Biofeedback Assisted Control of Respiratory Sinus Arrhythmia as a Biobehavioral Intervention for Depressive Symptoms in Patients after Cardiac Surgery: A Preliminary Study. Applied Psychophysiology and Biofeedback, 38, 1-9.

Biofeedback therapy has particularly developed over the last 30 years, and large research prospective studies consistently report positive results on the effectiveness of biofeedback for a variety of disorders, such as headache (migraine, mixed, and tension) (Bild & Adams, 1980; Budzynski, Stoyva, Adler, & Mullaney, 1973), essential hypertension (Nakao, Yano, Nomura, & Kuboki, 2003; Yucha et al., 2001), and urinary incontinence (Floratos et al., 2002; Theofrastous et al., 2002). In addition, many research findings reported that a biofeedback treatment, alone and in combination with other therapies, is effective for treating many medical and psychological disorders, including hypertension (Nakao et al., 2003; Yucha et al., 2001), but also, attentional disorders (Linden, Habib, & Radojevic, 1996; Monastra, 2005) and depression (Karavidas et al., 2007). Moreover, several biofeedback protocol are available, which address different disorders, including anxiety, depression, and chronic pain (Bassman & Uellendahl, 2003; Burke, 2003; Freeman, 2001; Kessler et al., 2001).

Biofeedback treatment basis relies on the bidirectional mind-body interaction, so that modifications in the mind and emotions affect the body, and, in turn, variation in the body activity also influences the mind and emotions. Especially, biofeedback requires training of the individuals, in order to achieve awareness, self-regulate, increase control over the body and brain, and increase flexibility in physiologic responding.

Recently, there has been growing interest in the application of bio-behavioral treatment, such as biofeedback, for both depression symptoms and cardiac diseases. Durmus and colleagues (2005) found that biofeedback was associated not only with improvements in pain and physical function scores, but they also demonstrated a significant reduction in depression and anxiety symptoms, in 50 women with a diagnosis of knee osteoarthritis. More recently, in a study by Karavidas and coworkers (2007) a small group of 11 participants with major depressive disorder received a 10 weeks treatments using HRV biofeedback. The

findings reported that, after four session, there were significant improvements in depression. Furthermore, improvements in depression symptoms persisted for the duration of the study.

Regarding depressed patients with cardiovascular diseases, in the last two decades, some studies have reported that biobehavioral interventions such as biofeedback can be effective in reducing cardiovascular risk by enhancing vagal regulation in patients with coronary heart disease (for a review, see Wheat & Larkin, 2010). One of the first study, by Cowan and colleagues (1990), tested the effectiveness of biofeedback in survivors of out-of-hospital ventricular fibrillation or asystole. Patients in the active group received psychosocial therapy, consisting of biofeedback focused on altering autonomic tone, cognitive behavioral therapy, and cardiovascular health education. The authors found that patients in the biofeedback group showed a reduced risk of cardiovascular death, and diminished all-cause mortality. Specifically, the authors reported that, in six patients, psychosocial treatment (including biofeedback) increased HRV and led to a better balance between sympathetic and parasympathetic activities (Cowan et al., 1990). Similarly, Del Pozo and coworkers (2004) studied the effect of a 6 weeks HRV biofeedback training on patients with coronary heart disease. Specifically, 61 patients were randomized to receive either 45 min of HRV biofeedback treatment or control condition. HRV biofeedback treatment consists of breath training with an emphasis on abdominal breathing. In addition, participants were requested to exercise at home for at least 20 min per day. The findings reported that CHD patients in the active condition showed increases in HRV, as measured by SDNN and rMSSD, at the end of the training. More importantly the results were maintained 18 week after the training ended. In addition, Nolan and coworkers (2005) carried out a smaller study on 46 patients with coronary heart disease, who were randomized to receive either 5 session of the active or the control condition treatment. The active condition includes training in cognitive behavioral skills and HRV biofeedback training, while the control condition consists in training in

cognitive behavioral skills and autogenic relaxation. The HRV biofeedback was designed to increase respiratory sinus arrhythmia and counter vagal inhibition immediately after stress. The findings showed that 5 sessions of biofeedback and brief behavioral-cognitive training yield enhanced vagal HR regulation during recovery from stress compared to autogenic relaxation and brief behavioral-cognitive training. In addition, patients receiving HRV biofeedback manifested reduced symptoms of emotional stress and depression. Patients in the control condition showed lower symptoms of emotional stress and depression, but these modifications were not associated to vagal cardiac control modifications.

Therefore, cardiorespiratory biofeedback, including HRV biofeedback, may be effective and reliable training for cardiac patients with comorbid depressive symptoms, since it seems to be effective in increasing vagal regulation, thus reducing cardiac risk in these patients, and reduce depressive symptoms, further lowering risk factors linked to depression.

Mechanism by which RSA biofeedback increases vagal tone

RSA-biofeedback (or HRV biofeedback) is a cardiorespiratory training, which stimulate differential systems involved in cardioregulatory aspect, such as respiratory sinus arrhythmia and baroreflex (BR) activity. In addition, the cardiovascular system, which is stimulated during the training, have resonance characteristics (deBoer, Karemaker, & Strackee, 1987; Vaschillo, Lehrer, Rishe, & Konstantinov, 2002). Specifically, three cardioregulatory phenomenon such as, HR modification, respiration and blood pressure oscillation are associated by one resonant frequency, that is about 0.1 Hz. In fact, Vaschillo and colleagues (2002) found that at this particular resonant frequency (0.1 Hz) the phase relationship between HR modification and blood pressure oscillations is exactly 180°, and the phase relationship between HR oscillations and respiration is exactly 0°(Vaschillo et al., 2002). What happens, exactly, is that when a person inhale there is an increase in HR

(respiration driven—RSA) and decrease in blood pressure. At the same time, the decrease in blood pressure stimulates the baroreceptors, resulting in a further increase in HR, and maximizing the respiratory induced increases in HR. Successively, during exhalation HR decreases (vagus nerve stimulation) and blood pressure increase (see Figure 5.1).

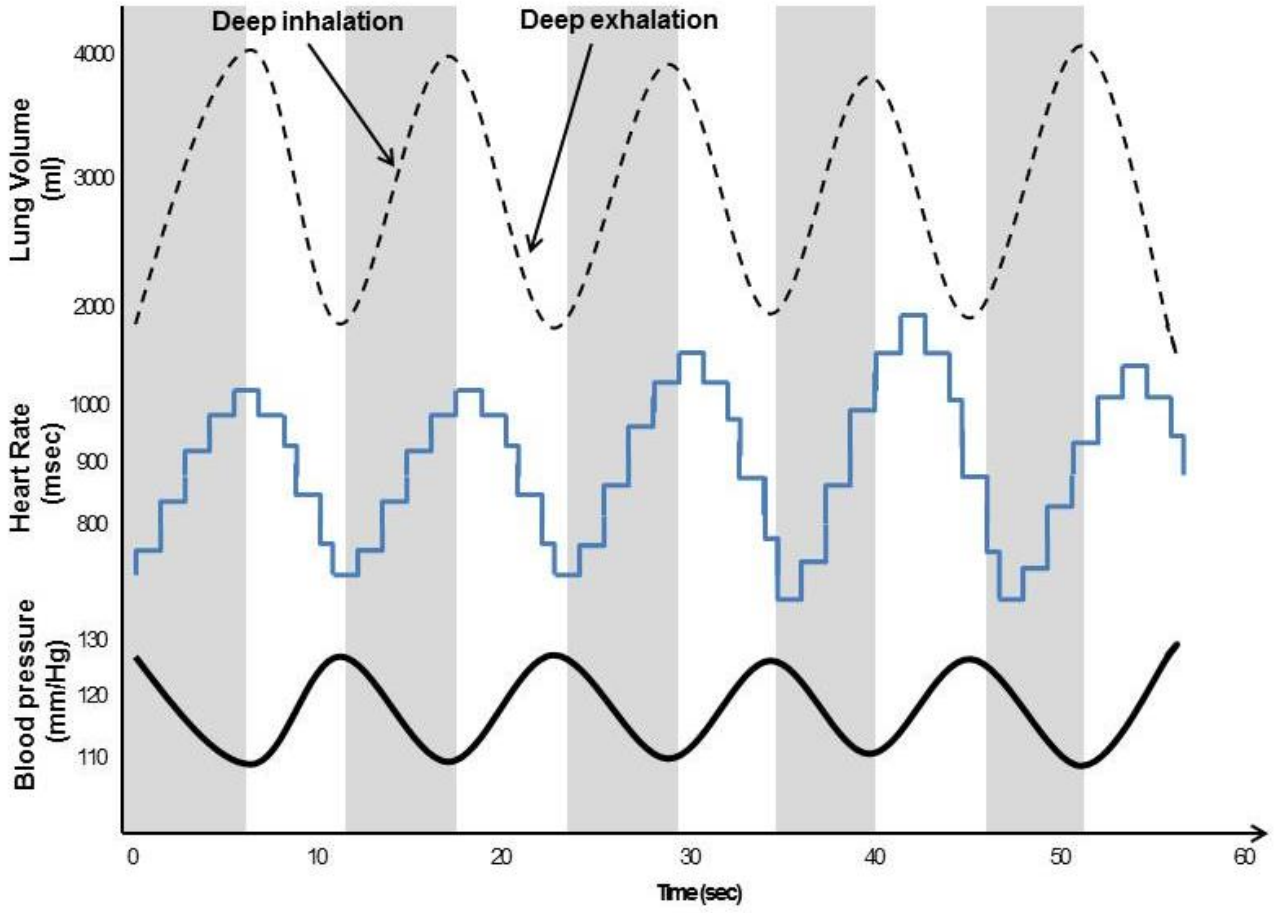


Figure 5.1 Diagrammatic representation of respiration, HR and blood pressure pattern during biofeedback breathing close to the individual's resonance frequency. The graphs show oscillations in HR almost completely in phase (close to 0°) with respiration, while blood pressure fluctuation is out of phase (at approximately 180°) with respiration and HR. Thus, other sources of variability are minimized.

