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PSYCHOBIOLOGICAL MECHANISMS UNDERLYING COGNITIVE DECLINE IN CARDIAC SURGERY PATIENTS

Direttore della Scuola: Prof.ssa Clara Casco

Coordinatore d'indirizzo: Prof. Alessandro Angrilli

Supervisore: Prof.ssa Daniela Palomba

Consulente: Dr. Carlo Valfrè

Dottorando: dott. Simone Messerotti Benvenuti

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CONTENTS

OVERVIEW

Cardiac surgery has been revolutionized by the development of heart-lung machine (or cardiopulmonary bypass). The adoption of this clinically safe and useful heart-lung machine was the rate-limiting step to the development of modern cardiac surgery. Since its inception, the number of cardiac surgery procedures has dramatically increased. Indeed, cardiopulmonary bypass has enabled the surgical treatment of coronary heart disease, valvular heart disease, congenital heart defects, and end-stage heart diseases requiring heart transplantation and mechanical assist devices or artificial hearts.

Although technological advances over the past four decades have decreased the major complications or mortality in cardiac surgery, a significant number of patients suffer from adverse neurological and cognitive outcomes which, in turn, remain an important cause of postoperative morbidity and are responsible for an increasing proportion of perioperative deaths. Adverse neurological and cognitive outcomes range in severity from fatal brain lesions to subtle cognitive decline, change in personality or behavior. The incidence of adverse cerebral outcomes such as focal neurological lesions, strokes or transitory ischemic attack is approximately 4% of cardiac surgery patients, while adverse cognitive outcomes such as generalized cognitive decline have been observed in approximately 50% at discharge and persist in 42% of patients 5 years after surgery.

Adverse neurological and cognitive outcomes after cardiac surgery are the result of multiple preoperative and/or intraoperative factors. While demographic, biomedical, and psychological disorders (i.e., anxiety and depression) represent preoperative variables associated with postoperative adverse outcomes, cerebral hypoperfusion, microembolization and neuroinflammation which occur intraoperatively also represent a major cause of impairment after surgery.

Despite a growing interest in adverse psychological outcomes after cardiac surgery, the psychophysiological mechanisms underlying postoperative cognitive decline have to be investigated yet. In this dissertation four studies will be described, that were meant to examine cognitive decline and depression after cardiac surgery and some psychophysiological mechanisms underlying the afore-mentioned phenomena.

The main aim of Experiment I was to provide further evidence about the preoperative relationships among anxiety, depression, cognitive dysfunctions and risk-stratification scores, namely the Stroke Index and European System for Cardiac Operative Risk Evaluation, in patients undergoing cardiac surgery. For this purpose, risk-stratification scores were calculated for 91 patients who had undergone a cognitive and affective psychological evaluation before surgery. It was found that both the risk-stratification scores showed significant correlations with cognitive performance whereas only the European System for Cardiac Operative Risk Evaluation was significantly associated also with anxiety and depression scores. Therefore, compared to the Stroke Index, the European System for Cardiac Operative Risk Evaluation takes into account the risk related to preoperative cognitive impairment, anxiety and depression in cardiac surgery patients. Experiment I also suggests the need for an appropriate psychological evaluation, possibly using tests age- and education-corrected, in order to provide further useful information concerning the preoperative psychological functioning of cardiac surgery patients.

The main goal of Experiment II and III was to investigate the hemodynamic cerebral factors underlying cognitive decline after cardiac surgery. Experiment II was designed to examine whether cerebral hypoperfusion may represent a predictor of cognitive decline in patients undergone cardiac surgery after controlling for common demographic and biomedical risk factors. The week before surgery, 31 right-handed patients had a neurosonology evaluation, which consisted of a bilateral middle cerebra arteries blood flow

velocity monitoring at rest with a multifrequency transcranial Doppler. Also, each patient underwent a cognitive evaluation before surgery and the day before discharge from hospital. Experiment II showed that hypoperfusion in the left middle cerebral artery selectively predicted the incidence of cognitive decline after surgery, whereas blood flow velocity in the right middle cerebral artery was unrelated to postoperative cognitive decline. Hence, cardiac surgery patients with reduced left cerebral blood flow velocity preoperatively are at greater risk for postoperative cognitive decline. Left cerebral hypoperfusion may also represent an independent predictor of cognitive decline in cardiac surgery patients.

Experiment III was designed to determine the effects of lateralization and type of microembolization on postoperative cognitive decline in patients who had undergone heart valve surgery. Transcranial Doppler was used to detect intraoperative microembolization in both middle cerebral arteries in 13 right-handed heart valve surgery patients. Cognitive evaluation was performed preoperatively, at discharge and 3 months after surgery. Experiment III showed that microembolization in the left middle cerebral artery significantly correlated with early and late (i.e., 3-month follow-up) postoperative cognitive decline while microembolization in the right middle cerebral artery was unrelated to early or late cognitive decline. Moreover, an association between solid microemboli with early but not late postoperative cognitive decline was noted. In contrast, gaseous microembolization was related to both early and late cognitive decline. There is evidence that cognitive decline may be more vulnerable to microembolization in the left than right middle cerebral artery. The present study also suggests that solid and gaseous microemboli are both similarly associated with early postoperative cognitive decline whereas, surprisingly, late postoperative cognitive decline is more likely to be related to gaseous than solid microemboli.

Given the relevant role played by depression as a risk factor for postoperative adverse clinical and cognitive outcomes, the main aim of the Experiment IV was to examine whether

EEG activity could reflect the influence of depression during an emotional imagery task requiring the subject being involved in a cognitive task (retrieval and imagery), which is emotionally laden. Psychological evaluation aimed at assessing depression and emotion regulation was performed in 35 patients postoperatively. Then, electroencephalography was recorded over Fz, Cz and Pz at rest as well as during an emotional imagery task in patients with depression (N = 12) and without depression (N = 23). There was no difference between groups in resting electroencephalographic activity, whereas patients with depression showed a significant reduced frontal theta power during the emotional imagery task compared to those without depression. Also, a significant correlation was selectively found between frontal theta power and reappraisal. The current study provides preliminary evidence for a mood modulation of cortical activity during an emotional imagery task in patients after cardiac surgery.

Taken together these experiments provide a better understanding of the psychological and physiological mechanisms underlying postoperative cognitive decline and depression in cardiac surgery patients. The present findings suggest that preoperative psychological status (Experiment I) and hemodynamic measures (Experiment II, III) should be taken into account to improve the diagnosis and treatment of postoperative psychological (i.e., cognitive and affective) outcome in cardiac surgery patients. Moreover, these findings suggest that depression may alter EEG activity related to cognitive and emotional processing in patients after cardiac surgery, thus contributing to psychological adverse outcomes (Experiment IV). In conclusion, the present thesis suggests the need for including preoperative and postoperative evaluation of cognitive and affective status as well as objective easy-to-use psychophysiological measures to accurately predict and/or treat patient's dysfunctional psychological outcomes. Specifically, a preoperative neurosonology evaluation with transcranial Doppler can detect patients at high risk for postoperative cognitive decline and,

therefore, guide intraoperative management of patients suggesting the need for brain monitoring. Intraoperatively, the use of brain monitoring with transcranial Doppler for the detection of cerebral microembolization and hypoperfusion can guide the cardiac surgery equipe in the operating theatre. Also, intraoperative brain monitoring can guide the psychophysiological rehabilitation by indicating those patients at high risk for postoperative cognitive dysfunctions. Finally, in order to reduce postoperative electroencephalographic deficits reflecting depression-related cognitive and emotional dysfunctions, the use of biobehavioral intervention such as neurofeedback could be taken into account. Overall, these findings also provide suggestions or implications for improving patient's well-being and health care interventions after cardiac surgery.

Keywords: Cardiac surgery; Cognitive decline; Depression; Emotion regulation; Hypoperfusion; Microembolization; Risk factors

1. GENERAL INTRODUCTION

1.1 Cardiac Surgery: The Technique of Cardiopulmonary Bypass and Its Applications

In the 19th century cardiac surgery had its beginnings with experiments on animals to repair penetrating lesions of the heart. The first successful repair of a stab wound of the heart in a man was reported by Rehn, a general practitioner from Frankfurt, in 1897. During the first half of the 20th century, important advances in cardiac surgery were obtained with innovative procedures for treating valvular and ischemic heart diseases and congenital lesions.

However, the 1950s saw the turning point of the speciality. In 1953, John Gibbon revealed that a still and bloodless field could be achieved during cardiac surgery, when he successfully repaired an atrial septal defect with the aid of the cardiopulmonary bypass (CPB). This is an apparatus designed to temporarily take over the function of the heart and lungs during surgery, maintaining the circulation of blood and the oxygen content of the body (Gibbon, 1954). The first successful coronary artery bypass operation was performed by Garrett in 1964. Within a few years, after the crucial studies by Favoloro at the Cleveland Clinic, coronary artery surgery with CPB had become established as the preferred surgical technique for myocardial revascularization.

The heart-lung apparatus was designed to perform the functions of both the human heart and lungs and, therefore, enables surgeons to repair defects in the heart while the patient's cardiac muscle and normal circulation are stopped. Blood flow through the heart and lungs is bypassed by directing venous blood flow away from the right atrium, vena cava, or femoral vein through a cannula connected to tubing filled with isotonic crystalloid solution. Then, venous blood flow is filtered, cooled or warmed, oxygenated, and returned to the patient's arterial circulation by a cannula inserted in the ascending aorta (or, alternatively, the

femoral artery). CPB circuit includes a reservoir, an oxygenator to add oxygen and remove carbon dioxide from the blood, a heart exchanger to cool or warm the blood, one or more filters to prevent particulate or gaseous materials from entering the patient, and a pump to propel the blood back into the patient. The patient is administered heparin to prevent clotting, and protamine sulfate is given after, to reverse effects of heparin. During the procedure, hypothermia is maintained; body temperature is usually kept at 28ºC to 32ºC. The blood is cooled during CPB and returned to the body. The cooled blood slows the body's basal metabolic rate, decreasing its demand for oxygen. Cooled blood usually has a higher viscosity, but the crystalloid solution used to prime the bypass tubing dilutes the blood.

The development of the heart-lung machine enabled the surgical treatment of coronary heart disease, valvular heart disease, congenital heart defects, and end-stage heart disease requiring heart transplantation and mechanical assist devices or artificial hearts. In the next Chapters, coronary artery disease, heart valve disease, aneurysm of ascending aorta will be described.

1.1.1 Cardiac Ischemic Diseases and Coronary Artery Bypass Grafting

The progressive occlusion of one or more of the heart's major arteries (i.e., left anterior descending, circumflex, and right coronary arteries) by atherosclerotic plaques characterizes coronary artery disease, although non-atherosclerotic types of coronary artery disease do occur (Figure 1.1). The clinical manifestation of coronary artery disease or coronary (ischemic) heart disease varies within a spectrum that encompasses myocardial infarction, forms of angina pectoris, chronic coronary artery disease, and sudden cardiac death. These syndromes result from complex interactions between the myocardium activity and coronary circulation, with coronary atherosclerosis as the main anatomic substrates for disease (Baroldi, 1991; Buja & Willerson, 1987). Previously considered a cholesterol storage disease, atherogenesis now represents a complex interaction of risk factors including alteration of the cells of the artery wall, the viscosity of blood and altered molecular messages that they exchange. Laboratory and clinic studies have demonstrated inflammation to play a major role in all stages of atherogenesis as well as in myocardial, systemic and local complications of atherosclerosis (Libby, 2002). Therefore, inflammatory response of the vessel wall to chronic, multifactorial injury can lead to the formation of the atherosclerotic plaques which, in turn, are regions of thickened intima and are composed of mixture of fibrous tissue, cells, and lipid (Buja, Clubb, Bilheimer, & Willerson, 1990; Pearson, Kramer, Solez, & Heptinstall, 1977; Schwartz & Mitchell, 1962). Initially, atherosclerosis is a focal disease, especially in the left anterior descending coronary artery and the proximal and distal right coronary artery. Then, atherosclerotic disease leads to extensive remodelling of the vessel wall. Although the presence of intimal placque, lumen is maintained by the dilation of the vessel. When the atherosclerotic disease is advanced, lumen narrowing occurs. Areas of severe narrowing (50% narrowing of lumen diameter, 75% of lumen area, is needed before blood flow is affected) often develop in the setting of multifocal ischemia.

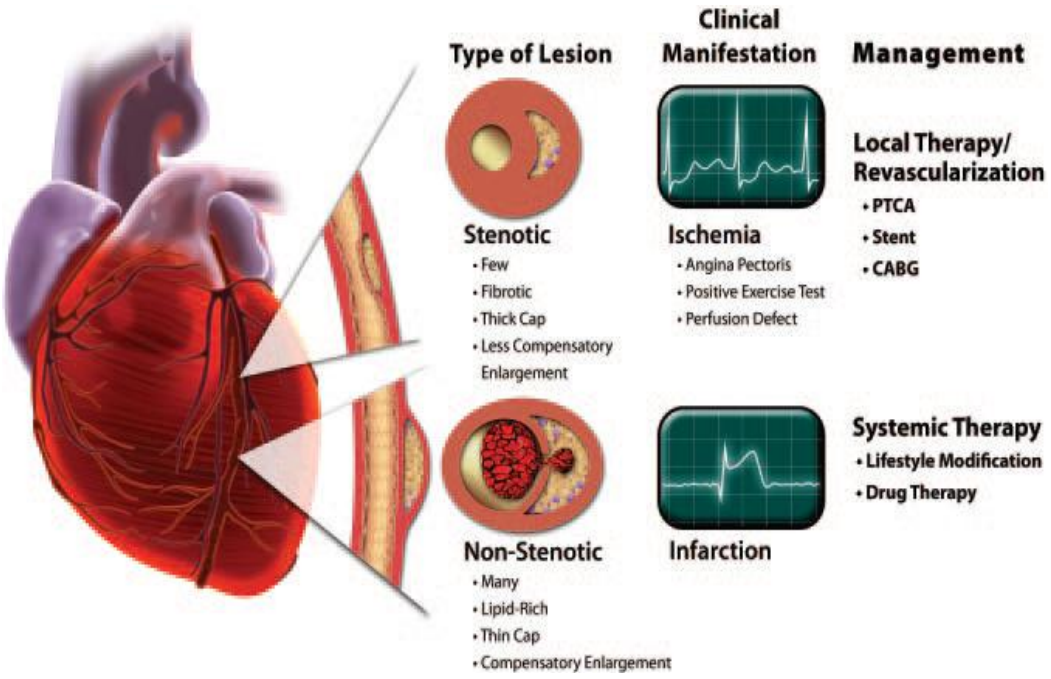

Figure 1.1 Diversity of lesions in human coronary atherosclerosis. Two morphological extremes of coronary atherosclerotic plaques are depicted. Stenotic lesions tend to have smaller lipid cores, more fibrosis, and calcification; thick fibrous caps; and less compensatory enlargement (positive remodeling). They typically produce ischemia appropriately managed by combined medical therapy and often revascularization for symptom relief. Nonstenotic lesions generally outnumber stenotic plaques and tend to have large lipid cores and thin, fibrous caps susceptible to rupture and thrombosis. They often undergo substantial compensatory enlargement that leads to underestimation of lesion size by angiography. Nonstenotic plaques may cause no symptoms for many years but when disrupted can provoke episode of unstable angina or myocardial infarction. Management of nonstenotic lesions should include lifestyle modification (and pharmacotherapy in high-risk individuals). Enlarged segments of schematic show longitudinal section (left) and cross section (right). Many coronary atherosclerotic lesions may lie between these 2 extremes, produce mixed clinical manifestations, and require multipronged management. Because both types of lesions usually coexist in given high-risk individual, optimum management often requires both revascularization and systemic therapy. PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft. From Libby & Theroux, 2005

In the last few years, coronary artery bypass grafting (CABG) has become the most common heart operation. CABG is a major surgical procedure performed under general anesthesia and takes on average from 3 to 5 h. The principle of coronary artery bypass

surgery is to provide a new blood supply for sections of the heart muscle whose own supply of arterial blood is restricted by a blocked artery. The conduit used to bypass the narrowed section and supply the new route for blood can be segments of saphenous vein removed from the leg and attached to the aorta and the coronary artery. The left anterior descending coronary artery is usually bypassed using the internal mammary artery, a blood vessel that usually supplies blood to the chest wall. The right internal mammary, radial, gastroepiploic, and epigastric arteries may be also used in CABG procedure. There is strong evidence that a bypass using a section of internal mammary artery is less susceptible to becoming blocked in the future. Only 60% of grafts using a vein are still open after ten years as opposed to more than 90% of grafts using internal mammary artery (Lytle et al., 1985).