During RSA-biofeedback, the individual is coached to breathe near to or at a particular resonant frequency, in order to increase HR oscillations (thus variability) by stimulating rhythmically not only the variation in HR, but also, the baroreceptors activity. More importantly, RSA-biofeedback near to or at the individual's particular resonant frequency allow to take advantage of the phase relationship between different systems, making possible to achieve the highest amplitudes of HR oscillations, thus magnifying HRV.

In biofeedback, daily practice is very important. In fact, the constant rhythmical stimulation of a resonant system increases the amplitude of system oscillations, leading to higher total variability. Hence, daily practice of RSA-biofeedback increase the baroreflex gain (Lehrer et al., 2003) and improve modulation of various autonomic functions (Lehrer et al., 2003).

So, RSA-biofeedback seems to be reliable and effective intervention to increase HRV and, thus, vagal control on the heart. Therefore, biofeedback can be a useful intervention in patients with CVDs or after cardiac surgery, in order to reduce cardiac risk factors. Furthermore, some studies reported biofeedback effectiveness in reducing perceived stress and depressive symptom, in both patients with and without cardiovascular disease.

5.2 Abstract

The current study investigated whether biofeedback training aimed at increasing respiratory sinus arrhythmia (RSA), a measure of cardiac vagal modulation, can reduce depressive symptoms in patients after cardiac surgery. This randomized controlled study enrolled 26 patients after first-time cardiac surgery. The patients were randomly assigned to an RSA-biofeedback group (N = 13) or to a standard rehabilitation group (N = 13). The biofeedback training consisted of five 45 min sessions designed to increase RSA. The outcome was assessed as changes in RSA and in the Centre for Epidemiologic Studies of Depression (CES-D) values from pre- to post-training. Both groups were comparable for demographic and biomedical characteristics. RSA increased significantly in patients who underwent RSA-biofeedback compared to controls. Moreover, the CES-D scores were reduced significantly from pre- to post-training in the RSA-biofeedback group compared to the controls. Changes in RSA were inversely correlated with changes in CES-D scores from pre- to post-training. These findings extend the effectiveness of RSA-biofeedback for increasing vagal modulation as well as for reducing depressive symptoms in post-surgical patients. Overall, the current study also suggests that this biobehavioral intervention may add to the efficacy of postoperative risk reduction programs and rehabilitation protocols in cardiac surgery patients.

Keywords: cardiac surgery; depressive symptoms; parasympathetic nervous system; respiratory sinus arrhythmia; vagal tone

5.3 Introduction

Undergoing cardiac surgery is a significant life event with a relevant impact on the affective status of patients. Among patients undergoing cardiac surgery, high rates of depression and anxiety, 25–30%, are reported (Langeluddecke et al., 1989; McKhann et al., 1997). Specifically, Langeluddecke and colleagues (1989) reported that 36% of patients prior to coronary artery bypass surgery (CABG), had a clinically significant score on the Center for Epidemiological Study of Depression scale (CES-D) (Radloff, 1977), whereas the incidence of anxiety measured with the Spielberger State Anxiety Inventory (STAI) (Spielberger et al., 1970) was approximately 30%.

Importantly, preoperative depression persist after cardiac surgery in up to 20% of patients (Vingerhoets, 1998). Several studies have shown that patients with postoperative depression are at greater risk for more cardiac morbidity and fatal cardiac events (Blumenthal et al., 2003; Connerney et al., 2001). Connerney and coworkers (2001) reported that major depressive disorder was an independent predictor of cardiac events one year after CABG even after controlling for other biomedical risk factors. In the largest study of depression as a risk factor for mortality in patients after cardiac surgery, Blumenthal and colleagues (2003) showed that patients with persistent (i.e., before as well as 6 months after CABG) mild or moderate to severe depression had a greater likelihood (i.e., more than twice) of death than those who were never depressed.

The psychophysiological mechanisms underlying depression as a risk factor for cardiovascular disease, cardiac morbidity, and/or fatal cardiac events after surgery are still debated. Both behavioral (i.e., poor adherence to cardiac treatment regimen) and biological (i.e., increased platelet aggregation) factors have been proposed as possible explanations. However, the strongest evidence implicates reduced autonomic tone on the heart in the development of cardiovascular diseases (Carney et al., 1995). Indeed, it is well-established

that depression is related to dysregulation of the hypothalamic pituitary-adrenal axis and increased sympathetic nervous system activity (Siever & Davis, 1985; Veith, 1994). Elevated sympathetic and/or reduced parasympathetic nervous system activities, in turn, have also been associated with ventricular fibrillation, ventricular tachycardia, and sudden cardiac death in patients with coronary heart disease (Podrid et al., 1990; Pruvot et al., 2000).

Respiratory sinus arrhythmia (RSA) has been widely used to assess cardiac autonomic modulation (Berntson et al., 1997; Grossman & Taylor, 2007). Several lines of evidence have documented that reduced RSA may be predictive of morbidity in individuals with cardiovascular diseases and may represent an index of poor vagal control as well as a marker of cardiovascular risk (Bigger et al., 1992; Hayano et al., 1990). Cross-sectional and longitudinal studies have also shown that reduced levels of RSA are linked to depression and/or depressive symptoms in nonsurgical populations (Balogh et al., 1993; Carney et al., 1995). However, discrepant findings have also been reported regarding the relationship between RSA and depression (Carney et al., 1988; Khaykin et al., 1998). Possible reasons for these inconsistent findings involve the heterogeneity of individuals diagnosed with depression (Gotlib & Hammen, 1992), small sample sizes, and the quantification of RSA without controlling for possible confounds such as respiration rate and depth (Grossman & Taylor, 2007).

Pharmacological treatments of depression in patients with cardiovascular diseases and, to a major extent, in patients after cardiac surgery also represent a challenge. Indeed, with the exception of selective serotonin reuptake inhibitors (SSRIs) that are not contraindicated in patients with cardiovascular diseases, norepinephrine reuptake inhibitors, and tricyclic antidepressants can exert a vagolytic effect (Agelink et al., 2002), yielding to reduced heart rate variability (HRV) (Schroeder et al., 2002), or anticholinergic effects (Feighner, 1999). Based on these findings, nonpharmacological treatments for depression in

patients with coronary heart disease have been developed. There is evidence that cognitive behavioral interventions and interpersonal therapy can be effective in reducing depression (Lett, Davidson, & Blumenthal, 2005). Interestingly, Carney and coworkers (2000) reported that cognitive behavioral therapy can also increase short-term HRV and reduce HR in severely depressed patients. However, in the largest study to date, while cognitive behavioral therapy was effective in lowering depression and increasing social support in patients after the onset of acute myocardial infarction, it failed to reduce cardiac morbidity and mortality (Berkman et al., 2003). Conversely, it is important to note that, although not mediated by change in depression, pharmacological therapy with SSRIs was associated with a reduction in risk of myocardial infarction, reinfarction and/or mortality. Specifically, the inhibitory effects of SSRIs on platelets have been implicated in reducing risk of myocardial infarction and/or mortality (Serebruany et al., 2001).

Although the effectiveness of psychological interventions for reducing risk factors related to coronary heart diseases is still debated (Lett, Davidson, et al., 2005), in the last two decades, several studies have reported that biobehavioral interventions such as biofeedback can be effective in reducing cardiovascular risk by enhancing vagal regulation in patients with coronary heart disease (for a review, see Wheat & Larkin, 2010). Specifically, Cowan and coworkers (1990) first reported that RSA-biofeedback training increased HRV and led to a better balance between sympathetic and parasympathetic activities in six cardiac patients. Del Pozo and coworkers (2004) extended this finding by showing that, compared to controls, RSA-biofeedback intervention increased HRV in patients with coronary heart disease six as well as 18 weeks after RSA training. More importantly, Nolan and coworkers (2005) reported that patients with coronary heart disease who had received five sessions of RSA-biofeedback showed increased parasympathetic HR modulation as well as reduced symptoms of depression compared to controls (i.e., without RSA-biofeedback).