This surgery is usually elective (except for the emergencies that may occur during heart attack), and the patient often plays a large role in deciding both when and whether to have the operation. In recent years, the indications for CABG have become better defined. The principal variables able to indicate those patients who are likely to benefit functional improvement and survival from CABG are reported in Table 1.1. Current estimates are that, worldwide, about 800,000 patients undergo CABG each year despite CABG is indicated for only about 20% of all patients with coronary artery disease (Roach et al., 1996). Indeed, patients undergoing CABG procedures are particularly prone to neurologic dysfunctions such as stroke, encephalopathy, and adverse cognitive outcomes, because they are relatively old and have atherosclerotic disease. Moreover, CABG surgery has several side effects such as a marked cerebral embolization of atherosclerotic plaque, air, fat, and platelet aggregates; cerebral hyperthermia after the discontinuation of CPB; hemodynamic fluctuations; and other inflammatory and neurohumoral derangements associated with surgery (Herskowitz & Mangano, 1996; Mangano, 1995; Mora & Murkin, 1995). These patient- and surgery-related

risk factors have to be taken into account before indicating CABG as treatment for patients with coronary artery disease.

Table 1.1 *Principal Indications for CABG*

Variable
Three-vessel disease
Left main coronary disease
Selected cases of two vessel disease
Failure of medical therapy (and unsuitability of patient for PTCA)
Failed PTCA
Recurrent symptoms post-CABG
Congenital coronary artery abnormalities

Note. PTCA = Percutaneous transluminal coronary angioplasty; CABG = Coronary artery bypass graft. From Waldstein & Elias, 2001

1.1.2 Surgery of Heart Valve Diseases

The heart's valves perform the vital function of maintaining blood flow in the correct direction. The *mitral* valve directs the flow of blood from the left atrium into the left ventricle, and the *aortic* valve allows blood to pass from the left ventricle into the aorta. The *tricuspid* and *pulmonary* valves perform the equivalent tasks on the right side, but are under considerably less pressure than the valves on the left side and - although they may suffer from similar disorders - are less likely to be so severely impaired as to require surgery. Problems with the heart valves and their functioning can be of two kinds: narrowing (stenosis), when the valve opening is constricted and blood flow reduced, and regurgitation, when some of the blood leaks back into sections of the heart from which it has just been expelled because the valve leaflets do not close properly (Figure 1.2). A poorly functioning valve in which the leaflets neither open nor close properly may cause both problems (Reddy & Punjaby, 2007).

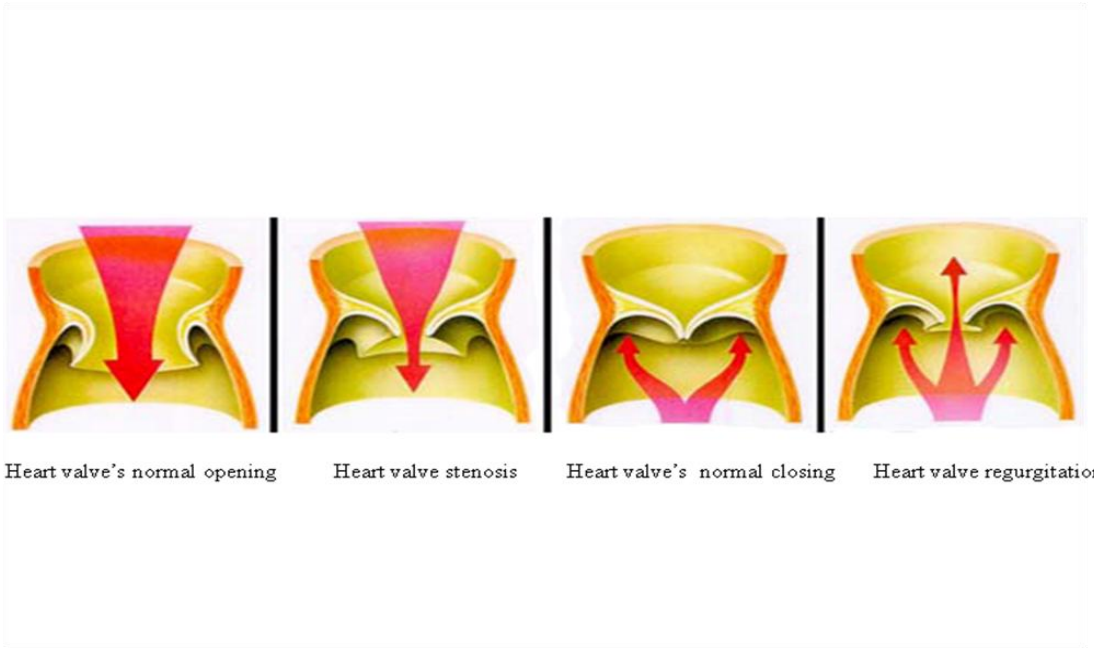

Figure 1.2 Normal and pathological valve's opening and closing (i.e., stenosis and regurgitation, respectively).

Aortic Valve Diseases

Aortic stenosis is the most common of valve lesions (with the possible exception of mitral valve prolapse). Although rheumatic heart disease was once considered a major cause of aortic stenosis, calcific disease now represents the major cause of aortic stenosis. The prevalence of aortic valve abnormality increases with age: aortic stenosis is present in 4% of adults aged > 80 years. Despite the importance of degenerative process, it is now well-established that atherosclerosis represents the etiopathogenesis of aortic stenosis (Mohler et al., 2001; Otto, Kuusisto, Reichenback, Gown, & O'Brien, 1994; Rajamannan et al., 2001). Indeed, the initial placque of aortic stenosis resembles that of coronary artery disease (Otto et al., 1994) and risk factors such as systemic inflammation, hyperlipidemia, and hypertension are held in common by aortic stenosis as well as coronary artery disease (Rajamannan et al., 2001). Aortic stenosis obstructs the left ventricular outflow and produces a pressure gradient between left ventricle and aorta during systole. This gradient is the additional pressure work (pressure overload) that left ventricle must develop to propel blood across the narrowed aortic valve: in other words, the left ventricle hypertrophies to generate sufficient pressure to maintain normal flow through the diseased valve. The normal area of the adult aortic valve is 3 - 4 cm^2. The criteria for severity of aortic stenosis are mild (valve area > 1.5 cm^2), moderate (valve area = 1.0 - 1.5 cm^2) and severe (valve area < 1.0 cm^2). Natural progression of the disease usually causes the decrease in the area of the aortic valve by an average of 0.12 cm^2 per year. Angina, dyspnea, or syncope (and other symptoms of heart failure) are classic symptoms of aortic stenosis and represent a dramatic inflection in the natural history of disease. Although there is little risk of sudden death in the asymptomatic state, it dramatically increases once symptoms have developed (Carabello, 2007).

Aortic regurgitation is caused by diseases of the valve leaflets or of the aortic root. Diseases affecting the valve leaflets are: congenital bicuspid valve disease, infective

endocarditis, rheumatic disease or leaflet calcification. Abnormalities inherent the aortic root composition are mainly responsible for its dilation (Gurvitz, Chang, Drant, & Allada, 2004). Such dilation, which is related to hypertension and aging, induces aortic regurgitation which, in turn, imparts a volume load on the left ventricle as the cardiac output that regurgitates into the left ventricular diastole must be compensated for by an increase in total stroke volume (Carabello, 1986). Hence, left ventricular dilation and hypertrophy compensate for the volume load in chronic aortic regurgitation. Left ventricular dilation is relatively more pronounced than hypertrophy and compliance is normal or increases. It must be recognized that the compensatory total stroke volume increases pulse pressure and systolic blood pressure and, therefore, aortic regurgitation is associated with pressure overload. Acute aortic regurgitation may present dramatically with pulmonary edema and low output failure. Chronic aortic regurgitation usually remains asymptomatic for several years before the development of exertional fatigue, dyspnea or angina. Compensation is provided by ventricular remodeling: in particular, the enlarged left ventricle can pump enough extra stroke volume to maintain adequate perfusion. However, when increased diastolic dysfunction and residual left ventricle volume lead to elevated left ventricular filling pressure, symptoms may appear (Carabello, 2007). Table 1.2 reports the indications for aortic valve replacement in both aortic stenosis and regurgitation (Reddy & Punjaby, 2007).

Table 1.2 *Indications for Aortic Valve Replacement in Aortic Stenosis and Chronic Aortic Regurgitation*

Aortic stenosis	**Aortic regurgitation**
Symptomatic severe aortic stenosis	Symptomatic severe aortic regurgitation
Asymptomatic patients with severe/moderate aortic stenosis undergoing associated heart surgery (coronary artery bypass graft; surgery on other heart valves/aorta)	Asymptomatic severe/moderate aortic regurgitation and: • left ventricular systolic dysfunction • undergoing associated heart surgery (coronary artery bypass graft, surgery on the aorta/other heart valves) • severe left ventricular dilation (end-diastolic diameter > 75 mm, end-systolic dimension > 55 mm)
Asymptomatic severe aortic stenosis and: • left ventricular systolic dysfunction • abnormal response to exercise (e.g. hypotension) • ventricular tachycardia • marked or excessive left ventricular hypertrophy (> 15 mm) • valve area < 0.6 cm^2	

From Reddy & Punjaby, 2007 (modified)

Mitral Valve Diseases

Mitral stenosis is still predominantly rheumatic in origin. The valvular lesions produced by the rheumatic process in patients with mitral stenosis are characterized by leaflet thickening, calcification, commissural fusion, chordal fusion or a combination of these processes (Enriquez-Sarano & Frye, 2007). The reduction of mitral orifice size during diastole and the loss of physiological valvular reserve (i.e., fixed mitral orifice irrespective of blood flow) are induced by the commissural fusion (Messika-Zeitoun et al., 2003; Mohan et al., 2002). When the normal area of the mitral valve (4 - 6 cm^2) is reduced to an area of 2 - 2.5 cm^2 (i.e., mild mitral stenosis), left atrial pressure is normal under resting condition, whereas it may abnormally increase with heart rate changes or excessive blood flow. As stenosis worsens (1.5 - 2 cm^2, i.e., moderate mitral stenosis), adequate left ventricular filling demands a progressive increase in left atrial pressure at rest, which establishes a diastolic pressure gradient across the mitral valve, and may increase markedly during sustained

exercise. Left atrial pressure is increased at rest and reduced cardiac output as well as dyspnea during mild exercise or even at rest occur when mitral orifice is < 1.5 cm^2 (i.e., severe mitral stenosis). The left atrial dilation is the compensatory mechanism elicited by increased pressure in the left atrium caused by mitral stenosis. This compensatory mechanism may induce atrial fibrillation and compromise left ventricular filling further due to loss of atrial systole and the rapid heart rate, which reduces diastolic filling time (Reddy & Punjaby, 2007). The onset of atrial fibrillation often produces abrupt clinical deterioration and is responsible for approximately a 20% reduction in cardiac output (Enriquez-Sarano & Frye, 2007). Also, left atrial dilation may lead to thrombus formation caused by increased local coagulability and reduced blood flow (Boyaci et al., 2004; Chen et al., 2003). Chronically elevated left atrial pressure causes pulmonary congestion and excessively elevated pulmonary pressure, leading to right ventricular dilation, tricuspid regurgitation, and to global heart failure (Fawzy et al., 2004). Life-threatening pulmonary edema occurs in advanced disease. Fatigue, dyspnea, and orthopnea are symptoms of mitral stenosis.

Mitral regurgitation is characterized by abnormal reversed blood flow from the left ventricular to the left atrium. Etiologic mechanism(s) can be organic if there is an intrinsic valve disease or functional if the valve is structurally normal but regurgitates due to an extravalvular abnormality (Enriquez-Sarano & Frye, 2007). The leaflet abnormalities include thickening (rheumatic disease), perforation (infective endocarditis) or prolapsed (i.e., organic etiology), whereas dilation of the left ventricle results in functional mitral regurgitation (i.e., functional etiology). Mitral regurgitation is often induced by degenerative etiology which, in turn, can be categorized as follows:

- *Mitral valve prolapse* with diffuse myxomatous infiltration. Mitral valve prolapse is a common and usually asymptomatic condition in which one or both of the mitral valve leaflets

bulge backwards into the left atrium during systole, producing mitral regurgitation. Most cases are idiopathic, characterized by myxomatous degeneration of the valve leaflet tissue.

- *Chordal rupture* usually occurs in patients aged > 50 years and involves more often the posterior than the anterior leaflet. It produces acute mitral regurgitation, the severity of which relates to the extent of chordal rupture.

- *Degenerative mitral regurgitation without prolapse* is usually associated with valve calcification or valve sclerosis, in which deformation of the valves or annulus is the main cause of regurgitation.

Ischemia, scarring, aneurysm, cardiomyopathy, or myocarditis can lead to left ventricular dysfunction and, therefore, to mitral regurgitation (i.e., ischemic and functional etiologies). Dysfunction or rupture of the papillary muscles related to infarction of the adjacent ventricular wall causes mitral regurgitation due to the flail leaflet.

Mitral regurgitation during systole volume-loads the left ventricle due to increased filling from the left atrium. Compensatory dilation and hypertrophy of the left ventricle occur in chronic disease. Progressive dilation of the left atrium prevents marked elevation of atrial pressure, and protects against the development of pulmonary hypertension and pulmonary edema. In acute mitral regurgitation characterized by pulmonary edema, symptoms are abrupt in origin whereas chronic mitral regurgitation remains asymptomatic until the left ventricle begins to fail. Fatigue, dyspnea, and orthopnea are symptoms of mitral regurgitation. Indications for mitral valve replacement in both mitral valve diseases, mitral stenosis and regurgitation, are reported in Table 1.3 (Reddy & Punjaby, 2007).

Table 1.3 *Indications for Mitral Valve Replacement in Mitral Stenosis and Chronic Mitral Regurgitation*

Mitral stenosis	**Mitral regurgitation**
Symptomatic moderate/severe mitral stenosis	Symptomatic severe mitral regurgitation
Asymptomatic moderate/severe mitral stenosis associated with: • pulmonary artery systolic pressure > 50 mmHg • recurrent embolic events on adequate anticoagulation • recent-onset atrial fibrillation	Asymptomatic severe mitral regurgitation with: • left ventricular dysfunction (left ventricular ejection fraction <60%) • left ventricular end-systolic diameter > 45 mm • pulmonary hypertension (pulmonary arterial systolic pressure > 50 mmHg) • recent-onset atrial fibrillation

From Reddy & Punjaby, 2007 (modified)

Tricuspid Valve Diseases

Tricuspid stenosis is usually rheumatic in origin and its anatomical features are similar to mitral stenosis, with fusion and shortening of the chordae and leaflet thickening. A reduction greater than 1.5 cm^2 in tricuspid valve area is related to increase of right atrial pressure and establishes a pressure gradient across the valve. When valve area is less than 1 cm^2, severe tricuspid stenosis occurs (Hess, Scherrer, Nicod, & Carabello, 2007). Pulmonary flow decrease may be associated with tricuspid stenosis increase: although this phenomenon may induce a paradoxical symptomatic improvement in patients with mitral stenosis by reducing pulmonary capillary pressure as well as pulmonary artery pressure, reduced cardiac output and right heart failure usually occur (Reddy & Punjaby, 2007). Dyspnea may improve as tricuspid stenosis becomes more severe, but it is replaced by symptoms of right heart failure (e.g., ascites, hepatomegaly, and edema). Despite tricuspid stenosis is mild and hemodynamically unimportant in most cases, severe tricuspid stenosis should be treated with valve surgery.