Though there is increasing evidence that biofeedback interventions can enhance vagal modulation and, in turn, reduce symptoms of depression and cardiovascular outcome in patients with cardiovascular diseases, research has yet to investigate the potential effectiveness of RSA-biofeedback for increasing vagal control for treating depressive symptoms in the context of rehabilitation after cardiac surgery. Accordingly, the aims of the present study were two-fold. First, we examined whether, compared to the treatment as usual (TAU), RSA-biofeedback plus TAU (RSA-biofeedback + TAU) increases vagal regulation, as measured by RSA, in patients after first-time cardiac surgery. Second, we investigated whether increased vagal control was related to reduced depressive and anxiety symptoms in patients who had undergone cardiac surgery.

5.4 Methods

Participants

Thirty-three consecutive patients (mean age = 60.7, *SD* = 8.1) who underwent first-time cardiac surgery were sequentially enrolled in the study. All the patients had undergone cardiac surgery at a regional highly specialized hospital and were admitted for rehabilitation between November 2010 and July 2011. Informed consent was obtained. Age greater than 75, an inability to read or understand Italian, visual or auditory impairments, the use of psychotropic drugs, other life-threatening medical illness, and prior cerebrovascular and/or neurological diseases were the exclusion criteria. Seven patients declined to participate because of scheduling for other rehabilitation protocols or unavailability. The remaining patients (N = 26) received information on the entire procedure of the study. All patients were also provided with information on physiological measures (i.e., HR, abdominal and thoracic

respiration, RSA) recorded during pre- and post-training assessments as well as during RSA-biofeedback intervention. They were told that learning to increase the size of HR changes in phase with abdominal breathing (i.e., RSA) would help them to exercise important responses that regulate the autonomic nervous system. Increased autonomic regulation, in turn, would improve patients' ability to cope with everyday stress (Lehrer, Vaschillo, & Vaschillo, 2000). Then, each patient was randomly assigned to the RSA-biofeedback + TAU group (N = 13) or to the TAU group (N = 13). All the patients were treated with beta-blocker and/or angiotensin-converting enzyme inhibitor medications. All the study procedures received local ethics committee approval.

The descriptive statistics for each group are reported in Table 5.1.

Psychological Measures

The psychological evaluation included a short clinical interview and three self-report questionnaires aimed at assessing depressive and anxiety symptoms. The depressive and anxiety symptoms questionnaires included:

1- CES-D (Fava, 1982; Radloff, 1977). The Cronbach's alpha of CES-D scale in the present study was 0.88.

2- STAI Y1/Y2 (Spielberger et al., 1970; Spielberger, 1996). The Cronbach's alpha of STAI Y1 and Y2 was 0.92 and 0.84, respectively.

Table 5.1. *A Comparison of the Demographic and Biomedical Characteristics of the Groups*

Variable	RSA-biofeedback +TAU (*N* = 13)	TAU (*N* = 13)	*p*
Age (years)	61.3 (8.1)	58.3 (9.0)	.38
Education (years)	10.9 (3.8)	9.7 (2.7)	.38
Male Gender (*N*, %)	11 (85)	12 (92)	.99
Surgical Procedure			.39
CABG (*N*, %)	4 (31)	8 (61)	
Heart Valve (*N*, %)	4 (31)	1 (8)	
Combined (*N*, %)	5 (38)	4 (31)	
Diabetes (*N*, %)	2 (16)	3 (23)	.99
Hypertension (*N*, %)	7 (54)	8 (61)	.99
Myocardial Infarction (*N*, %)	1 (8)	2 (16)	.99
Dyslipidemia (*N*, %)	5 (38)	9 (69)	.24
PTCA	1 (8)	3 (23)	.59
Smoking			.77
Actual (*N*, %)	2 (16)	3 (23)	
Past (*N*, %)	3 (23)	4 (31)	
No (*N*, %)	8 (61)	6 (46)	
HR (bpm)	72.7 (10.8)	75.5 (13.8)	.57
RR (ms)	845 (145)	836 (254)	.91
SBP (mmHg)	101.3 (7.4)	105.8 (9.1)	.18
DBP (mmHg)	65.4 (8.3)	64.0 (5.2)	.61
Abdominal Respiration (cycles/min)	16.4 (1.8)	15.0 (3.5)	.20
Log Thoracic Respiration (cycles/min)	3.0 (0.0)	2.9 (0.1)	.08

Notes: Data are *M* (*SD*) of continuous and *N* (%) of categorical variables. RSA = respiratory sinus arrhythmia; TAU = treatment as usual; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; HR = heart rate; bpm = beats per minute; RR = inter-beat intervals; SBP = systolic blood pressure; DBP = diastolic blood pressure

Physiological Recording

Physiological measures were recorded in a standardized way using a computerized recording system (ProComp Infiniti, Thought Technology; Montreal, Canada). Blood volume pulse (BVP) was recorded by means of a photoplethysmographic detection sensor attached to the left ring finger. The HR signal derived from the analog output of the BVP amplifier was processed via a 12-bit analog-to-digital converter with a sampling rate of 256 Hz and stored sequentially for spectral analysis. All the HR data were exported in the Kubios-HRV 2.0 (Kuopio, Finland) software to correct artifacts with a piecewise cubic spline interpolation method that generates missing or corrupted values into the RR series. Respiration was recorded with two strain gauges/tube filled with conduction fluid the respiration belt recorded thoracic and abdominal respiration, respectively.

RSA was employed as a reasonable and reliable measure of cardiac vagal regulation (Grossman & Taylor, 2007), during both the assessment and the training phases. The mechanisms that produce RSA comprehend the interaction between the cardiac and respiratory responses (Grossman, 1983), hence, respiration can confound the relationship between cardiac vagal control and RSA (Grossman & Taylor, 2007; Lehrer et al., 2006). Accordingly, in order to correct RSA calculation for respiration rate, the respiratory frequency range was calculated for each patient (i.e., maximum minus minimum respiratory frequency, expressed in cycles/min) and converted in Hz (i.e., from cycles/min to cycles/sec). Then, a fast Fourier transformation was applied to the variation of RR intervals occurring within the specific respiratory frequency range for each patient. Successively, RSA epochs were averaged for each assessment phase (i.e., pre-training and post-training assessments, see below). RSA values were expressed in ms^2.

According to the European Society of Hypertension international protocol (De Greeff, Arora, Hervey, Liu, & Shennan, 2008), pre-training resting left arm blood pressure

was measured by means of a Tensoval Duo Control machine (Hartmann; Heidenheim, Deutschland). Three readings were taken at 1 minute intervals, and averaged, according to the American Heart Association (Pickering et al., 2005) recommendations for blood pressure measurement.

Assessment

The day after admission for rehabilitation(i.e., pre-training, approximately 10 days after cardiac surgery), and at discharge from the hospital (i.e., post-training, approximately 25 days after cardiac surgery), all patients underwent the same assessment protocol. The assessment protocol consisted of a psychological evaluation assessing psychological disorders, particularly depression and anxiety symptoms. Self-report questionnaires for depressive and anxiety symptoms were administered individually before and after the training by a trained psychologist blind to the patient's group assignment (RSA-biofeedback + TAU or TAU only group). After the psychological evaluation, blood pressure was measured and HR and respiration were recorded over a 4-minute baseline to obtain the basal RSA. All physiological recordings were taken with the patients sitting on a semireclined armchair at a 70° angle after adaptation to the laboratory. No support for the legs was employed in order to avoid possible confound effect of body position on cardiovascular activity. The light was dimmed to provide a relaxing atmosphere and the temperature in the room was approximately 21ºC. During the basal physiological recordings, all patients were asked not to close their eyes to avoid differences in the procedure used during the assessment and biofeedback training phases. After the pre-training assessment, the patients were randomly assigned to the RSA-biofeedback + TAU group or to the TAU only group.

Intervention Protocol

Patients were randomized to receive either five sessions of RSA-biofeedback + TAU or the TAU protocol.