Tricuspid regurgitation is usually seen with dilation of the right ventricle, tricuspid annulus, right atrial myxoma, Ebstein's anomaly, carcinoid syndrome, endocarditis,

myxomatous degeneration of the tricuspid valve leaflets and supporting structures. Moreover, tricuspid regurgitation is usually functional and secondary to mitral valve disease (Hess et al., 2007). Tricuspid regurgitation volume-loads the right ventricle and leads to the symptoms and signs of right heart failure (e.g. edema, hepatomegaly, ascites, and muscular fatigue) caused by low cardiac output (Reddy & Punjaby, 2007).

Pulmonary Valve Diseases

Acquired pulmonary valve disease is extremely rare. The most common pulmonary valvular abnormality is the *pulmonary regurgitation* secondary to dilation of the valve ring in patients with severe mitral valve disease and in those with severe pulmonary hypertension. Infective endocarditis and rheumatic inflammation of the pulmonary valve may be seen. Physical symptoms of pulmonary regurgitation vary according to the presence or absence of pulmonary hypertension. Pulmonary regurgitation is well tolerated, producing negligible hemodynamic embarrassment. Prognosis is determined by the associated pulmonary hypertension (Hess et al., 2007).

Heart Valve Surgery

Heart valve disease can be surgically treated in three ways: 1) the injured *valve* can be surgically *reconstructed*; 2) constricted openings can be enlarged with a *balloon catheter*; 3) the *valve* can be *replaced*, either with an artificial valve or with a healthy valve from a pig's heart.

Surgical repair is usually performed on the mitral valve, particularly to relieve mitral stenosis with minimal or no calcification and mitral regurgitation. The procedure is the same as for other forms of open-heart surgery. The heart is stilled and the left atrial chamber opened, then the leaflets are reconstructed to allow the valve to close properly. The surgeon

can separate the leaflets and suture any damaged edges to ensure that they close efficiently whether the leaflets of the mitral valve have become stuck together as the result of rheumatic fever. Given there is no new valve to wear out, the advantage of this surgery is that the patient ordinarily does not have to follow a regimen of blood thinners as he or she would with a mechanical heart valve replacement.

In order to alleviate symptomatic rheumatic mitral stenosis, a balloon catheter can be used (i.e., percutaneous mitral balloon commissurotomy). The balloon catheter is usually used to open the leaflets enough to separate them from each other to accomplish this, the balloon catheter is threaded through the valve. When it is placed, the balloon at the tip of the catheter is inflated gently until it enlarges the opening. It produces good immediate hemodynamic outcome, results in clinical improvement in the majority of patients with mitral valve and has a low complication rate. Today, percutaneous mitral balloon commissurotomy is the preferred treatment for mitral stenosis for a selected group of patients with symptomatic rheumatic mitral stenosis (for details see, Palacios & Sanchez, 2007). In contrast, this procedure is rarely used for aortic stenosis because balloon dilation is not effective, and there is a risk that the calcified leaflets will break off and enter the bloodstream, causing a stroke.

For patients with extensive mitral valve calcification or severe fibrotic distortion and for those with aortic diseases (i.e., stenosis and regurgitation), valve replacement is the only option. Valve replacement is performed during open-heart surgery. Artificial valves are carefully sutured or sewn into the ring surrounding the valve opening, completely replacing the natural valve. Approximately 80% of patients who survive the first postoperative year are able to return to normal activity, even though those may previously have been severely restricted by fainting spells, by angina or by breathlessness from heart failure. The downside of the operation is that it causes a 5% mortality risk (somewhat higher than for CABG), partly because of the possibility of a stroke caused by loosened calcium latter being a risk in

any open-heart surgery. Convalescence may also be prolonged, especially for older people. An alternative to mechanical valves is the use of bioprostheses which are valves from pigs (Reddy & Punjaby, 2007). Although bioprostheses are less durable than mechanical valves and are vulnerable to structural deterioration, the newer generation of bioprosthetic valves offers longer operative-free survival than previous models (Cohn, Frazier, & Cooley, 2007).

1.1.3 Aneurysm of Ascending Aorta

Acquired diseases of the aorta are primarily induced by degenerative changes in the aortic wall. Aging, inflammation, connective tissue diseases, arteriosclerosis and hypertension are demographic and biomedical risk factors for the degeneration of the aorta and, therefore, for acquired aortic diseases. Among aortic diseases, thoracic aortic aneurysms may be located in the aortic root, transverse arch, thoraco-abdominal, descending, and ascending aorta. Specifically, aneurysms in the ascending aorta are induced by dissection or medial degeneration in more than 95% of cases. A generalized dilation of the aortic root (i.e., annuloaortic ectasia) can occur due to medial degenerative changes. Annuloaortic ectasia is often related to Marfan syndrome that is an inherited, autosomal disorder characterized by connective tissue defects. When thoracic aneurysms in the ascending aorta are greater than 5 cm in diameter, the rupture may occur (Davies et al., 2002; Juvonen et al., 1997).

The development of hypothermic circulatory arrest enabled surgeons to operate on aortic aneurysms in an unobstructed and dry operative field. The aneurysms of the ascending aorta are replaced with low-porosity woven Dacron graft. Aortic replacement is recommended for repair in patients with Marfan syndrome. A composite valve graft (bioprosthetic or mechanical valve), a stentless porcine root or a cryopreserved homograft is used to replace diseased aortic root. Although aortic root replacement is also performed in patients with annuloaortic ectasia, some groups have used aortic valve sparing techniques in selected patients (Birks, Webb, Child, Radley-Smith, & Yacoub, 1999; Gott et al., 1996).

These methods remove the entire aneurismal segment and reconstruct the aorta with a Dracon graft; however, the native valve is replaced into the inner wall of the graft where the valve can perform its normal function. These methods lower the risk of thrombosis and obviate the need for anticoagulants after surgery. Despite these advantages, the valve sparing techniques in patients with connective tissues disorders are still debated.

1.2 Why Cardiac Surgery is associated with Postoperative Cognitive Decline?

Adverse neurological outcome and postoperative cognitive decline (POCD) are complications which occur frequently after cardiac surgery with an incidence of approximately 4% (Roach et al., 1996) and 50% (Newman et al., 2001), respectively. Adverse neurological and cognitive outcomes are the result of multiple preoperative factors, including biomedical and psychological dysfunctions as well as intraoperative events such as cerebral hypoperfusion, embolization or neuroinflammatory processes related to cardiopulmonary bypass (CPB) during surgery. In particular, while adverse cerebral outcomes such as focal neurological lesions strokes or transient ischemic attack mainly occur due to macroemboli production (62%) (Arrowsmith, Grocott, Reves, & Newman, 2000; Kam & Calcroft, 1997; Magdy, 2007), adverse psychological outcomes such as generalized cognitive decline have been observed following intraoperative cerebral hypoperfusion as well as microembolization (Likosky, Caplan, & Weintraub, 2004; Liu et al., 2009; Roach et al., 1996; Stump, Rogers, Hammon, & Newman, 1996).

CPB can cause cognitive deficits through several mechanisms, but cerebral microembolization and hypoperfusion are believed to be the most important. With respect to microembolization, Abu-Omar, Balacumaraswami, Pigott, Matthews, & Taggart (2004) found that, compared to off-pump CABG (i.e., without CPB), there is a 7-fold increase in microemboli in on-pump CABG (i.e., with CPB) and a 22-fold increase in open procedures (e.g., heart valve surgery, and combined procedure) (Table 1.4).

Table 1.4 *Number and Proportion of Gaseous and Solid Microemboli Detected in Three Patient Groups*

	Microemboli		
Procedure	Total median (IQR)	Gaseous (%)	Solid (%)
OPCABG	40 (28–80)*	88	12†
ONCABG	275 (199–472)*	72	28†
Open procedures	860 (393–1321)*	78	22†

Note: *Comparison of the total number of microemboli between the 3 groups: $p < .01$. †Comparison of the proportion of gas and solid microemboli in the 3 groups: $p < .05$. IQR = interquartile range; OPCABG = off-pump coronary artery bypass graft; ONCABG = on-pump coronary artery bypass graft. From Abu-Omar et al., 2004 (modified)

Possible sources of cerebral microemboli during on-pump CABG and open procedures may be the ascending aorta, carotid arteries, intracerebral arteries, or intracardiac cavities (Borger, Ivanov, Weisel, Rao & Peniston, 2001). Specifically, the potential source of solid microembolization may be the left atrial appendage and left ventricle; particles may form within the bypass circuit whether the anticoagulation is inadequate (Abu-Omar et al., 2004). Lipid microembolization during CPB may arise from the use of cardiotomy suction and denaturation of proteins, whereas the manipulation of atherosclerotic aorta may result in cholesterol microemboli (Barbut et al., 1994). Moreover, blood cell aggregation and platelet during CPB can represent other source of microembolic load. On the other hand, the potential source of gaseous microemboli during CPB is air entering the coronary artery during arteriotomy and being returned to the left ventricle through the Thebesian veins (Abu-Omar et al., 2004). Gaseous microemboli can also enter the central venous lines via the venous cannula of CPB. Gaseous microembolization may enter the circulation during the flushing and filling of coronary conduits, at initiation of CPB, through the bypass circuit and during cardiac ejection after open procedures. Also, gaseous microemboli are more likely to grow in size during rewarming when gas solubility decreases.

Interestingly, Abu-Omar et al. (2004) reported that the largest proportion of microemboli occurred during aortic manipulation in patients undergoing on-pump surgery (cannulation, decannulation, and application and removal of crossclamp and sideclamp) (Table 1.5). Specifically, Abu-Omar et al. showed that aortic manipulation accounts for approximately 56% of the total microembolic load, whereas 24% occurred during CPB. Indeed, the ascending aorta is the site of surgical manipulation during CABG (i.e., cannaluation/decannulation, cross-clamp application/removal), whereas other potential sources of emboli are not mechanically manipulated (Barbut et al., 1994). Embolization of the atherosclerotic debris can also occur when the aorta is not surgically manipulated because of the "sandblast" of the CPB (Borger, Ivanov, et al., 2001).

Table 1.5 *Number and Proportion of Microemboli during Different Events in Patients Undergoing On-Pump Surgery*

	Total gas and solid		Gaseous		Solid	
Operative event	Median (IQR)	Percentage of total	Median (IQR)	Percentage of total gas	Median (IQR)	Percentage of total solids
Aortic cannulation and crossclamping	26 (8–67)	13%	41 (20–100)	13%	8 (3–30)	12%
During CPB	145 (60–265)	24%	108 (43–199)	24%	24 (9–76)	26%
Removal of aortic crossclamp, sideclamping, decannulation	148 (56–504)	43%	123 (43–381)	42%	31 (6–135)	46%
Other (chest opening and closure, harvesting of conduits)	11 (2–68)	20%	6 (1–59)	21%	2 (0–8)	16%

Note: IQR = interquartile range; CPB = cardiopulmonary bypass. From Abu-Omar et al., 2004 (modified)

Along with microembolization, cerebral hypoperfusion is an important intraoperative risk factor for POCD (Fearn et al., 2001; Likoski et al., 2004). The most vulnerable areas of the brain in hypoperfusion are the watershed areas at the junction of the major cerebral arterial territories (Gilman, 1965). During CPB, systemic flow rate is usually based on body surface and the degree of hypothermia and adjusted according to indices of the adequacy of organ perfusion. It is well-established that low pump flow with concurrently arterial

hypotension is related to decreased cerebral blood flow. Specifically, Soma and colleagues (1989) showed that cerebral blood flow is directly related with pump flow rate, despite the independent effects of mean arterial pressure and pump flow rate on cerebral blood flow remain still controversial (for a review see Arrowsmith et al., 2000). Importantly, non-pulsatile perfusion has been linked to reduced endothelial shear stress and nitric oxide production which, in turn, may lead to increased vascular resistance and end-organ dysfunction (Macha et al., 1996). In addition to systemic (arterial or "pump") blood flow and cerebral perfusion pressure, cerebral blood flow is influenced by other factors including temperature, acid-base management strategy, oxygen saturation, depth of anesthesia and packed cell volume (Schell et al., 1993). Interestingly, cerebral hypoperfusion seems to be strongly influenced by the duration of CPB. Indeed, several studies have shown that patients who have prolonged duration of CPB are at greater risk of cerebral hypoperfusion (and microembolization) and, therefore, are at greater risk of postoperative neurological and cognitive dysfunctions. The progressive cerebral vasoconstriction, which occurs during prolonged duration of CPB, may lead to a gradual decrease in cerebral blood flow (Prough et al., 1991; Rogers et al., 1988), which, in turn, is associated with adverse cognitive outcome in cardiac surgery patients. Moreover, a prolonged CPB has been related to a patient's inability to produce sufficient cardiac output. These patients are more prone to developing a hypoperfusive brain lesions and POCD (Likoski et al., 2004). Thus, although the influence of systemic blood flow, flow character and cerebral arterial pressure on cerebral blood flow during CPB is still debated, prolonged periods of cerebral hypoperfusion and arterial hypotension can be considered relevant intraoperative risk factors for adverse cognitive outcome (Arrowsmith et al., 2000; Fearn et al., 2001).

In recent years, however, some studies have raised important questions about the mechanisms underlying neurological and cognitive dysfunctions after cardiac surgery. In

particular, Jensen, Hughes, Rasmussen, Pedersen, & Steinbrüchel (2006) showed, in a randomized prospective controlled trial, that POCD was similar in patients undergone off-pump and on-pump CABG. If, as Jensen et al. (2006) have shown in their study, the incidence of cognitive decline is not influenced by the presence (i.e., on-pump) or the absence (i.e., off-pump) of CPB and if, as the large body of studies has shown in the last two decades, microemboli are the major causes of POCD, the potential mechanisms underlying postoperative cognitive deficits have to be further investigated (Samuels, 2006). On the one hand, it can be suggested that microembolization cannot be completely attributed to extracorporeal circulation as previously believed. The manipulation of the heart and great vessels and clamping and declamping of the aorta, required to implant the grafts in off-pump CABG, even without breaching the cardiac chambers, is likely to be enough to release showers of microemboli which, in turn, produce the most common cognitive deficits such as lack of memory, confusion or inattention (Samuels, 2006). On the other hand, it is clear that other risk factors are implicated in postoperative cognitive deficits than intraoperative microembolization and cerebral hypoperfusion related to extracorporeal circulation. It is noteworthy that preoperative demographic, psychological and biomedical variables can represent important risk factors for POCD. Specifically, patient's age, education level and gender are significant predictors of postoperative cognitive outcome after cardiac surgery (Arrowsmith et al., 2000). Along with demographic variables, emotional disorders, especially anxiety and depression, can affect postoperative cognitive performance (Andrew, Baker, Kneebone, & Knight, 2000; Stroobant & Vingerhoets, 2008). Furthermore, patients with more severe cardiac disease and cardiac dysfunctions and with preoperative cerebrovascular disease (e.g., history of stroke, and transient ischemic attack) are more likely to sustain perioperative and postoperative cognitive dysfunctions (Savageau, Stanton, Jenkins, & Klein, 1982; Shaw et al., 1987; Sotaniemi, 1980; Turnipseed, Berkoff, Belzer, 1980). Also, there is

evidence that the presence of diabetes mellitus is a risk factor for poor cognitive outcome because it may impair cerebral blood flow autoregulation that is characterized by increased oxygen extraction, during CPB (Croughwell et al., 1990). Finally, it has recently been shown that genetic factors may account for adverse cognitive outcome in patients after cardiac surgery (Newman et al., 1995, Newman et al., 1994). The possession of apolipoprotein E ε-4 allele has been linked to decline in several cognitive functions at discharge from the hospital and 6 weeks after surgery (Tardiff et al., 1997).

Taken together, these findings suggest that postoperative adverse cognitive outcome has a multifactorial etiology that includes an interaction between pre and intraoperative risk factors. In the next Chapters, pre and intraoperative risk factors for POCD in patients undergoing cardiac surgery will be described.

1.2.1 Transcranial Doppler Findings: the role of Intraoperative Cerebral Hypoperfusion and Microembolization in Cognitive Decline

Transcranial Doppler instruments analyze blood flow by having the sound source and the observer at the same location (i.e. the transducer). The ultrasonic beam crosses the intact adult skull at points known as "windows" and is reflected by the blood cells of all blood vessels flowing in its path. There are three natural ultrasonic cranial windows. They comprise locations where the bone is sufficiently thin to allow penetration with the ultrasound beam, or are located where natural foramina serve the same purpose. The three ultrasonic windows in the cranium, which are used for insonation of the major intracranial arteries, are the *transtemporal*, *transforaminal* or *suboccipital*, and *transorbital* windows. The window is selected according to the vascular pathway that is intended to study. These windows allow direct assessment of the middle cerebral artery (left and right), the posterior cerebral artery (left and right), the anterior cerebral artery (left and right), the internal carotid artery (left and right), the basilar artery, or the anterior communicating artery (Figure 1.3), which, along with posterior communicating artery (left and right), are considered part of the Circle of Willis (Moore & Dalley, 2007; Purves et al., 2008).

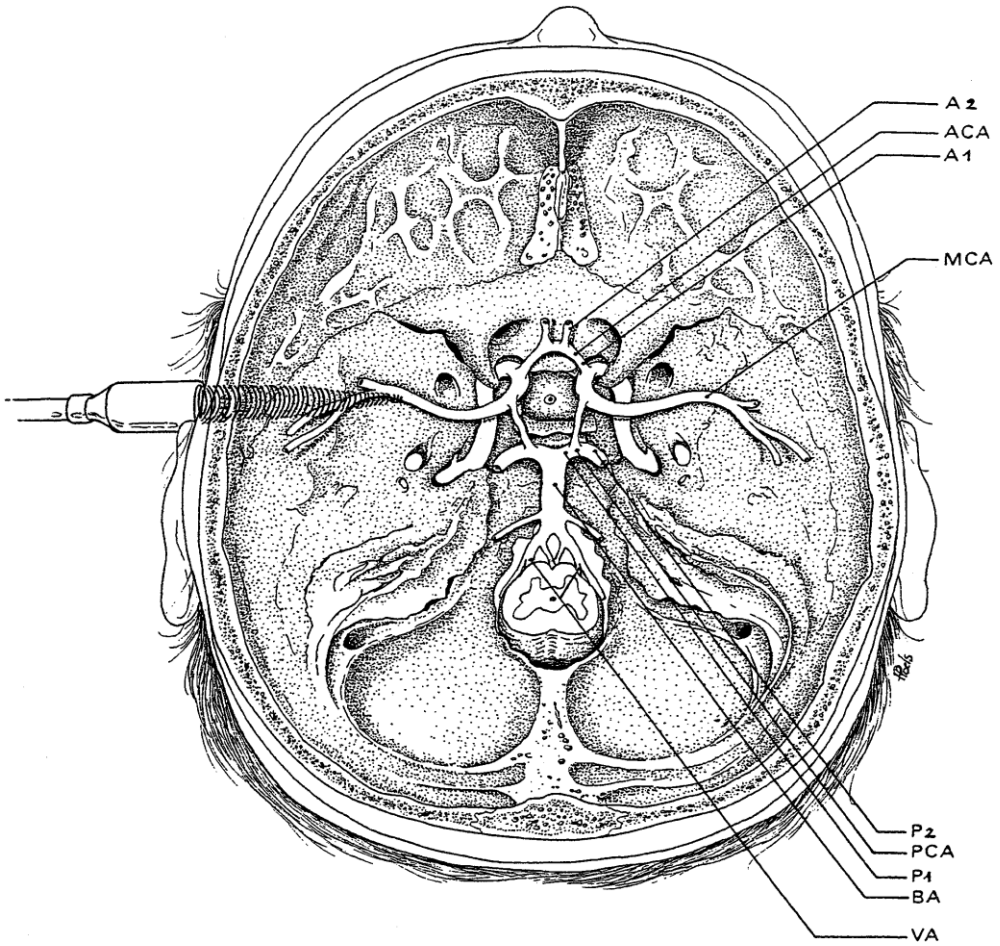

Figure 1.3 Insonated vessels: the middle (MCA), anterior (ACA with A1 and A2), and posterior (PCA with P1 and P2) cerebral arteries may be sampled through the thin temporal bone. The basilar arteries (BA) and vertebral arteries (VA) can also be measured. From Stroobant & Vingerhoets, 2000

The Circle of Willis is a circle of arteries that supply blood to the brain. The arrangements of the brain's arteries into the Circle of Willis create redundancies or collaterals in the cerebral circulation. Therefore, if one part of the circle or one of the arteries supplying the circle becomes narrowed or blocked (stenosed), blood flow from other blood vessels can often preserve the cerebral perfusion to avoid symptoms of ischemia (de Boorder et al., 2006). Specifically, the right and left posterior cerebral arteries arise from the basilar artery, which is formed by the left and right vertebral arteries. The left and right internal carotid arteries arise from the right and the left common carotid arteries. The posterior communicating artery is given off as a branch of the internal carotid artery just before it

divides into its terminal branches – the middle cerebral arteries and anterior cerebral arteries. Finally, the anterior communicating artery connects the two anterior cerebral arteries which, in turn, form the anterolateral portion of the Circle of Willis (Figure 1.4).

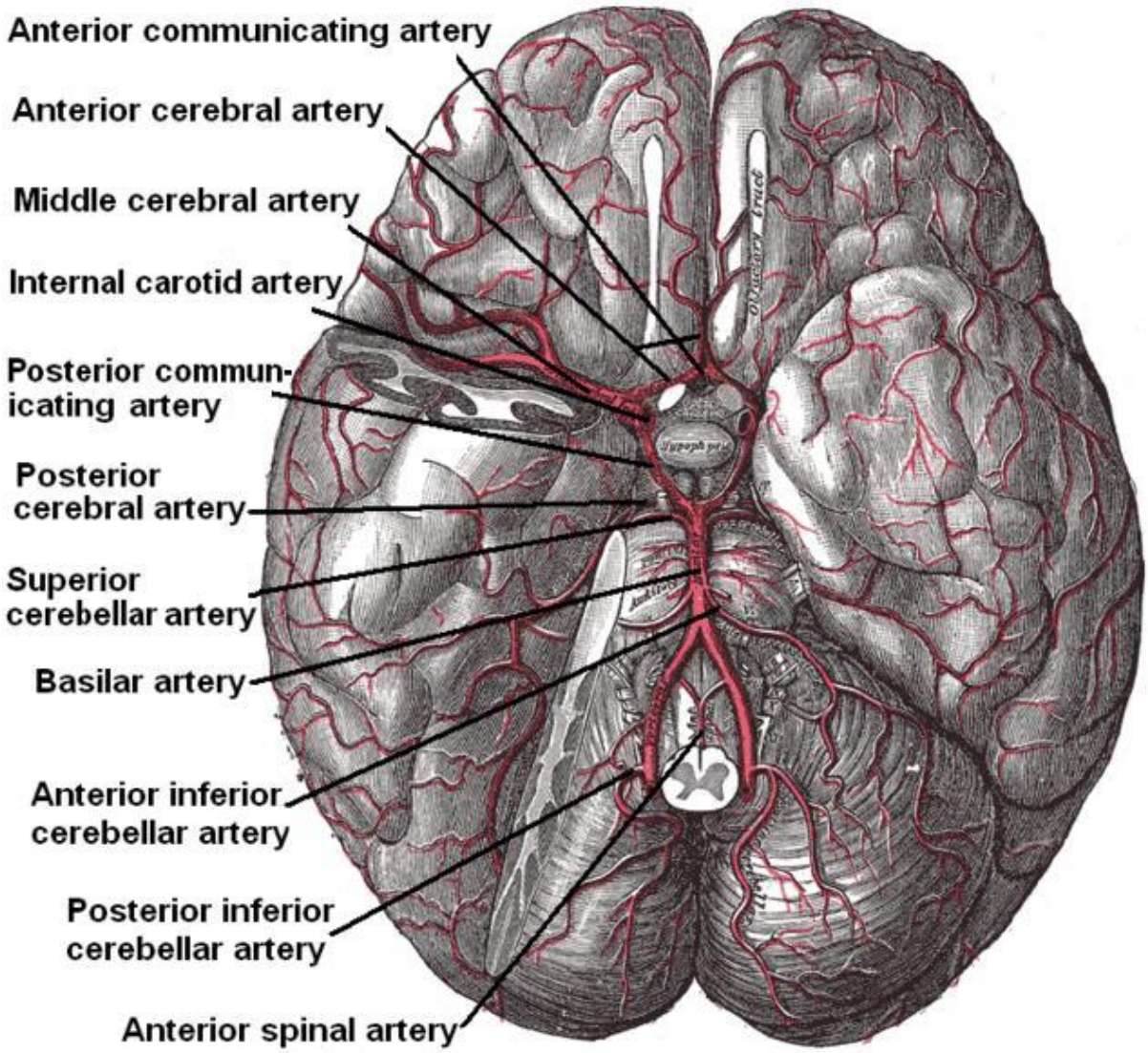

Figure 1.4 The brain and arteries at base of the brain. Circle of Willis is formed near center. The temporal pole of the cerebrum and a portion of the cerebellar hemisphere have been removed on the right side. Inferior aspect (viewed from below).

Thus far, the transtemporal window is the most commonly insonated in transcranial Doppler cognitive activation studies because the middle cerebral artery is the direct continuation of internal carotid arteries and carries 70-80% of the total hemispheric blood

flow (Figure 1.5). The branches of the middle cerebral arteries irrigate the frontal lobe with orbitofrontal, prefrontal, pre-Rolandic and Rolandic arteries, the parietal lobe with the anterior parietal, posterior parietal, angular and temporaloccipital arteries, and the temporal lobe with temporopolar, anterior temporal, middle temporal, and posterior temporal arteries. Moreover, middle cerebral arteries are the usually easiest arteries to find and most sonographers make them their first target in a transcranial Doppler exam. More importantly, middle cerebral arteries studies showed significant cerebral blood flow velocity increases during cognitive tasks, whereas posterior cerebral arteries measurement has been preferred for perceptual visual-stimulation studies given the importance of posterior brain regions in visual perception (for a review see Stroobant & Vingerhoets, 2000). Also, there is evidence for important rise in cerebral blood flow velocity in anterior cerebral arteries during mathematical tasks (Kelley et al., 1992). Cerebral blood flow velocity in other basal cerebral arteries has been rarely linked to cognitive performances and, therefore, has been rarely investigated in transcranial Doppler activation studies.

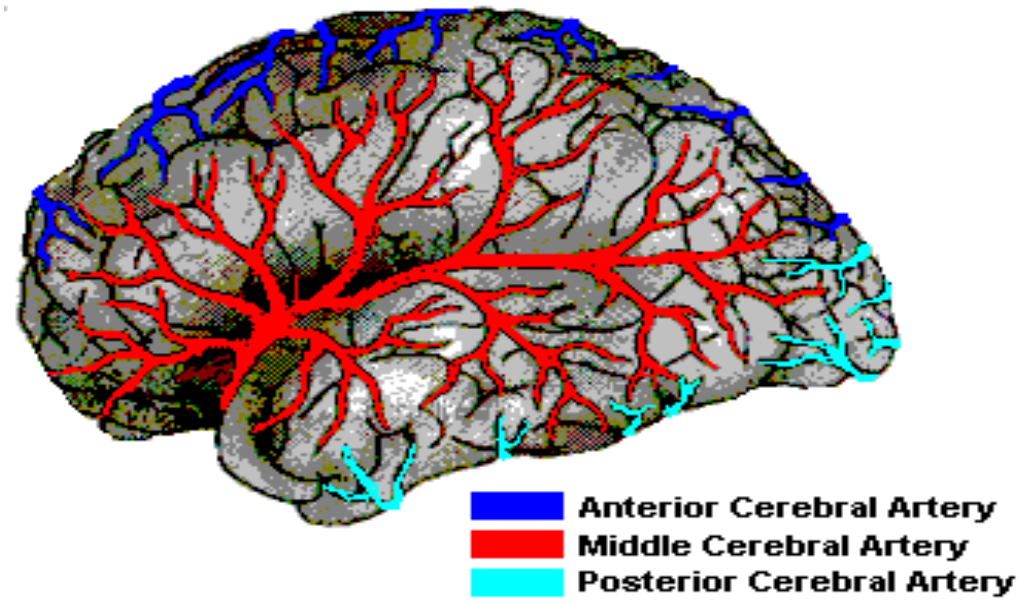

Figure 1.5 Brain areas irrigated by the anterior cerebral arteries, middle cerebral arteries and posterior cerebral arteries.

Once the middle cerebral arteries are detected, spectral analysis or Fast Fourier Transformation analysis allows a visual display and further analysis of the received signal. In short, Fast Fourier Transformation analysis provides a way of presenting three-dimensional Doppler data in two dimensions. Velocity (or frequency) is displayed on the vertical scale, time on the horizontal scale, and signal intensity (amplitude) is displayed as the brightness of a point. The maximum velocity follower (envelope curve) is a line drawn electronically on the visual Fast Fourier Transformation display, corresponding to the maximum velocity of the cardiac cycle. The most common type of mean velocity used is time-averaged, area-averaged mean velocity value derived by placing a line on the horizontal axis of the envelope curve of the cardiac cycle so that the area above the line, V1, is equal to the area below the line, V2 (Figure 1.6) (McCartney, Thomas-Lukes, & Gomez, 1997). This measure is also considered as the mean of the maximum velocities. In many studies the mean velocity and cerebral blood flow velocity are used interchangeably. Therefore, mean velocity values are ordinarily used for data recording and analysis in calculating average velocities over certain time of period (e.g., at rest or when a cognitive task is performed). The cerebral blood flow velocity is expressed in cm/s.

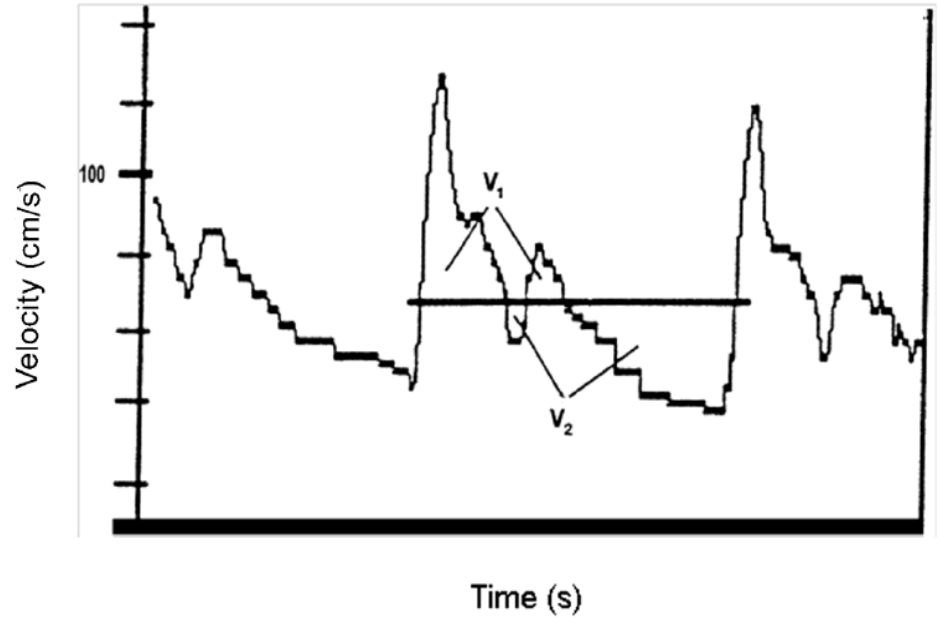

Figure 1.6 Time-averaged (mean) CBF velocity, denoted by the horizontal line. The areas above (V1) and below (V2) this line are equal. Vertical line (y-axis) = velocity (cm/s); horizontal line (x-axis) = time (s). From McCartney et al., 1997

Transcranial Doppler sonography has been widely used during cardiac surgery to examine cerebral hemodynamics in order to detect microembolization and to assess cerebral blood flow velocity (Russel & Brucher, 2002; Stump et al., 1996). In particular, intraoperative microembolization can be detected with transcranial Doppler as the amount of reflected ultrasound caused by an embolus is great compared to that normally caused by the red blood cells (Figure 1.7).