RSA-biofeedback was designed to increase RSA and, therefore, to counter vagal inhibition associated with depressive symptoms (Lehrer, Vaschillo, & Vaschillo, 2000). The RSA-biofeedback training was scheduled approximately once a day within a two-week period, and each session lasted about 45 minutes. The RSA-feedback was presented through a 15-inch monitor connected to a Biograph Infiniti biofeedback machine (Thought Technology; Montreal, Canada). Before starting the first biofeedback training session, the patients were informed about the feedback system and about the physiological measures being monitored (i.e., HR, abdominal and thoracic respiration). Further, they were informed about RSA measure and introduced to RSA-biofeedback procedure. After BVP sensor and respiration strain gauge attachment, the patients were trained to recognize the signals on the screen, specifically thoracic (white line) and abdominal (blue line) breathing and heart rate tachogram (red line). After they familiarize with the signals, two six min RSA trainings were performed. Physiological feedback was monitored visually showing a concurrent HR beat-to-beat tachogram (i.e., beats/min) (red line) as well as thoracic (white line) and abdominal (blue line) breath respiration (i.e. cycles/min) (see Figure 5.2). The beat-to-beat tachogram and abdominal respiration were superimposed on the same axes and the on-line moving feedback display was updated at successive 30-second periods.

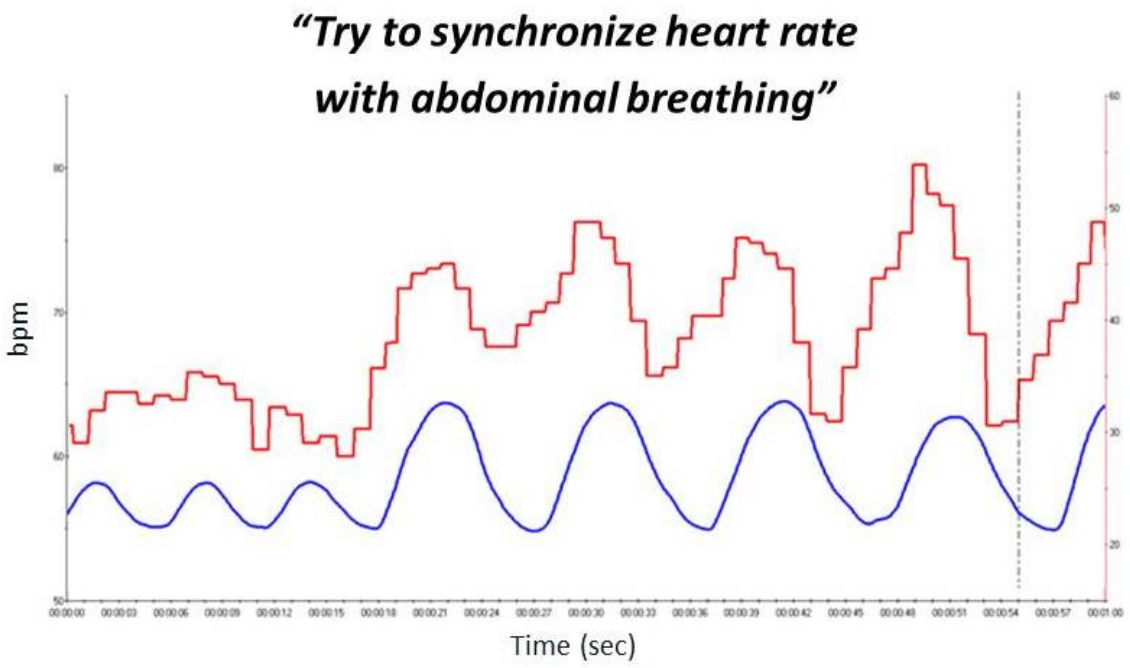


Figure 5.2 Screenshot from a session of Biofeedback. On the screen (duration 1 minute) are represented thoracic (white line) and abdominal (blue line) breathing and heart rate tachogram (red line). The task asked to the patient was: "Try to sincronize heart rate (the red line) with abdominal breating (the blue line)".

During RSA-biofeedback training session, patients were instructed to maximize RSA using the tachogram display (red line) and abdominal respiration (blue line). Specifically, the RSA-biofeedback training goal was to synchronize the HR (red line) with abdominal breathing (blue line). Patients were told to breathe approximately in phase with HR fluctuations, in order to maximize the increases and decreases in HR that accompany breathing and, therefore, to increase RSA amplitude (Lehrer et al., 2000). To facilitate HR/breathing synchronization and to maximize RSA amplitude, all the patients were instructed to breathe abdominally and regularly at a decreased rate (i.e., 6 cycles/min) (Del

Pozo et al., 2004; Nolan et al., 2005); for the specific instructions given in the current study to use biofeedback without pacing stimulus and to breathe abdominally, see (Lehrer et al., 2000, pp. 186-187). Each patient was reminded not to breathe too deeply to avoid hyperventilation symptoms. No pacing stimulus was provided during the first training session. After the completion of each session, patients were also encouraged to practice abdominal breathing for 15 minutes per day. All RSA-biofeedback sessions were conducted in the same setting used during the pre- and post-training assessment.

Both groups (RSA-biofeedback + TAU or the TAU) received standard treatment. TAU consisted of daily counseling sessions such as dietary and smoking cessation counseling, weight management, and stress management according to the guidelines of the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation (Balady et al., 2000; Task Force, 1996).

Statistical Analysis

Analysis of variance (ANOVA), with the group (RSA-biofeedback + TAU, TAU) as the between-subjects factor, was applied to compare age, education, resting HR, inter-beat intervals (IBI), abdominal and thoracic respiration rate, and blood pressure of the two groups.

Fisher's exact test or chi-square analyses were conducted to compare the two groups in terms of demographic, biomedical, and behavioral variables.

Separate mixed analyses of covariance (ANCOVAs) with group (RSA-biofeedback + TAU, TAU) as a between-subject factor, time (pre-training assessment, post-training assessment) as a within-subject factor, and age and gender as covariates were conducted on the physiological measures, namely HR, IBI, abdominal and thoracic respiration rate and RSA, as well as on the psychological measures, namely the STAI Y1/Y2, and CES-D scores.

Age and gender were entered as covariates a priori because of their influence on RSA (Craft & Schwartz, 1995).

Kolmogorov-Smirnov-test for normal distribution was performed for each dependent variable, showing that all data were normally distributed ($p > .11$) except for thoracic respiration. This latter measure was normalized using logarithmic transformation.

Partial eta-squared (η_p^2) was reported as a measure of the effect size. The η_p^2 values considered to represent small, medium, and large effects are .01, .06, and .14, respectively (Cohen, 1977). Fisher's LSD test was used for post-hoc analyses.

Moreover, hierarchical linear regression analyses were used to test if changes in RSA from pre- to post-training periods can predict changes in psychological questionnaires scores (i.e., CES-D, STAI Y1 and Y2) from pre- to post-training periods, while controlling for abdominal respiration rate.

A p value of $< .05$ was considered statistically significant. All statistical analyses were performed using STATISTICA 6.1 (StatSoft Inc., Tulsa, OK, USA).

5.5 Results

Characteristics of Patients Who Underwent RSA-biofeedback plus TAU and TAU

Fisher's exact test and the chi-square analysis revealed no group differences for gender, surgical procedure, diabetes, hypertension, myocardial infarction, dyslipidemia, PTCA, and smoking. Similarly, ANOVA yielded no group differences for age ($F(1, 24) = 0.80$, $\eta_p^2 = .03$), education ($F(1, 24) = 0.80$, $\eta_p^2 = .03$), RR ($F(1, 24) = 0.01$, $\eta_p^2 = .0005$), HR ($F(1, 24) = 0.32$, $\eta_p^2 = .01$), abdominal ($F(1, 24) = 1.71$, $\eta_p^2 = .07$) and log thoracic respiration ($F(1, 24) = 3.33$, $\eta_p^2 = .12$), systolic, blood pressure ($F(1, 24) = 1.90$, $\eta_p^2 = .07$), and diastolic blood pressure ($F(1, 24) = 0.26$, $\eta_p^2 = .01$).

Effects of Biofeedback on Physiological Measures

The group by time ANCOVA on RSA yielded a main effect for the group ($F(1, 22) = 11.26$, $p < .01$, $\eta_p^2 = .34$), and a group × time interaction effect ($F(1, 22) = 14.6$, $p < .001$, $\eta_p^2 = .40$). This interaction is depicted in Figure 5.3. Post-hoc Fisher's LSD comparisons showed a significant increase in RSA from pre- to post-training in the RSA-biofeedback + TAU group ($p < .001$), whereas no significant difference in RSA from pre- to post-training was found in the TAU group ($p = .85$). Also, compared to the patients who received TAU, the patients who underwent RSA-biofeedback + TAU had significantly greater RSA in the post-training ($p < .0001$). ANCOVA analyses did not show any main effect for group and time on RR (all p's > .70), HR (all p's > .61), abdominal (all p's > .12) and log thoracic respiration (all p's > .24). Moreover, no group × time interaction effects were found for RR ($F(1, 22) = 0.06$, $p = .81$, $\eta_p^2 = .003$), HR ($F(1, 22) = 0.05$, $p = .82$, $\eta_p^2 = .002$), abdominal ($F(1, 22) = 2.54$, $p = .13$, $\eta_p^2 = .10$) and log thoracic respiration ($F(1, 22) = 1.86$, $p = .19$, $\eta_p^2 = .08$).