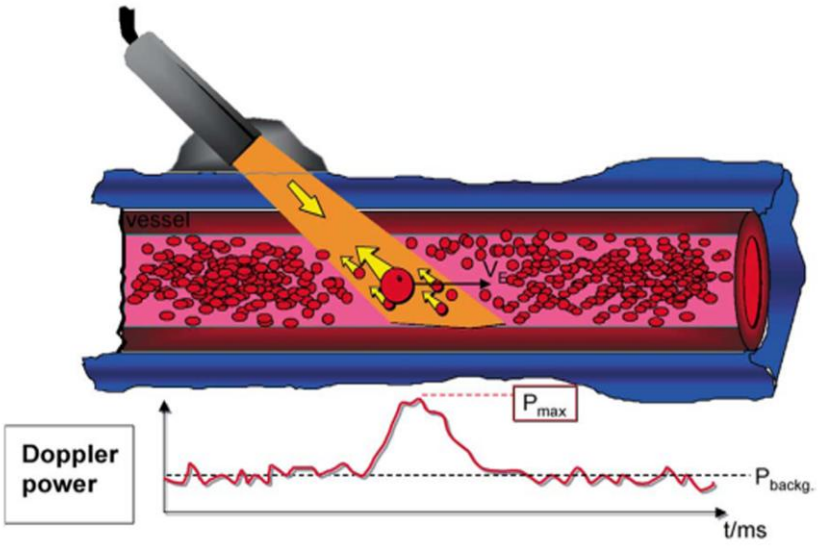

Figure 1.7 Cerebral microembolus detection using ultrasound showing an increase of reflected ultrasound power (Pmax) caused by an embolus compared to the background power (Pbackg.) reflected by red blood cells. From Russel, 2002

Although microembolization may not cause immediate symptoms, there is evidence that it may cause cognitive impairment if emboli enter the cerebral circulation in significant numbers (Pugsley, Klinger, & Paschahs, 1994). Indeed, transcranial Doppler studies have recently confirmed that intraoperative microembolization and hypoperfusion are directly associated with POCD (Hogue, Gottesman, & Stearns, 2008; Russel, 2002), especially with attentional (Borger, Peniston, et al., 2001; Deklunder, Prat, Lecroart, Roussel, & Dauzat, 1998; Deklunder, Roussel, Lecroart, Prat, & Gautier, 1998; Fearn et al., 2001; Pugsley et al., 1994; Stump et al., 1996), short-term and episodic memory (Borger, Peniston, et al., 2001, Pugsley et al., 1994; Stump et al., 1996), working memory (Deklunder, Prat, et al., 1998; Deklunder, Roussel, et al., 1998; Fearn et al., 2001), and psychomotor dysfunctions (Borger, Peniston, et al., 2001; Deklunder, Roussel, et al., 1998; Pugsley et al., 1994) after cardiac surgery. Specifically, Pugsley and colleagues (1994) showed that when the number of microemboli was higher than 1,000 during CABG surgery, 43% of patients had POCD at

their cognitive evaluations at eight weeks compared with 8.6% of patients with fewer than 200 microemboli. More recently, several studies using transcranial Doppler monitoring during surgery have replicated this finding, showing that the number of microemboli is directly associated with early POCD (Deklunder, Roussel, et al., 1998; Fearn et al., 2001). In addition, Stump and colleagues (1996) suggested that hypoperfusion may be the main cause of POCD when cerebral perfusion is decreased in order to minimize intraoperative microembolization. Hypoperfusion may also limit the washout of emboli: the watershed cerebral zones represent preferred sites for persistent microemboli in the cerebral circulation.

Interestingly, a few studies have also investigated the potential role of asymmetric intraoperative cerebral microembolization and hypoperfusion in cognitive decline (Bokeriia et al., 2007; Fearn et al., 2001; Jacobs et al., 1998; Lee et al., 2003). Jacobs and colleagues (1998) found that POCD in both nonverbal and verbal tasks was associated with microembolization in the right middle cerebral artery in patients whose right hemisphere was dominant. An association between POCD (especially in verbal memory tasks i.e. the Digit Span Test forward) and microembolization in the left middle cerebral artery was also observed in patients with left hemisphere predominance (Bokeriia et al., 2007; Fearn et al., 2001; Lee et al., 2003). Further evidence indicates that intraoperative hypoperfusion in the left, not in the right, middle cerebral artery is associated with early verbal POCD (Fearn et al., 2001). Taken together, these findings indicate that intraoperative cerebral microembolization and hypoperfusion may induce specific cognitive impairment in accordance to the brain region to which those are delivered, also suggesting a differential impact of lateralized intraoperative events on postoperative cognitive dysfunctions.

1.2.2 Electroencephalography and Event-Related Potentials: Evidence for Cognitive Decline

Electroencephalography (EEG) has been used pre, intra and postoperatively to detect changes in brain function which, in turn, may be associated with adverse neurological and cognitive outcomes (Bashein et al., 1992; Edmonds, Griffiths, Van der Laken, Slater, & Shields, 1992; John, Prichep, Chabot, & Isom, 1989; Toner, Newman, Taylor, & Smith, 1997). EEG is the recording of electrical activity along the scalp. EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain (Niedermeyer & da Silva, 2004). EEG activity reflects the summation of the synchronous activity of thousands or millions of neurons that have similar spatial orientation. In particular, pyramidal neurons of the cortex are the source of the most EEG signal because they are well-aligned and fire together. Scalp EEG activity shows oscillation at a variety of frequencies. Several of these oscillations have characteristic frequency ranges, spatial distribution and are associated with different states of cerebral functioning (e.g., cognitive activity, waking, and meditation). Most of cerebral signal observed in the scalp EEG falls in the range of 1-30 Hz (activity above or below this range is likely to be artifactual under standard clinical recording techniques). The main frequency bands are:

1. Delta (δ) is the frequency up to 4 Hz. It is seen normally in babies; it is also seen in adults during slow wave sleep. It may occur focally with subcortical lesions and in general distribution with diffuse lesions, metabolic encephalopathy hydrocephalus or deep midline lesions.
2. Theta (θ) ranges from 4 Hz to 7.5 Hz and is seen normally in young children. However, it may be seen abnormally in drowsiness or arousal in older children and adults. Excessive θ for age is abnormal activity: it can be seen in focal subcortical lesions (Hughes & John, 1999) and in generalized distribution in

diffuse disorder or metabolic encephalopathy or deep midline disorders. In contrast, it has been also associated with reports of relaxed, creative, and meditative states (Cahn & Polich, 2006).

3. Alpha (α) ranges from 8 Hz to 12 Hz. This is a "posterior basic rhythm" seen in parietal and occipital regions of cortex on both hemispheres. It emerges with closing eyes and with relaxation, and attenuates with eye opening or during cognitive activity. Also, a diffuse α can be abnormal and occur in comatose patients.
4. Beta (β) ranges from 13 Hz to 30 Hz and is seen usually on both hemispheres in symmetrical distribution and is most evident in frontal regions. β is linked to mental activity (Steriade, 1999), active concentration but also with anxiety and obsessive thoughts. Rhythmic β is associated with various pathologies and drug effects. It may be reduced or absent in areas of brain damage.
5. Sensorimotor Rhythm (SMR) ranges from 12 Hz to 15 Hz over sensorimotor strip. SMR is initiated by reduction in efferent motor activity and afferent somatosensory input, and is suppressed during movement or imagination of a movement (Sterman & Egner 2006). The neural substrates of SMR are localized in the ventrobasal nuclei of the thalamus, conducting afferent somatosensory information to the motor cortex. The suppression of somatosensory information and reduction in muscle tone induce a change in ventrobasal nuclei firing patterns, shifting from non-rhythmic and fast to rhythmic and systematic bursts of discharges that result in the appearance of SMR brainwaves (Sterman & Egner 2006). A reduced SMR may be abnormally seen in patients with epilepsy (Sterman & Egner, 2006), with attention deficit and hyperactivity disorder

(Lazzaro et al., 1999; Monastra et al., 1999), with Gilles de la Tourette syndrome (Messerotti Benvenuti, Buodo, Leone, & Palomba, 2011).

In cardiac surgery literature, pre and postoperatively, it has been frequently used quantitative techniques to extract and quantify data from the time-domain EEG (i.e., variations of voltage as a function of time) and convert them into frequency-domain EEG, namely in terms of waveforms frequency, amplitude and phase. Once EEG has been acquired and preliminary processing, an epoch length must be selected (e.g., 1-s segment of EEG). Then, spectral analysis or Fast Fourier Transformation analysis allows a visual display and further analysis of the received signal. In frequency analysis, the EEG is decomposed into its frequency components. These can be clustered together into broad band such as θ activity (4-7.5 Hz) or the individual frequency component can be kept separate and treated as a continuous function over a broad range of frequencies, such as 1-40 Hz (Pivik et al., 1993). The EEG band is then quantified according to the root-mean square average amplitude within that band or in terms of power (the square of the amplitude) within the band. Importantly, measures of absolute power or relative power can be derived. The first, absolute power, is the amount of EEG activity into one band without relationship to other bands. In contrast, the second, relative power, is the amount of EEG activity in a frequency band divided by the amount in all bands.

Neurological and neuropsychological deficits following cardiac surgery have been related to an increase in slow frequency power (Edmonds et al., 1992; John et al., 1989; Sotaniemi, Sulg, & Hokkanen, 1980). Sotaniemi et al. (1980) showed that the presence of early postoperative neurological deficits represents a predictor of EEG abnormalities several years after cardiac surgery. In particular, EEG abnormalities consisted of an increase in slow frequency power (δ band, 1 - 3.5 Hz), presence of δ-wave disturbances and sharp waves found in 78% of patients 10 days after surgery. EEG abnormalities persisted 1 year after

surgery in 29% and 20% respectively for patients who showed and who did not show clinical sign of postoperative brain damage (Sotaniemi, Mononen, & Hokkanen, 1986; Sotaniemi et al., 1980). More recent evidence not only confirmed but also extended previous findings by showing a significant increase in slow frequency bands power (δ and θ) in over one third of CABG and valve replacement patients (Mazzoni et al. 1993). Toner, Taylor, Newman, & Smith (1998) reported that, compared to age-matched controls, cardiac surgery patients had more preoperative EEG abnormalities (i.e., enhanced δ power, reduced θ and α power) which, in turn, may indicate the presence of cerebrovascular accidents. One week after surgery, Toner et al. (1998) found a reduced EEG power in all frequencies, especially δ and θ bands; at 2 months, the most reduction was found in the two fast frequency (α and β), while δ and θ return to preoperative levels. Interestingly, an association between EEG and cognitive dysfunctions was found 2 months after surgery, that revealed the importance of evaluating cerebral deficits as a consequence of CPB procedure after patients have recovered from cardiac surgery.

Intraoperatively, EEG has been used for monitoring both brain ischemia (Edmonds & Singer, 1996; Florence, Guerit, & Guegen, 2004) and the depth of the anesthesia, that is the pharmacological neuroprotection achieved by burst suppression or electrical silence patterns during manoeuvres at high risk for emboli or in the presence of unexpected embolic burden (Figures 1.8 and 1.9) (Nussmeier, Arlund, & Slogoff, 1986; Zanatta et al., 2011). Intraoperative brain monitoring through EEG usually consists of bipolar bilateral frontocentral channels (F3-C3'/F4-C4'). Moreover, compressed spectral analysis of EEG with absolute power and a “spectral edge frequency” of 95% (frequency below which 95% of the total power is contained) are usually extracted and quantified from time-domain EEG in the operating theatre (Zanatta et al., 2011). Indeed, intraoperative absolute power and spectral edge frequency 95% are more sensitive analyses than visual EEG analyses for detecting

cerebral ischemia and microembolization (Figure 1.8), variations in anesthesia (Figure 1.9), and hypothermia during intervention (Florence et al., 2004; Zanatta et al., 2011).

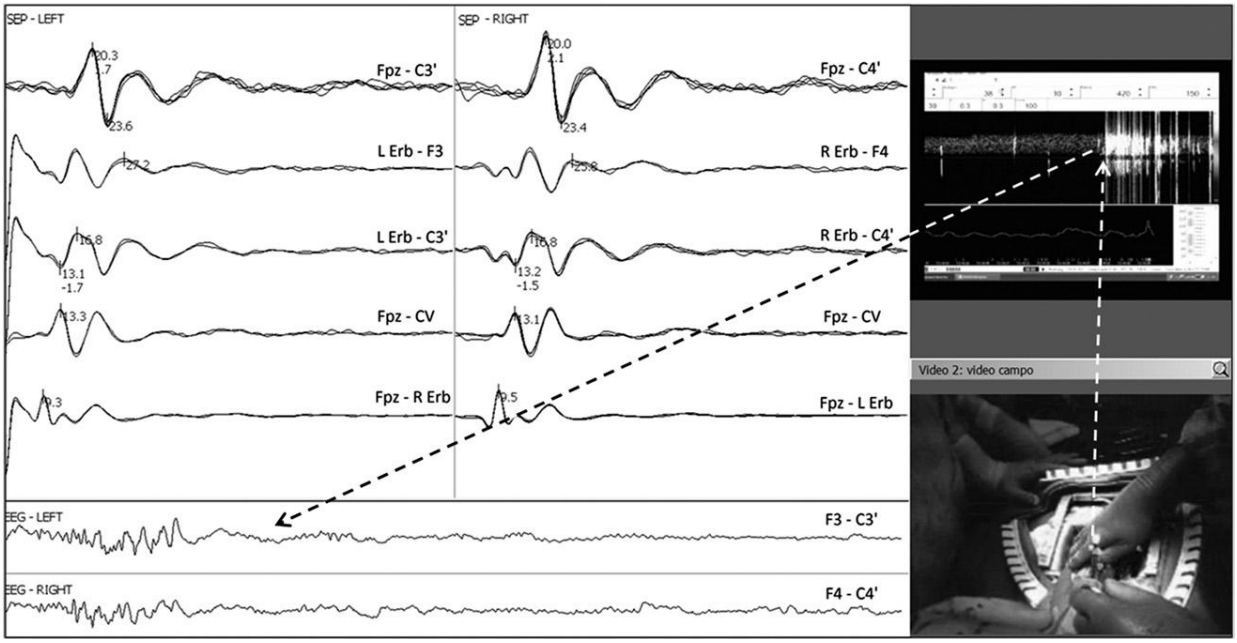

Figure 1.8 Valve surgery: multimodal brain monitoring after declamping the aorta with Embolex (i.e., an umbrella device used to collect atheroemboli). Note the shower of gas microemboli on the monolateral right transcranial Doppler, and the subsequent flattening of the EEG. Somatosensory evoked potentials amplitudes and latency did not change. Dashed lines indicate the associations between surgical manoeuvres, microembolic showers, and flattening of the EEG. From Zanatta et al., 2011

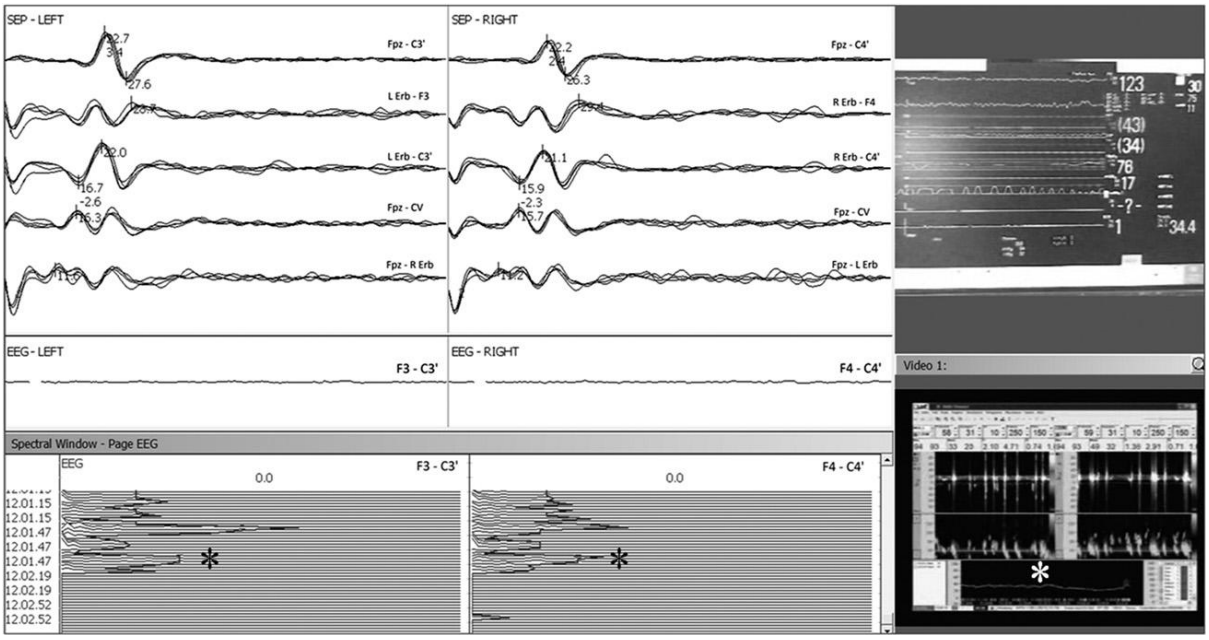

Figure 1.9 Valve surgery: multimodal brain monitoring after declamping the aorta with an infusion of a bolus of sodium thiopental. Asterisks indicate the time of infusion of thiopental on transcranial Doppler blood flow velocity trend and on compressed spectral analysis. The recording time of the EEG window was 12.02.52. Note the isoelectric EEG and flattening of the EEG spectra. Note also the reduction in trend velocity and isolated microembolic signals on the bilateral transcranial Doppler, whereas the amplitude and latency of the somatosensory evoked potentials remained unchanged. From Zanatta et al., 2011

Taken together, these findings provide evidence for the association between electrocortical abnormalities and POCD in cardiac surgery. Specifically, decrease in EEG power after surgery may be related to global and regional cerebral hypoperfusion and, therefore, to an altered cerebral metabolism (Toner et al., 1998) which, in turn, are possible mechanisms underlying POCD. Indeed, a decrease in cerebral blood flow and in hemispheric oxygen metabolism has been linked to an increase in δ and a decrease in α relative power in cardiac surgery patients (Henriksen, Hjelms, & Lindeburgh, 1988; John et al., 1989). Regional EEG slowing found in CPB patients may indicate that cerebral blood flow falls below the critical volume for a specific brain region (Venn et al., 1987).

Evoked potentials and event-related potentials (ERPs) are voltage fluctuations that are related in time to some physical or mental occurrence. These potentials can be recorded from the human scalp and are extracted from the EEG by means of filtering and signal averaging

(Picton et al., 2000). The evoked potentials are electrical manifestation of the brain's reception of and response to an external stimulus and can be classified in pattern-shift visual, brain stem auditory, and short-latency somatosensory evoked potentials. These evoked potentials can be used as reliable diagnostic tests that show reproducible results in neurological and neurophysiological clinical practice. They are usually recorded to provide objective measure of function of sensory systems and tracts (Chiappa, 1997). In cardiac surgery literature, somatosensory evoked potentials are usually recorded intraoperatively because they can provide direct information on the integrity of the somatosensory pathway (i.e., the brain cortex, cervical-thalamic junction, and peripheral nerve) and indirectly indicate the level of perfusion in the middle cerebral arteries (Guerit, 1998). Somatosensory evoked potentials may also be able to detect ischemia in cortical areas distant from the somatosensory cortex (Stecker et al., 1996; Zanatta et al., 2011).

ERPs are stable sequences of negative and positive EEG peaks after a stimulus within a period of several hundred milliseconds. The waveforms contain components that span a continuum between the endogenous potentials (information processing that may or may not be evoked by the eliciting event) or exogenous potentials (obligatory responses elicited by the physical characteristics of the stimulus in the external world). ERPs can accurately measure when processing activities take place in the brain because the temporal resolution of these measurements is on the order of the milliseconds. In contrast, despite multichannel recordings may allow the estimation of the cerebral location of brain processing elicited by a given stimulus, the spatial resolution is limited (Picton et al., 2000).

In cardiac surgery, the most commonly used ERPs paradigm has involved the detection of an improbable target stimulus in a train of standard stimuli (i.e., the "odd-ball" paradigm). This paradigm elicits large ERPs component and provides useful information on how the brain evaluates probability and discriminates stimuli. The odd-ball paradigm has

been adapted to the study of several cognitive processes such as attention, memory and language (Picton et al., 2000). Although it is better to employ paradigm more specific to the processes that is intended to study, many other paradigms share similar characteristics of the odd-ball task. Also, it is important to consider whether the ERPs recorded in these paradigms can be interpreted more parsimoniously in terms of odd-ball paradigm (i.e., discriminability and probability) than in terms of more complex processes. For these reasons and to adapt the task to the population studied, clinical research using ERPs has commonly recorded P300 potential elicited by an odd-ball task, that is a highly sensitive and reproducible paradigm for the evaluation of cognitive processes in several metabolic, hemodynamic, or neurological disorders (Grimm et al., 1988; Grimm, Oder, Prayer, Ferenci, & Madl, 1990; Grimm, Stockenhuber, et al., 1990; Madl et al., 1994; Madl et al., 1993; Polich, Ehlers, Otis, Mandell, & Bloom, 1986). This potential objectively reflects relevant aspects of cognitive function and is considered a "cognitive" neuroelectric phenomenon because it is generated during psychological tasks when participants attend and discriminate stimuli that differ from one another on some dimension (Polich & Kok, 1995). Specifically, the P300 component indexes cerebral activities underlying revision of the mental representation induced by incoming stimuli (Donchin, 1981). After initial sensory processing, an attention-driven comparison process evaluates the representation of the previous event in working memory - a process distinct from, although related to, sensory stimulus feature mismatch detection (Heslenfeld, 2003; Kujala & Näätänen, 2003). If no stimulus attribute change is detected, the current mental model of the stimulus context is maintained, and only sensory evoked potentials are recorded (N100, P200, N200). If a new stimulus is detected, attentional processes induce a change or "updating" of the stimulus representation that is concomitant with P300 (Polich, 2007).

The P300 component is measured by assessing its latency and amplitude. Latency (ms) is defined as the time from stimulus onset to the point of maximum amplitude within a time window. Amplitude (μV) is defined as the difference between the mean pre-stimulus baseline voltage and the largest peak of the ERP waveform within a time window (e.g., 250-500 ms, although the range can vary depending on task conditions, subject age, stimulus modality etc.). Scalp distribution of P300 potential is defined as the amplitude change over the midline electrodes (Fz, Cz, Pz), which typically increases from the frontal to parietal electrode sites (Johnson, 1993). P300 latency increases with age and is a cognitive correlate of information processing, such as alertness, memory updating, and stimulus evaluation (Picton, 1992). The P300 amplitude varies with the improbability of the targets during the odd-balls whereas the latency varies with the difficulty of discriminating the target stimulus from the standard stimulus. Its typical peak latency is 300 ms when a young adult participant is required a simple discrimination. In contrast, patients with reduced cognitive function show a smaller and later P300 than age-matched normal participants (Picton, 1992). Indeed, cognitive P300 event-related potential measurement is a component related to information and cognitive processing that allows quantification of impaired cognitive function (Grimm, Stockenhuber, et al., 1990; Polich et al., 1986). It is noteworthy that, compared to amplitude, P300 latency has shown greater sensitivity and specificity in reflecting the degree of cognitive deficit and/or decline in different clinical populations such as patients with dementing illness (Neshige, Barrett, & Shibasaki, 1988; Polich et al., 1986), with multiple sclerosis (Honig, Ramsay, & Sheremata, 1992) or those underwent cardiac surgery (Kilo et al., 2001; Zimpfer et al., 2004).

The use of the P300 technique has proved to be even more sensitive than EEG and standard psychometric tests for detecting subclinical impairment of cognitive brain function (Grimm, Stockenhuber, et al., 1990; Madl et al., 1994; Pozzessere et al., 1991). Specifically,

latencies of P300 elicited by auditory odd-ball task significantly increased in 308 patients 7 days after CABG surgery (mean peak latency: from 366 ms to 376 ms) whereas it was almost normalized at 4-month follow-up (mean peak latency: 369 ms) (Figure 1.10) (Kilo et al., 2001). Zimpfer et al. (2004) extends previous findings by showing that, compared to nonsurgical controls, CABG patients had prolonged latency at 7-day, 4-month and 3-year follow-up (Figure 1.11). Moreover, changes in P300 latency were significantly associated with Trail Making Test A (TMT A) from preoperative to 3-year follow-up. Taken together, these findings provide further evidence for cognitive decline related to cardiac surgery. It may also be suggested that cerebral hypoperfusion and microembolization caused by CPB technique may induce irreversible damage to brain tissue resulting in cognitive dysfunctions, which, in turn, may be reflected by prolonged cognitive P300 latencies.

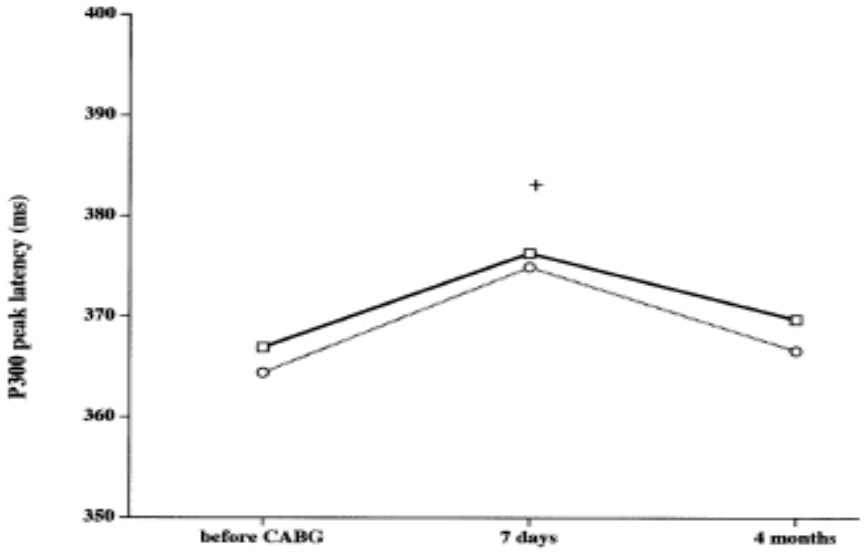

Figure 1.10 Cognitive P300 peak latencies before coronary artery bypass grafting, at 7-day and at 4-month follow-up. (Solid line = P300 peak latencies recorded at CZ; Dotted line = P300 peak latencies recorded at FZ; + = Impairment of P300 peak latencies, $p < .05$ versus preoperative). From Kilo et al., 2001 (modified)

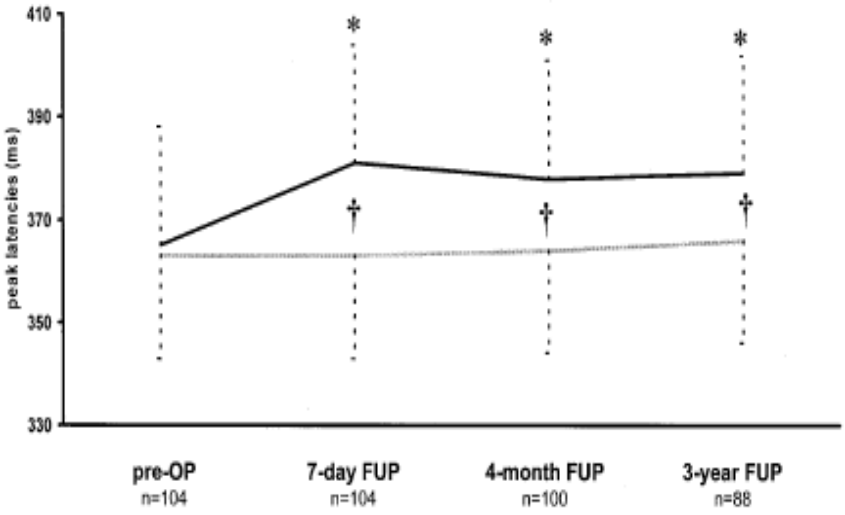

Figure 1.11 Cognitive P300 peak latencies. The black line represents patients undergoing coronary artery bypass grafting; the gray line represents age- and sex-matched controls. $^{*}p < .05$ compared with preoperative values; $^{\dagger}p < .05$ within the two groups. (FUP = follow-up; pre-OP = preoperative). From Zimpfer et al., 2004 (modified)

1.2.3 Brain Imaging and Cognitive Decline after Cardiac Surgery

Evidence from brain imaging studies showed that POCD is associated with cerebral abnormalities. Aberg et al. (1984) found 2 patients to have cerebral infarctions visible on the computed tomography scans after CABG. Cognitive testing revealed POCD in one case and an essentially normal postoperative state in the other.

Studies using magnetic resonance imaging provided evidence for postoperative brain lesions caused by cardiac surgery procedures in patients who had undergone CABG. Specifically, Toner et al. (1994) found one third of patients to have postoperative brain lesions caused by CABG. Simonetta et al. (2000) discovered postoperative lesions in 12.5% of patients on magnetic resonance imaging 5 to 7 days after CABG or valve surgery. Interestingly, studies described above also found a significant proportion of patients to have abnormal scans before surgery. In particular, Toner et al. (1994) revealed that only patients with preoperative abnormal magnetic resonance imaging showed new brain lesions after cardiac surgery whereas patients with preoperative normal magnetic resonance imaging did not develop postoperative changes. This latter finding suggests that the presence of preoperative cerebrovascular accidents may be a risk factor for postoperative new brain lesions (Waldstein & Elias, 2001). Moreover, an association between magnetic resonance imaging and cognitive performance has been found. While Simonetta et al. (2000) found that patients with abnormal magnetic resonance imaging were more likely to show cognitive deficits, Toner et al. (1994) observed cognitive dysfunctions in all patients who developed new brain lesions.