Effects of RSA-biofeedback on Symptoms of Depression and Anxiety

The group by time ANCOVA on CES-D scores yielded a significant group × time interaction effect ($F(1, 22) = 4.31$, $p < .05$, $\eta_p^2 = .16$). Post-hoc Fisher's LSD comparisons showed a significant decrease in CES-D scores from pre-training to post-training in the RSA-biofeedback + TAU group ($p < .02$), whereas no significant difference in the CES-D scores from pre- to post-training was found in the control group ($p = .95$). No significant differences between groups in the pre- ($p = .27$) and post-training ($p = .37$) in the CES-D scores were noted.

In the case of STAI Y1, the group by time ANCOVA did not reveal a significant main effect for the group ($F(1, 22) = 0.55$, $p = .47$, $\eta_p^2 = .02$), time ($F(1, 22) = 1.16$, $p = .29$, $\eta_p^2 = .05$), or group × time ($F(1, 22) = 1.28$, $p = .27$, $\eta_p^2 = .05$). Similarly, the group by time

ANCOVA on the STAI Y2 scores failed to show a significant main effect for the group ($F(1, 22) = 1.22$, $p = .28$, $\eta_p^2 = .05$), time ($F(1, 22) = 0.31$, $p = .58$, $\eta_p^2 = .01$), or group × time ($F(1, 22) = 2.51$, $p = .13$, $\eta_p^2 = .10$). All means (*SD*) and statistical details are reported in Table 5.2.

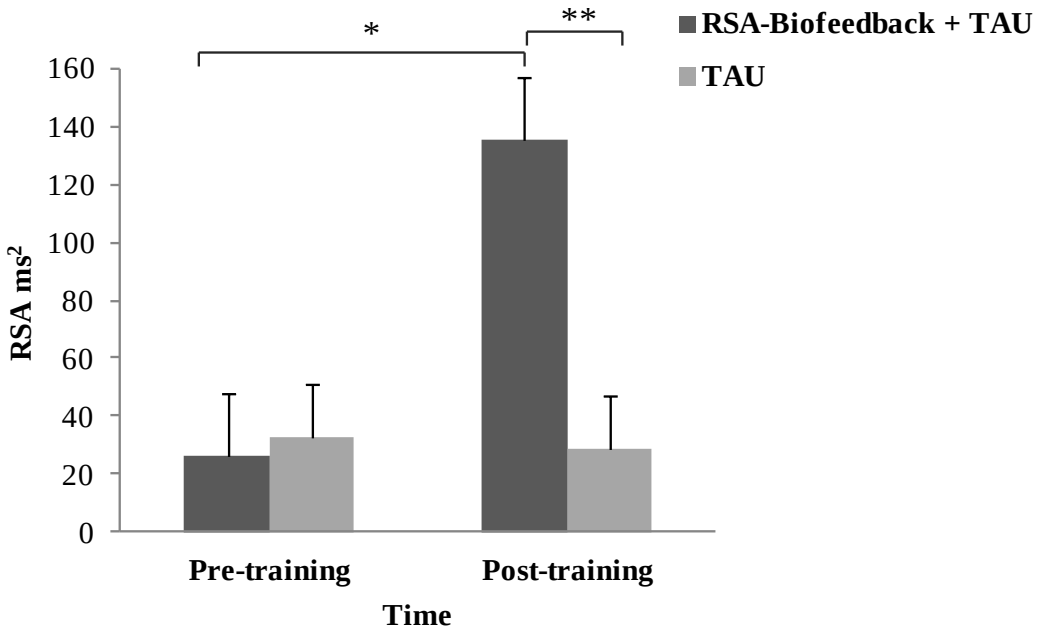


Figure 5.3. Pre- and post-training respiratory sinus arrhythmia (RSA) values (ms^2) in RSA-biofeedback group and controls. ANCOVA revealed a significant Group × Time interaction effect ($p < .001$). *Post-hoc Fisher's LSD comparisons, $p < .001$; **Post-hoc Fisher's LSD comparisons, $p < .0001$

Table 5.2. *ANCOVA on Depression, State and Trait Anxiety Scores from Pre- to Post-training in Patients Who Underwent RSA-biofeedback + TAU and TAU*

Variable	Pre-training	Post-training	*p*	η_p^2
CES-D			< .05	.16
RSA-biofeedback + TAU	15.3 (11.2)	8.9 (4.5)	.02	
TAU	11.8 (6.9)	11.7 (7.8)	.95	
STAI Y1			.27	.05
RSA-biofeedback + TAU	46.0 (8.9)	42.2 (6.5)		
TAU	45.2 (7.6)	43.8 (8.0)		
STAI Y2			.13	.10
RSA-biofeedback + TAU	43.9 (6.3)	43.6 (4.9)		
TAU	47.6 (7.8)	43.7 (5.7)		

Notes: Data are *M* (*SD*). ANCOVA = analysis of covariance; RSA = respiratory sinus arrhythmia; TAU = treatment as usual; CES-D = Center for Epidemiological Study Depression; STAI Y1-Y2 = State and Trait Anxiety Inventory

Relationship between RSA, CES-D, and STAI Y1/Y2 Scores

Hierarchical linear regression analyses showed that changes in CES-D scores were predicted by changes in RSA from pre- to post-training periods (β = -.50, p = .03). In contrast, changes in RSA were not related to changes in STAI Y1 (β = .15, p = .55) and Y2 (β = .06, p = .81) scores. It is worth noting that changes in abdominal respiratory frequency did not predict changes in any psychological scores (all p's > .26).

5.6 Discussion

The present study examined the potential effectiveness of RSA-biofeedback training for increasing RSA, as a measure of vagal modulation, in patients who underwent first-time cardiac surgery. It also aimed to elucidate whether an increase in vagal control would reduce depressive and/or anxiety symptoms. We found that, compared to the patients who received TAU, RSA significantly increased from pre- to post-training in patients who underwent RSA-biofeedback + TAU training. Moreover, the patients who underwent RSA-biofeedback + TAU were characterized by a reduction in depressive symptoms from pre- to post-training compared to patients who underwent the standard rehabilitation protocol only (i.e., TAU group). Although not significant, patients who underwent RSA-biofeedback + TAU had more depressive symptoms than patients who received TAU in the pre-training period. While the mean (*SD*) score on CES-D was 11.8 (6.9) in TAU group, in RSA-biofeedback +TAU group it was 15.3 (11.2) that falls close to the CES-D cut-off value for mild depressive symptoms (i.e., 16). It is important to note that RSA-biofeedback group showed a significant reduction in the CES-D scores from pre- to post-training (from 15.3 to 8.9), whereas CES-D scores did not change in TAU group (pre-training = 11.8, post-training = 11.7). Consistent with these findings, linear regression analyses showed that changes in RSA were selectively associated with changes in CES-D scores but not in STAI Y1 and Y2 scores from pre- to post-training. Moreover, it is worth noting that this association between changes in RSA and CES-D scores was independent of abdominal respiration rate.

These novel findings add to the literature on the biobehavioral treatment of cardiovascular disease by showing that the effectiveness of RSA-biofeedback intervention for increasing vagal modulation extends to patients after cardiac surgery, even under beta-blocker medication. More importantly, our study suggests the effectiveness of RSA biofeedback in treating depressive symptoms as revealed by the association between changes

in RSA and CES-D scores from pre- to post-training. These preliminary findings complement recent studies that have documented RSA-biofeedback effectiveness in enhancing vagal control (Cowan et al., 1990; Del Pozo et al., 2004; Nolan et al., 2005), as well as for reducing depressive symptoms in patients with coronary heart disease (Nolan et al., 2005). The current results are also in line with previous findings showing the effectiveness of RSA-biofeedback in several clinical populations such as patients with asthma (Lehrer et al., 1997; Lehrer et al., 2004), chronic obstructive pulmonary disease (Giardino, Chan, & Borson, 2004), fibromyalgia (Hassett et al., 2007), or in healthy individuals (Lehrer et al., 2003).

RSA-biofeedback training may add to the efficacy of cognitive behavioral psychotherapy designed to treat depressive symptoms in patients who have undergone first time cardiac surgery. Indeed, cognitive behavioral interventions are aimed at treating depression by enhancing the cognitive priming of positive emotion, relaxation, and pleasurable social activities as well as by inhibiting cognitive rumination on negative events and negative self-talk. However, the psychophysiological networks and autonomic nervous system pathways that mediate the influence of cognitive behavioral therapy on depression and/or anxiety are still partially unknown. In contrast, our preliminary findings suggest that RSA-biofeedback training may independently enhance HR vagal modulation and reduce depressive symptoms with beneficial effects on postoperative patients' functional and clinical outcome. Although the crucial mechanisms underlying the effectiveness of RSA-biofeedback in enhancing vagal modulation are still debated (Wheat & Larkin, 2010), it is plausible that RSA-biofeedback may increase peripheral HR modulation by making the baroreceptors more efficient (Lehrer et al., 2000; Lehrer et al., 2003). However, given that the baroreflex gain was not recorded in the current study, the likelihood of that possibility is indeterminable.