1.3 Risk Factors for Cognitive Decline after Cardiac Surgery: Demographic, Biomedical and Affective Status

In the last two decades, a great number of studies has investigated the biomedical variables that may represent risk factors for cognitive decline after cardiac surgery (Ho et al., 2004; Newman et al., 1995; Selnes et al., 1999). Correlational analysis revealed that there is an obvious increasing risk for cognitive decline following CABG with increasing *age* (Newman et al., 1995; Newman et al., 1994; O'Brien et al., 1992; Sotaniemi et al., 1986; Townes et al., 1989). Age may also be associated with the extent of cardiovascular disease patients. It has been observed that older patients are more likely to be less able to maintain an appropriate cerebral blood flow autoregulation (Newman et al., 1995; Newman et al., 1994) and to be more exposed to intraoperative microemboli (Stump, Tegeler, Newman, Wallenhaupt, & Roy, 1992). Newman et al. (1995) have reported that the *educational level* of patients undergoing cardiac procedures represents another demographic predictor of POCD. Years of education protect individuals from cognitive decline after cardiac surgery, despite the mechanism by which this education-related protection occurs is still unknown (Ho et al., 2004; Newman et al., 1995). The differential outcomes related to *gender* have been investigated rarely although it is well-established that women have higher levels for morbidity and mortality following cardiac surgery (Edwards, Carey, Grover, Bero, & Hartz, 1998).

Interestingly, Newman et al. (1995) found a genetically driven association between the *apolipoprotein E ε-4* allele, which has been implicated in Alzheimer disease, and POCD at discharge and 6 weeks postoperatively. This finding suggests that genotype, which may affect neuronal repair and maintenance, is an important predictor of cognitive decline after CPB surgery and that individuals with this genotype may be at greater risk for POCD.

Moreover, several biomedical variables have been associated with cognitive decline after cardiac surgery. Patients with more *severe cardiac disease* may be more vulnerable to POCD (Lee, Brady, Rowe, & Miller, 1971; O'Brien et al., 1992). Selnes et al. (1999) found that histories of *diabetes* and *syncope* were associated with elevated risk of psychomotor and verbal memory decline, respectively. The preoperative *cerebral arterial pressure* was related to change in domain of attention: higher mean cerebral arterial pressure readings were related to better performance 1 month after surgery. Elevated *total cholesterol* levels have been shown to be a significant predictor of cognitive dysfunctions at 1-month after surgery, especially for psychomotor speed. Finally, individuals with *cerebrovascular diseases* as evidenced by abnormalities on magnetic resonance imaging are more likely to have a poor cognitive performance postoperatively (Simonetta et al., 2000; Toner et al., 1994).

Undergoing cardiac surgery remains a significant life-event, with an important psycho-emotional impact on patients and their families. *Anxiety* and *depression* are commonly reported in patients prior to cardiac surgery (Gardner & Worwood, 1997). Preoperative incidence of depression measured with the Center for Epidemiological Studies of Depression (CES-D) (Radloff, 1977) scale varies between 27% and 36% (Langeluddecke, Fulcher, Baird, Hughes, & Tennant, 1989; McKhann, Borowicz, Goldsborough, Enger, & Selnes, 1997), while 30% of cardiac surgery patients have clinically elevated scores on the Spielberger State Anxiety Inventory (Spielberger, Gorusch, & Lushene, 1970). It is well-recognized that preoperative anxiety and depressive symptoms persist postoperatively for most patients undergone cardiac surgery and, therefore, these emotional disorders are major predictors of postoperative anxiety and depression (Magni et al., 1987; McKhann et al., 1997; Strauss et al., 1992). Indeed, Magni et al. (1987) found that preoperative anxiety accounts for 29% of the variation in postoperative anxiety level, whereas 34% of the variation in postoperative depressed mood was significantly predicted by preoperative depression scores.

McKhann et al. (1997) found that, compared to 13% of patients not depressed prior to surgery, more than 50% of patients with preoperative depression were depressed 1 month after surgery. Moreover, several studies reported that both preoperative and early postoperative depression represent a significant and independent risk factor for subsequent cardiac events and/or mortality after cardiac surgery (Blumenthal et al., 2003; Burg, Benedetto, & Soufer, 2003; Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001; Scheier et al., 1999). Scheier et al. (1999) observed a two-fold increased odds of having a cardiac event within 6 months after surgery in patients with depressive symptoms. Also, Connerney et al. (2001) reported that major depressive disorder is an independent predictor of cardiac events in the 12 months 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 et al. (2003) reported that patients with persistent (i.e., before as well as 6 months after CABG) mild or moderate to severe depression have greater likelihood (i.e., more than twice) of death than those who are never depressed. Tully, Baker, & Knight (2008) have also shown that preoperative anxiety symptoms are significantly associated with increased mortality risk after adjustment for common mortality risk factors (e.g. age, sex, and unstable angina).

Furthermore, it is well-established that emotional states can affect cognitive performance (Lezak, Howieson, & Loring, 2004), especially attention and executive functions. Since it is a common perception that anxiety and depression may be associated with POCD, several studies have recently investigated the association between anxiety, depression and cognitive decline after cardiac surgery (Andrew et al., 2000; McKhann et al., 1997; Stroobant & Vingerhoets, 2008). Andrew et al. (2000) found that both preoperative and postoperative high levels of depression and anxiety were predictive of POCD on tests of attention and verbal memory. However, they reported that, despite postoperative levels of

anxiety and depression were related to POCD, once preoperative mood status was accounted for, these associations were no longer significant. Also, changes in mood status from preoperative assessment to postoperative assessment were not related to the incidence of cognitive decline. These findings clearly provide evidence for the exclusive role of preoperative mood status as a predictor of postoperative mood disorders and cognitive deficits in cardiac surgery patients. Stroobant & Vingerhoets (2008) reported that the Grooved Pegboard Test (pre- and postoperatively) and TMT (preoperatively) scores were significantly related to depression, despite no associations between anxiety, depression and other cognitive scores were found. Also, Stroobant & Vingerhoets (2008) extend previous findings by showing that impaired performance in Grooved Pegboard Test at 6 months and 3 to 5 years after surgery was associated with higher preoperative depression. This latter result is in line with previous literature showing that slowed psychomotor functioning is one of the cardinal features of depression (Sobin & Sackheim, 1997).

In contrast, McKahnn et al. (1997) reported no correlation between preoperative depression and preoperative cognitive performance, and similarly, no correlation between postoperative depression and postoperative cognitive scores. Moreover, they reported minimal correlations between changes in depression and cognitive performance. Nevertheless, they did not analyze the potential role of preoperative depression as a predictor of POCD as well as the association between anxiety and POCD.

Although the relationship between mood states and POCD should be further investigated to fully understand the role played by affective status on cognitive performance, overall, these findings suggest that anxiety and, even more, depression may represent important risk factors for cognitive decline after cardiac surgery.

1.4 Limitations of Previous Research

Previous researches have several limitations which curtail the ability of the afore-mentioned studies to claim that they provide a comprehensive account of the psychological and/or psychophysiological mechanisms underlying cognitive decline after cardiac surgery. First, despite literature has described the relationships between anxiety, depression and cognitive decline and between anxiety depression and adverse outcomes after cardiac surgery (Andrew et al., 2000; Blumenthal et al., 2003; Burg et al., 2003; Connerney et al., 2001; Stroobant & Vingerhoets, 2008; Tully et al., 2008), to our knowledge, no studies have investigated the potential association between cognitive and affective status and biomedical risk as calculated by risk-stratification scores, preoperatively.

Second, although research has documented that intraoperative cerebral hypoperfusion and microembolization are risk factors for POCD, to our knowledge, only few studies have examined whether preoperative psychophysiological variables can be risk factors for such decline (Simonetta et al., 2000; Toner et al., 1994). Given the strong association between cerebral blood flow velocity in middle cerebral arteries and cognitive performance (for a review see, Stroobant & Vingerhoets, 2000), this issue could be investigated through transcranial Doppler recording, preoperatively.

Third, although it is widely acknowledged that heart valve surgery represents a major risk factor for intraoperative microembolization in comparison with CABG (Abu-Omar et al., 2004; Thiel, Zimmer, Stertmann, Kaps, & Hempelmann, 1997), surprisingly only few studies have specifically examined the association between intraoperative embolization and POCD in heart valve surgery patients (Braekken, Reinvang, Russel, Brucher, & Svennevig, 1998; Hermann, Ebert, Tober, Hann, & Huth, 1998).

Fourth, despite depression is commonly reported in patients after cardiac surgery and is a significant and independent risk factor for postoperative cognitive and emotional

dysfunctions, to our knowledge, no studies have examined the influence of depression on EEG activity at rest and during an imagery task, requiring both cognitive and emotional processing.

These limitations, which are related to individual elements of the various studies and experiments that have examined them, are covered in the introductions of each of the four experimental chapters that follow.

1.5 Aims of Thesis and Outline of the Studies

With the goal of increasing our understanding of POCD, this thesis investigates the psychological and psychophysiological mechanisms that drive cognitive decline after cardiac surgery. The primary purpose of the current thesis was to investigate whether the preoperative psychological status can be related to biomedical risk. It is hoped that in uncovering the underlying relationships between psychological and biomedical risks, physicians will assess preoperative cognitive functioning, anxiety and depression to have a more complete risk score of patients undergoing cardiac surgery.

The experiment reported in chapter two examined the relationship between cognitive performance, emotional status and biomedical risk in cardiac surgery patients. The main aim was to examine whether increased biomedical risk was associated with impaired cognitive performance, anxiety and depression preoperatively. This study also compared the associations of two risk-stratification scores, namely the Stroke Index and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) with cognitive scores, anxiety and depression in patients undergoing cardiac surgery. A long-term clinical and psychological follow-up (i.e., 3/12 months after surgery) is still ongoing to provide further evidence for the predictive value for patient's outcome of a more comprehensive risk score, which takes into account preoperative cognitive and emotional status, on the one hand, and biomedical risk factors, on the other hand.

The current thesis also aims to examine the psychophysiological variables implicated in POCD as possible mechanisms underlying cognitive decline in cardiac surgery patients. The understanding of psychophysiological mechanisms of POCD can lead researchers to develop easy-to-use psychophysiological protocols in order to improve the diagnosis of postoperative psychological dysfunctions and its consequences on patients and their relatives quality of life, and to conserve heath care resources. Therefore, to examine the potential

hemodynamic mechanisms underlying POCD, the experiments in chapter three were designed. The first experiment aimed to investigate whether preoperative hypoperfusion in middle cerebral arteries could be related to cognitive decline after cardiac surgery. Moreover, it was examined whether cerebral hypoperfusion in left or right middle cerebral artery would differentially account for POCD in patients undergoing cardiac surgery. Preoperative cerebral hypoperfusion was hypothesised as a potential psychophysiological mechanism and an independent risk factor for cognitive dysfunction after cardiac surgery.

The second experiment reported in chapter three was designed to determine the role of asymmetry and the nature of microembolization on postoperative cognitive decline in patients who had undergone heart valve surgery. The aim of this study was twofold. First, it examined whether the massive microembolic load during cardiac surgery induces specific cognitive impairment in accordance to the brain region to which they are delivered. Second, whether solid or gaseous microemboli have a differential impact on early or late POCD was also considered.

Given the relevant role played by depression as a risk factor for postoperative adverse outcomes, the experiment in chapter four was designed to examine the potential influence of depression on cognitive and emotional processing in patients after cardiac surgery. Specifically, the current experiment was carried out to investigate whether depression may alter EEG activity during an imagery task, which involves cognitive and emotional processing, in patients after cardiac surgery. Secondarily, it examined whether the depression-related alterations in EEG activity were also associated with emotion dysregulation, thus contributing to adverse cognitive and clinical outcomes in cardiac surgery patients.

2. STUDY I: BIOMEDICAL AND PSYCHOLOGICAL RISK FACTORS IN CARDIAC SURGERY

In cardiac surgery literature, research has focused on the construction of scoring systems for the prediction of early perioperative adverse outcomes such as stroke and mortality (Nashef, Roques, Gauducheau, Lemeshow, & Salamon, 1999; Newman et al., 1996). Those risk-stratification scores commonly include demographic (e.g., age, and gender) and biomedical variables (e.g., angina pectoris, and hypertension). Along with demographic and biomedical risk factors, preoperative psychological dysfunctions have been linked to adverse peri and postoperative outcomes in patients undergoing cardiac surgery, potentially contributing to the preoperative risk scores. Indeed, preoperative anxiety, depression and cognitive performances are relevant predictors for early postoperative psychological dysfunctions which, in turn, are associated with a prolonged hospitalizations and mortality after cardiac surgery (Blumenthal et al., 2003; Connerney et al., 2001; Roach et al., 1996; Tully et al., 2008). However, it has not yet been taken into account the inclusion of psychological risk factors (e.g., cognitive deficits, anxiety, and depression) to increase the potential predictive value of the most common risk-stratification scores. The relationship between preoperative psychological dysfunctions and biomedical risk factors has to be examined to provide preliminary evidence for the inclusion of psychological variables in the risk-stratification scores.

2.1 Abstract[1]

Several composite risk score indices, the most common being the Stroke Index and the European System for Cardiac Operative Risk Evaluation, have been developed to predict perioperative events such as cerebrovascular accidents or death. The main aim of the present study was to compare the preoperative associations between the Stroke Index or the European System for Cardiac Operative Risk Evaluation with anxiety, depression, memory, attention, and executive functions scores in patients undergoing cardiac surgery. Ninety-one patients were required to perform a preoperative psychological evaluation. Trail Making Test A and B, Memory with 10 and 30 s interference, Digit Span Test, Phonemic Fluency, State and Trait Anxiety Inventory, and Center for Epidemiological Study of Depression Scale were administered. The Stroke Index and the European System for Cardiac Operative Risk Evaluation were also considered for each patient. Correlations between the Stroke Index or the European System for Cardiac Operative Risk Evaluation, mood, and neuropsychological scores were performed. Results: Seventy-seven patients completed the psychological evaluation. The Stroke Index was significantly correlated with Trail Making Test A (ρ = 0.40, p < .002), Trail Making Test B (ρ = 0.38, p < .002), Memory with 10 s (ρ = 0.34, p < .004) and 30 s (ρ = 0.40, p < .002) interference, and Phonemic Fluency (ρ = 0.29, p < .02), but not with Digit Span Test (ρ = 0.18, p = .13), State and Trait Anxiety Inventory Y1 (ρ = 0.08, p = .44), State and Trait Anxiety Inventory Y2 (ρ = 0.06, p = .56), and Center for Epidemiological Study of Depression Scale (ρ = 0.11, p = .31) scores. The European System for Cardiac Operative Risk Evaluation was significantly correlated not only with Trail Making Test A (ρ = 0.49, p < .002), Trail Making Test B (ρ = 0.42, p < .002), Memory with 10 s (ρ = 0.23, p < .05) and 30 s (ρ = 0.35, p < .003) interference, Phonemic Fluency (ρ =

[1] Abstract published in Messerotti Benvenuti, S., Palomba D., Zanatta, P., Mazzarolo, A. P., & Valfrè, C. (2011). Biomedical and psychological risk in cardiac surgery: is EuroSCORE a more comprehensive risk measure than stroke index? *European Journal of Cardiothoracic Surgery, 39,* e102-e106.

0.28, $p < .02$), and Digit Span Test ($\rho = 0.28$, $p < .02$) but also with State and Trait Anxiety Inventory Y1 ($\rho = 0.27$, $p < .03$), State and Trait Anxiety Inventory Y2 ($\rho = 0.23$, $p < .05$), and Center for Epidemiological Study of Depression Scale ($\rho = 0.26$, $p < .03$). While both the Stroke Index and the European System for Cardiac Operative Risk Evaluation account for the relationship between biomedical and cognitive risk factors in predicting perioperative risk, only the European System for Cardiac Operative Risk Evaluation also accounts for affective dysfunctions, which, in turn, have been proved to represent risk factors for perioperative adverse events. Therefore, compared with the Stroke Index, the European System for Cardiac Operative Risk Evaluation can be considered a more complete risk index in predicting perioperative risk. Data also suggest that a comprehensive preoperative evaluation of biomedical, mood, and cognitive performances might provide a more accurate mirror of the actual risk in patients undergoing cardiac surgery.