Although not directly investigated in the present study, RSA-biofeedback may reduce postoperative cardiac events by acting on pathophysiological mechanisms underlying the influence of depression on cardiovascular diseases morbidity and/or mortality, especially the altered autonomic nervous system activity (Carney et al., 2000). Additional research is needed to compare the efficacy of RSA-biofeedback and pharmacological therapy with SSRIs in reducing depressive symptoms as well as risk of cardiac mortality and morbidity in patients with cardiovascular diseases and/or in those individuals who underwent cardiac surgery (Berkman et al., 2003; Lespérance et al., 2007).

Another speculative explanation for the current findings may lie in the relationship among RSA-biofeedback, medullary neurons in the cardiorespiratory network, and cortical frontal-limbic circuits (Benarroch, 1997; Thayer & Lane, 2000). Given that, during RSA-biofeedback, patients are engaged in maintaining concentration in a targeted physiological index (i.e., RSA), biofeedback may increase vagal regulation by evoking concurrently generalized emotional self-control and focused attention. This psychological response may be associated with a brain network that involves the prefrontal and anterior cingulated cortex, which, in turn, are neural substrates of goal-directed behavior and emotion, respectively (Thayer & Lane, 2000). The prefrontal and anterior cingulate cortex are, in turn, connected with the amygdala, insula, parabrachial nucleus, lateral hypothalamus, and medullary neurons involved in the parasympathetic and sympathetic modulation of the heart and, therefore, have been linked to neurocardiac regulation (Benarroch, 1997; Thayer & Lane, 2000). Interestingly, Kubota and colleagues (2001) reported that a meditation procedure can increase vagal modulation as well as prefrontal cortex activity. Although there is evidence for an interface between cardiac regulation and cognitive-emotional functioning, future research on the effectiveness of biofeedback training is warranted to examine this potential relationship.

The current findings should be interpreted in light of a number of possible methodological issues. First, this study used a relatively small sample size; therefore, the present results need to be replicated to fully understand the effectiveness of RSA-biofeedback in treating depressive symptoms in patients after cardiac surgery. Nonetheless, the effect size, which indicates the proportion of the variance in the dependent variable that is related to the independent variable(s), showed large group × time effects on RSA (η_p^2 = .40) and CES-D scores (η_p^2 = .16). Second, although the pre-training mean score of RSA-biofeedback group on CES-D was close to the cut-off value for mild depressive symptoms (i.e., 16), cardiac surgery patients enrolled in the present study were not diagnosed as depressed. Moreover, given that CES-D is considered a screening measure for depressive symptoms, it is not definitive for supporting a diagnosis of depression. To overcome this limitation, future studies should extend the present findings by including patients who met the diagnostic criteria for major and minor depression according to the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (DSM-IV, Association American Psychiatric, 1994). Third, all the patients were treated in the hospital with a beta-blocker and/or angiotensin-converting enzyme inhibitor medication which, in turn, influenced cardiovascular physiology and, therefore, the blood pressure, HR, and RSA values. However, the pharmacological treatment was a part of these cardiac patients' standard clinical care in this post-surgical context and was the same between the RSA-biofeedback + TAU group and the TAU group. Fourth, we employed photoplethysmography instead of electrocardiogram, which, in turn, is the gold-standard method to measure HR, HRV, and RSA. Nonetheless, several studies have reported that the parameters of photoplethysmographic variability are highly correlated with HRV and RSA extracted from electrocardiogram (Lu et al., 2008). Fifth, the lack of a non-contingent RSA biofeedback group makes it somewhat difficult to understand whether the results observed in the present study may be fully attributable RSA

biofeedback intervention or to incidental factors. Therefore, future investigations should include a non-contingent RSA feedback group to test more rigorously the efficacy of RSA biofeedback against such a genuine placebo controls. Finally, although the current study showed that RSA is modifiable through biofeedback in an acute timeframe, we did not conduct follow up evaluations, so we do not know whether the current results on RSA and depressive symptoms will be long-lasting (Wheat & Larkin, 2010). This latter limitation makes it somewhat difficult to evaluate the real effectiveness of RSA-biofeedback for reducing depressive (and anxiety) symptoms in cardiac surgery patients. The questionnaires used in the current study, especially the STAI Y2 that evaluates persistent anxiety, imply ratings that should be performed over an extended period of time. Clearly, future research is warranted to replicate and extend the present findings by conducting long-term follow-up studies to demonstrate the longevity of the improvements in RSA and depressive symptomatology in postsurgical patients. Future studies should also investigate the effectiveness of RSA-biofeedback on trait anxiety over a longer period than two weeks.

The current study, investigate, in addition to the standard cardiac rehabilitation program, the effectiveness of RSA-biofeedback training for increasing vagal modulation as well as for reducing depressive symptoms in patients after cardiac surgery. Our preliminary findings may extend the potential effectiveness of RSA-biofeedback to the post-surgical period and suggest that this novel biobehavioral training may add to the efficacy of postoperative risk reduction programs and cardiac rehabilitation protocols.

CHAPTER 6

GENERAL DISCUSSION

6.1 A summary of main findings

In this thesis four studies have been described that were primarily meant to investigate the psychophysiological mechanisms underlying the relationship between depression and increased cardiac risk in patients after first time cardiac surgery, and, secondarily, to test the effectiveness of a biofeedback training in reducing cardiac risk in these patients.

Results of the first study that examined the association between depression and altered autonomic control on the heart, confirmed and extended previous data on depressed patients with CVDs. Specifically, the findings yielded that also depressed patients after first time cardiac surgery had reduced HRV and, particularly, lowered vagal control on the heart, compared to patients without depression. In addition, a sympathovagal dysfunction, characterized by increased LF/HF ratio, mainly influenced by reduced vagal control on the heart, was seen in depressed patients compared to those without depression. These findings suggest that the depression-reduced HRV relationship extends to patients after cardiac surgery, and that depression may be selectively related to impaired parasympathetic activity in these patients, independently of anxiety. These findings add to the well-known role of increased sympathetic cardiac control, as one possible physiological mechanisms linking depression to cardiovascular diseases (Carney et al., 2001; Carney et al., 2005) providing the evidence that support the relationship between depression and reduced vagal cardiac modulation.

As discussed across the thesis, other physiological mechanisms that may link depression to increased cardiac risk have been reported. Specifically, inflammation response and platelet activation process received consistent support. Even though, reduced HRV and inflammation response markers or platelet activation process have been generally described as independent pathways, recently Carney and Freedland (2009) proposed that a low HRV, that reflect reduced vagal control on the heart, may be associated with higher levels of inflammation response and platelet activation markers. These markers, commonly reported in depressed patients with CVDs, may contribute to the increased morbidity and mortality associated with depression.

The present results provide further support to the importance of carefully assess depression in patients after cardiac surgery in order to control for autonomic dysfunction related to cardiac morbidity or mortality.

One further issue was the identification of which emotional regulation strategies may be impaired in cardiac patients with depression. Accordingly, in the second study, the relationship between depression and emotion regulation strategies in patients after cardiac surgery, was investigated. The findings showed that depressed patients reported using significantly more suppression of emotion, but not cognitive reappraisal, compared to nondepressed individuals. Gross and John (2003) reported that individuals who frequently use suppression of emotion, show a tendency to experience more negative mood. In fact, individuals who suppress emotions deal with stressful situations by masking their feelings and suppressing external displays of both positive and negative emotions. This, in turn, leads to unsuccessful mood regulation, reduced positive emotion experience and expression, increased negative emotions, including feelings of inadequacy and inauthenticity and negative thought about emotions. In this context, cognitive theories of depression postulate that negative or maladaptive cognitive styles such as the negativity biases (the tendency for

negative interpretation to predominate over positive) play a role in the etiology and maintenance of depression disorders (Shook, Fazio, & Vasey, 2007).

Findings from the present thesis add to the literature on negativity biases by showing that suppression of emotions, a negative style to face emotions, was partially responsible for the observed diminished vagal control in depressed patients who underwent first time cardiac surgery. Suppression of emotions may leads to increased morbidity and mortality risk linked to depression. Therefore, increased trait levels of emotion suppression should be addressed, in order to reduce the effect of depression on sympathovagal imbalance in cardiac surgery patients.

While the first and second study were mainly focused on effects of depression or emotion regulation strategies on HRV at rest, the third study was designed to examine whether postoperative depression would be associated with altered autonomic changes during emotional stressors, in patients after cardiac surgery. Altered stress response, especially to emotional stressors, have been associated to the development of depression through different behavioral and psychophysiological pathways. By assessing cardiac vagal modification during three emotional imagery tasks (e.g., pleasant, neutral and unpleasant), finding of the third study yield a direct association between postoperative depression and vagal withdrawal during emotional stressors. Patients with postoperative depression had significantly greater emotional response, characterized by disproportionate vagal withdrawal, specifically during unpleasant imagery, compared to nondepressed patients after surgery. Therefore, the findings suggest that the vagal withdrawal, other than sympathetic activation, during unpleasant emotional stressors, in patients who underwent cardiac surgery, may mediate the conferral of cardiac risk by depression. These results add to the well-known role of pure sympathetic response during emotional stressors. In fact, many studies have reported increased sympathetic reactivity during emotional stressors in depressed patients (Matthews,

Nelesen, & Dimsdale, 2005; Thornton & Hallas, 1999). In addition, cardiac hyper-reactivity during emotional stressors have been shown to increase the risk of developing hypertension (Carroll et al., 2001; Treiber, Turner, Davis, & Strong, 1997), coronary heart disease and congestive heart failure (Phillips, 2011). Conversely, some studies have found a reduction in parasympathetic response during emotional stressors in depressed patients (Salomon, Clift, Karlsdóttir, & Rottenberg, 2009). The attenuated vagal response seen in depressed patients may reflect a compensatory response, caused by incessant activation of hypothalamic-pituitary-adrenal axis (Barton et al., 2007; Weber et al., 2000), and may lead to increased cardiac risk through reduced variability of heart rate both at rest and in response to emotional stressors.

In this context, Henry and colleagues (2007) recently proposed a dimensional model of mixed state and depression, that includes both emotional hypo- and hyper-reactivity. According to this model, individuals with emotional hyper-reactivity are characterized by feeling emotions of unusual intensity, and higher instability of the tonality of mood. Conversely, individuals with emotional hypo-reactivity are characterized by a general emotional inhibition in all dimensions. The distinction between hypo- and hyper-reactive depression may be useful to understand differences in cardiovascular reactivity. It can be hypothesized that specific depression types may be selectively associated not only with opposite patterns of emotional reactivity, but also with different patterns of cardiovascular reactivity to stressors. Either cardiac hyper- or hypo-reactivity may be pathophysiological mechanisms leading to increased cardiac risk in depressed patients. Therefore, the present results underline the need to identify the mechanisms by which depression types are specifically associated with peculiar reactivity pattern and to identify particular interventions focused at improving specific emotional and cardiovascular reactivity patterns in depressed patients.

Finally, the research was focused on potential non pharmacological treatment of depression in cardiac patients. Common cardiac rehabilitation programs include psychotherapeutic intervention (interpersonal therapy and cognitive behavioral therapy), life style modification and bio-behavioral intervention (relaxation training). These interventions, whether generally effective in improving mood disorders, were found ineffective in cardiac risk reduction. Rather, there is increasing evidence that cardiorespiratory biofeedback, namely, RSA-biofeedback, can enhance vagal control on the heart, reduce symptoms of depression and, in turn, improve cardiovascular outcome in patients with cardiovascular diseases (Cowan et al., 1990; Del Pozo et al., 2004; Nolan et al., 2005). The fourth study was designed to investigate whether a short RSA-biofeedback training could increase vagal control on the heart (as measured by RSA) at rest, and reduce depressive symptoms in patients after first time cardiac surgery. The findings showed that compared to the patients who received standard rehabilitation protocol, vagal control on the heart significantly increased from pre to post-training in patients who underwent both RSA-biofeedback training plus standard rehabilitation. Furthermore, the patients who underwent RSA-biofeedback showed a significant reduction in depressive symptoms from pre to post-training compared to patients who underwent the standard rehabilitation protocol only.

These results are of particular importance, in light of the fact that depression treatment in cardiac patients is a challenge. In fact, many pharmacological treatment (such as tricyclics, MAOIs, lithium, barbiturates and second-generation antidepressants) are not recommended or even contraindicated in these patients (Carney et al., 2002; Cohen et al., 2000; Glassman et al., 2002). In addition, psychotherapeutic interventions (i.e., cognitive behavioral therapy and interpersonal therapy) and bio-behavioral intervention (i.e., stress management, progressive muscle relaxation, autogenic training) while effective in reducing depression, have been found to be ineffective in reducing cardiac risk (Lett, Davidson, et al.,

2005; van Dixhoorn & White, 2005). Conversely, RSA-biofeedback was found to be effective in increasing cardiac vagal control, that in turn, has been associated with a reduction of the cardiac risk profile (Thayer & Lane, 2007). Furthermore, the reduction in depressive symptoms may lead to additional reduction in cardiac risk.

In conclusion, the present findings support the hypothesis that a short training of RSA-biofeedback can be efficiently added to cardiac rehabilitation programs as a substitute of pharmacological treatment in depressed patients after cardiac surgery.

6.2 Limitations of the research

The current findings should be interpreted in light of a number of possible limitations. First, in the studies investigating the psychophysiological mechanisms underlying the relationship between depression and cardiac risk, HRV has been recorded without accounting for respiration rate. Yet, HRV indexes may be influenced and confounded by respiration without reflecting only the influence of vagal control on the HR (Grossman & Taylor, 2007). However, since the respiratory frequency band, in the human adult, usually range from about 9 to 24 breath per minute (0.15 - 0.4 Hz) HRV indexes associated with vagal regulation (i.e., HF band) is thought to be mediated mainly by fluctuations of vagal-cardiac nerve activity and can provide a reliable index of vagal activity (Berntson et al., 1997; Eckberg, 2003; Grossman & Taylor, 2007; Hedman et al., 1995). In addition, there is large evidence that even HRV recordings uncontrolled for respiration rate can be an independent predictor of a negative outcome in medically ill populations, especially in patients with cardiovascular diseases (Bigger et al., 1993; Kleiger et al., 1987; Rich et al., 1988). HRV recording uncontrolled for respiration rate can show reduced HRV in depressed patients with coronary heart disease (Carney et al., 1995; Stein et al., 2000) or after myocardial infarction (Carney et al., 2001) compared to nondepressed individuals. Therefore, even if HRV recording uncontrolled for respiration represents a reliable index of vagal influence on the heart, controlling for respiration rate would provide more precise information on the pathophysiological mechanism leading to increased cardiac risk.

Second, the studies reported in this thesis did not include patients with a diagnosis of major depression disorder, but enrolled patients with clinically relevant depressive symptoms, as measured by the CES-D questionnaire (Radloff, 1977). Although CES-D has shown good psychometric properties, it has been validated in a large community population and covers the most symptomatic elements of depression such as sleep disturbance, poor

appetite or fatigue, it cannot replace a psychiatric evaluation using structured criteria defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013). Although, depressive conditions include subclinical symptoms that are milder or briefer compared to diagnose of major depression. Even though mild and short-lasting symptoms may have moderate to little impact on a person's life, mild but persistent symptoms may be detrimental to a person's adjustment. In fact, research has shown, that subclinical depression may predict the development of major depression or other emotional problems, and may result in significant impairment in affective and social functioning (Gotlib, Lewinsohn, & Seeley, 1995; Horwath, Johnson, Klerman, & Weissman, 1992; Wells et al., 1989; Zonderman, Herbst, Schmidt, Costa, & McCrae, 1993). Furthermore, many studies have reported an association between subclinical depressive symptoms and not only major depression, with reduced HRV (Agelink, Boz, et al., 2002; Carney et al., 2000; Yeragani et al., 1995). More importantly, it has been recently shown that there is a dose-response relationship between depression severity and cardiac events, specifically, more severe depression resulted to be associated with earlier and more severe cardiac events (Lichtman et al., 2008). Therefore it seems important, especially in cardiac surgery patients, to accurately monitor not only patients with major depression but also patients with subclinical depressive symptoms.

Finally, in the biofeedback study, the lack of adequate control condition (i.e., heart rate biofeedback or relaxation training), makes it somewhat difficult to understand whether the findings may be specifically attributable to RSA-biofeedback training effects, or more generally to the biofeedback intervention. In fact, the biofeedback training may involve a top-down mechanism, activated by focused attention and concentration. During a biofeedback training, patients are engaged in maintaining concentration and focused attention on the feedback signal (whether visual or acoustic) and/or on the targeted

physiological index (i.e., HR, RSA). Focused attention has been linked with the activation of the prefrontal and anterior cingulate cortex that in turn, are part of a wide brain network that have been associated with cardiovascular control of the heart (Thayer & Lane, 2000). Interestingly, Kubota and colleagues (2001) reported that a meditation procedure, that produce an increased prefrontal cortex activity can in turn, improve vagal modulation on the heart.

Some studies reported the effectiveness of EMG and thermal biofeedback (McGinnis, McGrady, Cox, & Grower-Dowling, 2005) and neurofeedback (Hammond, 2005), in reducing depressive symptoms, but no results have been reported on the effectiveness of these biofeedback intervention in improving vagal control of heart function. Therefore it seems important, to compare the influence on parasympathetic activity on the heart of both an RSA-biofeedback and an adequate biofeedback control condition.

6.3 Directions for future research

In order to overcome the above-mentioned limitations and to extend the current findings, future research should further investigate alteration of the ANS as the potential psychophysiological mechanisms linking depression to increased cardiac risks. In order to better understand the psychophysiological mechanisms that underlie the depression-increased cardiac risk relationship, future research should examine the neural mechanisms that regulate the autonomic nervous system control.

Depression, as a disorder of the regulation of mood and emotion, has been shown to be associated with abnormalities in the morphometry and activity of different cerebral structures, including the prefrontal cortex, the anterior cingulate cortex, the hippocampus and the amygdala [see Drevets (1998) for comprehensive review]. Reduced mean gray matter volume of the left subgenual prefrontal cortex have been found in familial bipolar and unipolar depressed (Drevets et al., 1997). In addition, decreased metabolism of the dorsolateral and dorsomedial prefrontal cortex and the anterior cingulate gyrus have been reported in depressed patients, compared to controls (Mayberg et al., 1997).

Interestingly, all these structures modulate, through tonic inhibition, the neural structures implicated in emotional behaviors, such as the amygdala, the mediodorsal nucleus of the thalamus, and the ventral striatum (the ventromedial caudate and the nucleus accumbens). Depressed patients have been reported to have abnormally increased metabolism in the amygdala and the medial thalamus (Greicius et al., 2007).

More importantly, many lines of evidence suggested that the structures involved in emotion regulation circuit (i.e., prefrontal cortex, amygdala and hippocampus), are involved in the modulation of the cardiovascular function. Nevertheless, the neural control of cardiovascular activity is not clear. Benarroch (1993, 1997) described the central autonomic network, that affect heart rhythms through vagus nerve influence on the sinoatrial node. The

central autonomic network includes prefrontal cortical areas, such as the orbitofrontal cortex and medial prefrontal cortex, the amygdala, the insula and the hypothalamus. Specifically, the prefrontal cortex, the anterior cingulate cortex, and the amygdala all have projections to the hypothalamic and medullary neurons involved in the modulation of parasympathetic and sympathetic branches of the ANS (see Figure 6.1) (Balaban & Thayer, 2001; Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004; Thayer & Lane, 2000; Wong, Massé, Kimmerly, Menon, & Shoemaker, 2007).

Hypoactivation of the prefrontal cortex that have been reported in depressed patients would lead to activation (decreased inhibition) of the central nucleus of the amygdala, this, in turn, may activate specific pathways leading to increase in the sympathetic outflow and/or reduced parasympathetic influence on the heart. First, the amygdala activation may increase sympathetic activity on heart, by decreasing inhibition on neurons in the caudal ventrolateral medulla (CVLM), that, in turn, cause activation of neurons in the rostral ventrolateral medulla (RVLM). RVLM neurons specifically control sympathetic activity. Second, the amygdala activation may reduce parasympathetic activity, by inhibition of neurons in the nucleus of the solitary tract, that, in turn produce the inhibition of neurons of the nucleus ambiguus (NA) and neurons of the dorsal vagal motor nucleus (DVN), causing a reduction of parasympathetic activity. These effects would produce a sympathovagal imbalance on the heart, characterized by increased HR and decrease HRV (Thayer & Lane, 2009). This wide central autonomic network have been proposed to control the interplay of parasympathetic and sympathetic outputs on the sinoatrial node variability of the heart rate time series (i.e., the HRV) (Benarroch, 1993; Benarroch, 1997; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012; Thayer & Lane, 2009).

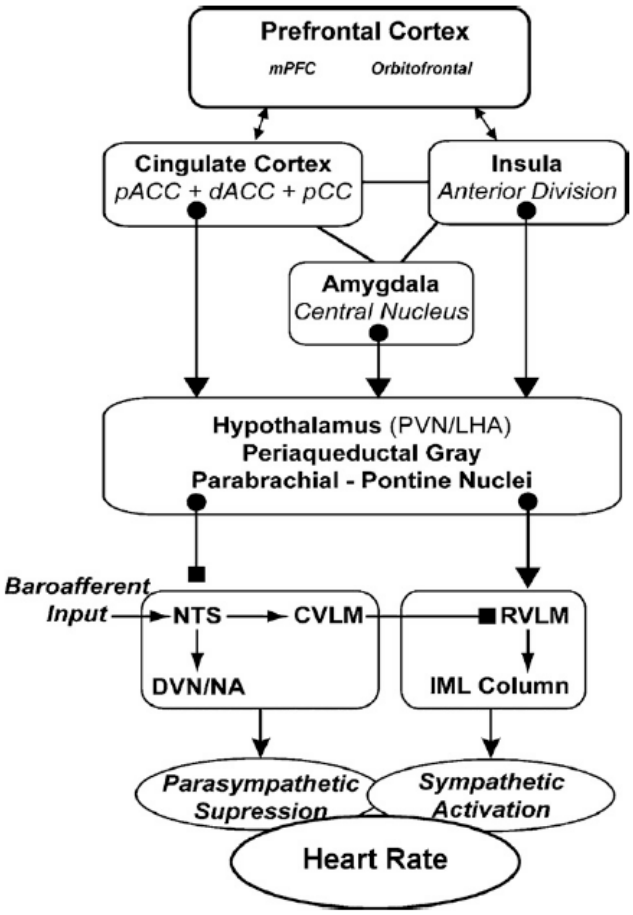


Figure 6.1. Schematic diagram representing the pathways by which the prefrontal cortex might influence parasympathetic and sympathetic control of heart rate. The prefrontal, cingulate, and insula cortices form an interconnected network with bi-directional communication with the amygdala. The amygdala is under tonic inhibitory control from the prefrontal cortex. The activation of the central nucleus of the amygdala inhibits the nucleus of the solitary tract (NTS) which in turn inhibits inhibitory caudal ventrolateral medullary (CVLM) inputs to the rostral ventrolateral medullary (RVLM) sympathoexcitatory neurons, and inhibits vagal motor neurons in the nucleus ambiguous (NA) and the dorsal vagal motor nucleus (DVN). In addition, the central nucleus of the amygdala activate sympathoexcitatory neurons in the RVLM (Thayer & Lane, 2009).

Arnsten and Goldman-Rakic (1998) proposed that, during emotional stressor, the prefrontal cortex is inhibited in order to allow more automatic processes, mediated by subcortical structures such as the amygdala, to control behavioral responses (Arnsten & Goldman-Rakic, 1998). This selective prefrontal inactivation helps to organize fast adaptive responses to threat, but may often be maladaptive in human society. In fact, in modern human society, cognitive and emotional flexibility are necessary for self-regulation and adaptation to environmental demands. Prolonged prefrontal inactivity may lead to hypervigilance, defensiveness, and perseveration, thus contributing to the vulnerability associated with many psychiatric disorders, including depression.

To verify if both the pathways involved in the central autonomic control of the heart (i.e., central control of either sympathetic or parasympathetic cardiac influence) are altered in depressed patients, future research should include functional and/or structural cerebral measurement recorded simultaneously with cardiovascular activity. Useful evidence may also come from connectivity analysis that may provide further information on the neural pathways linking central structures to both parasympathetic and sympathetic control on the heart. In addition, both indexes of parasympathetic (i.e., HF of HRV, RSA) and sympathetic activity (pre ejection period time) should be included to obtain a more accurate information on both the branches of ANS activity on the heart in depressed patients.

6.4 Conclusions

Taken together, these findings provide steps for understanding the psychological and psychobiological mechanisms underlying the relationship between depression and increased cardiac risk. The present findings confirm previous results on the association between depression and impaired vagal control on the heart. This relationship have also been shown to be partially mediated by altered emotion regulation strategies, specifically, by excessive suppression of emotions. In addition, depressed cardiac patients have been found to show altered vagal response to emotional stressors. These findings add to the literature on stress response in depressed patients by showing that depression is not only related with increased sympathetic activation to stressors, but result, as well, to be associated with vagal withdrawal during unpleasant stressors.

Therefore, postoperative depression should be accurately monitored, in order to improve cardiac outcomes in patients after cardiac surgery. In addition, these results suggest the need for emotion regulation training which may be useful to reduce the risk associated with altered emotional regulation both at rest and in response to emotional stressors.

More importantly, these findings provide new evidence supporting the usefulness of a short RSA-biofeedback intervention, in increasing vagal control on the heart and improving depressive symptoms. This biofeedback training should be usefully added to standard cardiac rehabilitation protocols in order to reduce the depression-related cardiac risk factors.

In conclusion, the present thesis provides further information to explain the psychophysiological mechanisms underlying the relationship between depression and increased cardiac risk, and more importantly, yields evidence in support of the effectiveness of biofeedback training in patients after cardiac surgery.

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