Keywords: Anxiety; Cardiac surgery; Cognitive functions; Depression; Risk factors; Risk scores

2.2 Introduction

The present study was designed to investigate the relationships between mood, cognitive performance and biomedical risk-stratification scores in patients undergoing cardiac surgery. Each patient underwent a psychological evaluation aimed at assessing anxiety, depression and cognitive performance, preoperatively. Moreover, the Stroke Index (Newman et al., 1996) and the logistic EuroSCORE (Nashef et al., 1999) were calculated as the most used risk-stratification scores for perioperative cerebrovascular accidents or mortality, respectively. EuroSCORE has been also used to develop a risk-stratification system especially for high risk patients undergoing cardiac surgery (Roques et al., 1999).

Both risk indexes comprise demographic and biomedical variables: age, diabetes, unstable angina, previous heart surgery, history of vascular, neurological and/or pulmonary disease are included in the Stroke Index (Newman et al., 1996); patient-related factors (i.e., age, sex, chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, serum creatinine, active endocarditis), cardiac-related factors (i.e., unstable angina, left ventricular dysfunction, recent myocardial infarct, pulmonary hypertension) and operation-related factors (i.e., emergency operation, other than isolated coronary artery bypass graft, thoracic aortic surgery, critical preoperative state, ventricular septal rupture) are included in the EuroSCORE (Nashef et al., 1999; Roques., Michel, Goldstone, & Nashef, 2003).

Most of the above-mentioned demographic and biomedical variables have been independently associated with cognitive functioning such as memory, attention and language performances (Hoth, Poppas, Moser, Paul, & Cohen, 2008; Kozora et al., 2008; Rao, Jackson, & Howard, 1999; Schaie, 1996; Shimada et al., 2009). Moreover, mood disorders like anxiety and depression have also shown relationships with most of the Stroke Index and the EuroSCORE variables (Kozora et al., 2008; Thomas, Kalaria, & O'Brien, 2004; Woo, Kumar, Macey, Fonarow, & Harper, 2009). Preoperative mood and cognitive performances are also relevant predictors for early postoperative psychological dysfunctions which, in turn, are associated with a prolonged hospitalizations and mortality after cardiac surgery (Blumenthal et al., 2003; Connerney et al., 2001; Roach et al., 1996; Tully et al., 2008). Connerney et al. (2001) reported that major depressive disorder is an independent predictor of cardiac events in the 12 months 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 et al. (2003) reported that patients with persistent (i.e., before as well as 6 months after CABG) mild or moderate to severe depression have greater likelihood (i.e.,

more than twice) of death than those who are never depressed. Tully et al. (2008) have also shown that preoperative anxiety symptoms are significantly associated with increased mortality risk after adjustment for common mortality risk factors (e.g. age, sex, and unstable angina).

In spite of the relationships between mood, cognitive performances and most of biomedical risk variables, the associations between the global risk-stratification scores and psychological functioning have yet to be investigated. Also, it is important to examine whether the inclusion of preoperative psychological evaluation assessing cognitive status and mood could potentially increase the predictive value of biomedical risks scores for clinical and medical outcomes in patients undergoing cardiac surgery. Finally, it is still unknown whether the two measures (Stroke Index and EuroSCORE) or one better than other can differentially account for psychological risk associated with demographic and biomedical risk factors.

2.3 Methods

Participants

Following local ethic committee's approval, 91 patients were required to give written informed consent and were recruited in the study. Incapability to read or understand Italian language, visual or auditory impairments and use of psychotropic were the exclusion criteria. Patients were prevalently males (52%) with a mean age of 64.5 years (*SD* = 10.7) (range from 27 to 82 years) and a mean education of 8.4 years (*SD* = 4.3), as reported in Table 2.1. Fourteen patients failed to complete the test battery and were excluded from the correlational analyses.

Table 2.1 *Characteristics of Patients Enrolled in the Study*

Variable	Included in the analysis *N* = 77	Not included in the analysis *N* = 14	*p*
Sex, male (%)	65	50	.29*
Age (years)	64.5 (10.7)	72.2 (7.1)	.01†
Education (years)	8.4 (4.3)	5.6 (2.2)	.02†
Body Mass Index (Kg/m^2)	27.8 (4.8)	26 (5.1)	.21†
Cardiovascular Pathology			
- Coronary Artery Disease (%)	21	29	.50§
- Aneurysm of Ascending Aorta (%)	1	0	.99§
- Valve Disease (%)	35	50	.29*
- Combined Cardiac Pathology (%)	43	21	.13*
Stroke Index	73.4 (25.1)	83.3 (17.3)	.16†
EuroSCORE (%)	4.8 (3.7)	7.6 (6.2)	.03†
Blood Pressure (mmHg)	79.2 (12.1)	78 (9.5)	.73†
Heart Rate (bpm)	65.1 (12.9)	72 (15.3)	.08†
Left Ventricular Ejection Fraction (%)	60.9 (13)	66.6 (10.8)	.20†

Note: Data are *M* (*SD*) of continuous and *N* (%) of categorical variables. *Chi-square test; †Statistical unpaired T-test; §Fisher's exact test. EuroSCORE: European System for Cardiac Operative Risk Evaluation; Bpm: beats per minute

Risk Scores and Psychological Evaluation

Stroke Index score was calculated for each patient, according to the criteria reported by Newman and colleagues (1996). Risk score was computed as follows: age [(age-25)*1.43], history of symptomatic neurological diseases (18 points), diabetes (17 points), history of vascular diseases (18 points), unstable angina (14 points), prior heart surgery (16 points), history of pulmonary diseases (15 points). Higher Stroke Index scores represent a higher risk of cerebrovascular accidents during cardiac surgery.

The EuroSCORE was determined for each patient using the logistic regression model of EuroSCORE (Roques et al., 2003) based on the following variables: age, sex, chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, serum creatinine, active endocarditis, unstable angina, left ventricular dysfunction, recent myocardial infarct, pulmonary hypertension, emergency operation, other than isolated CABG, thoracic aortic surgery, critical preoperative state and ventricular septal rupture. Higher EuroSCORE values predict a higher risk of mortality due to cardiac surgery.

The psychological evaluation included self-report questionnaires and tests aimed at assessing anxiety, depression and cognitive performances such as memory, attention and executive functions. All self-report questionnaires and tests were preoperatively administered individually by a trained psychologist blind to patient's Stroke Index and EuroSCORE values.

The anxiety and depression questionnaires were selected according to their sensitivity, specificity and reliability and consisted of:

1- State-Trait Anxiety Inventory (STAI Y1-Y2) (Spielberger et al., 1970; Spielberger, Pedrabissi, & Santinello, 1996) which is composed by two 20-items scales that measure state or trait anxiety, respectively. State anxiety represents the subject's current and transitory anxiety whereas trait anxiety indicates a long lasting and

persistent anxiety. In fact, test-retest reliability with a one-month interval is very high for STAI Y2 (r = 0.82) which evaluates stable trait of anxiety whereas it is moderate for STAI Y1 (r = 0.49) which, in turn, investigates time-dependent or fluctuant anxiety (Spielberger et al., 1996). The scores range between 20 and 80 for both scales, with higher scores representing higher anxiety.

2- Center for Epidemiological Studies Depression Scale (CES-D) (Fava, 1982; Radloff, 1977) which consists of 20 items representing the most common symptoms of depression. The scores range from 0 to 60, with higher scores indicating higher depressive symptoms. Although the CES-D scale was designed to be sensitive to possible depressive reactions to events in a person's life, test-retest reliability of CES-D is adequate (r = 0.54); it provides the evidence that CES-D scores are similar across time and across a wide variety of demographic characteristics in the general population (Fava, 1982).

The selection of cognitive tests was made according to the recommendations of the Statement of Consensus on Neurobehavioral Assessment (Murkin, Newman, Stump, & Blumenthal, 1995) and took the following issues into account:

1- The cognitive domain of the test;
2- The sensitivity and reliability of the test;
3- The practice effect;
4- The availability of parallel form;
5- The physical balance and time required to perform the test;
6- The overall balance of the cognitive functions evaluated in the battery.

Based on the above-mentioned considerations, the cognitive tests were as follows:

1- Trail Making Test A and B (TMT A and B) (Giovagnoli et al., 1996; Reitan, 1958). Participants were required to connect numbered circles drawing lines with a pencil

(Part A). Part B required participants to connect alternatively numbered and alphabetic circles. These tasks investigated executive functions, such as attention, psychomotor speed and cognitive switching skills. Scores were expressed in seconds. Lower scores indicate better performances (i.e., shorter completion times).

2- Memory with interference 10 s / 30 s is a dual task test (Peterson & Peterson, 1959). Participants were required to remember a sequence of three consonants while counting up in two's for either 10 or 30 s. These tests evaluated working memory skills during an interference task. Scores ranged from 0 to 9. A lower score indicates worse performance.

3- Digit Span Test (Orsini et al., 1987; Wechsler, 1945) is a short term memory task, which involves memorizing an incremental series of numbers that examiner reads aloud. Participants were required to remember and repeat them orally. Scores ranged from 2 to 8. A lower score indicates reduced short term memory span.

4- Phonemic Verbal Fluency (Mondini et al., 2003). Participants were required to name words beginning with a particular consonant (e.g., C, P and S) given by the examiner that investigates lexical access and frontal strategic search processes. Scores were calculated as the number of words produced. A lower score indicates worse performance.

Statistical Analysis

Fourteen patients who failed to complete the test battery were excluded from the correlation analyses. Chi-square test or Fisher's exact test for categorical and unpaired t-test for continuous variables were performed in order to outline whether preoperative medical and demographic characteristics of patients included in the statistical analyses were similar to those who were not included.

Stroke Index, EuroSCORE, anxiety, depression and cognitive scores were calculated for each patient. Correlations were calculated between Stroke Index or EuroSCORE, anxiety, depression and cognitive scores. All correlations were conducted using non parametric Spearman's correlation coefficient. A *p-value* of < .05 was considered statistically significant. STATISTICA 6.1 (Stat Soft Inc., Tulsa, OK, USA) software was used for each statistical analysis.

2.4 Results

Significant differences were observed between included and not included groups in age, education and EuroSCORE, Table 2.1 (p. 68).

Significant correlations were found between the Stroke Index and TMT A, TMT B, Memory with 10 and 30 s Interference, and Phonemic Fluency scores. The Stroke Index did not show any significant associations with Digit Span Test, STAI Y1, STAI Y2, and CES-D scores. EuroSCORE, instead, showed significant correlations with TMT A, TMT B, Memory with 10 and 30 s Interference, Phonemic Fluency, Digit Span Test as well as with STAI Y1, STAI Y2, and CES-D. All statistical details are reported in Table 2.2.

Table 2.2 *Spearman's Correlations Coefficients between Stroke Index or EuroSCORE and Anxiety, Depression and Scores in Cognitive Tests*

Measure	Stoke Index	EuroSCORE
	ρ	ρ
Trail Making Test A[§]	.40**	.49**
Trail Making Test B[§]	.38**	.42**
Memory with 10 sec interference[†]	-.34**	-.23*
Memory with 30 sec interference[†]	-.40**	-.35**
Phonemic Fluency[†]	-.29*	-.28*
Digit Span Test (forward) [†]	-.18	-.28*
State-Trait Anxiety Inventory Y1[§]	.08	.27*
State-Trait Anxiety Inventory Y2[§]	.06	.23*
Center for epidemiological study depression scale[§]	.11	.26*

Note: *Spearman's correlation, $p < .05$; **Spearman's correlation, $p < .01$; [§]Higher scores indicate worse functions; [†]Higher scores indicate better functions. EuroSCORE: European System for Cardiac Operative Risk Evaluation

As shown in Figure 2.1, scores on CES-D and STAI Y2 were significantly related to the EuroSCORE but not to the Stroke Index risk scores.

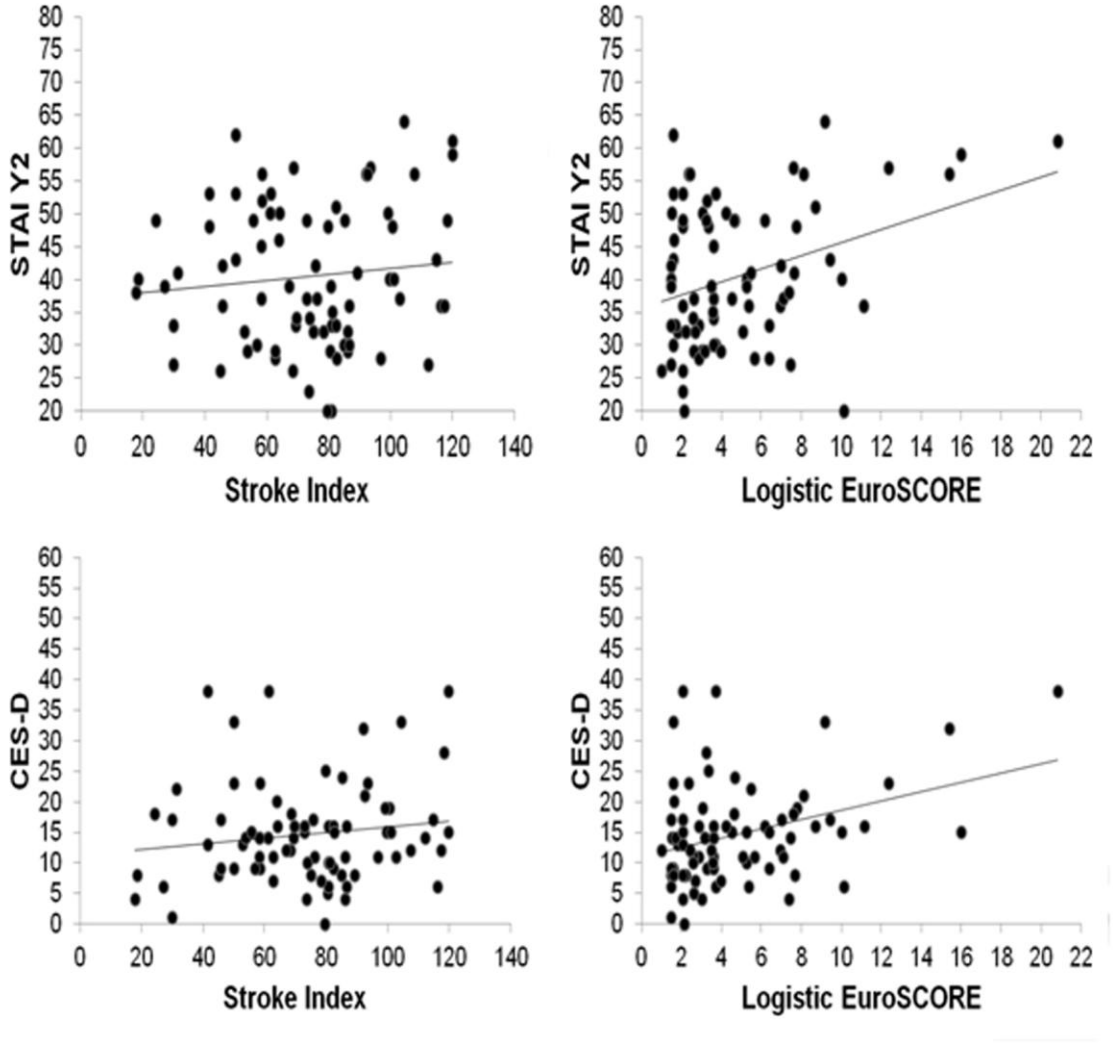

Figure 2.1 Correlations between trait anxiety (STAI Y2), depression (CES-D) and Stroke Index (left) or EuroSCORE (right).

2.5 Discussion

Many risk factors such as age, diabetes, unstable angina and left ventricular dysfunction comprised in the Stroke Index and EuroSCORE have been previously associated with anxiety and depression (Kozora et al., 2008; Thomas et al., 2004; Woo et al., 2009) as well as with cognitive deficits especially memory, attention and executive functions (Hoth et al., 2008; Kozora et al., 2008; Rao et al., 1999; Schaie, 1996; Shimada et al., 2009). In the present study, in line with previous literature, the Stroke Index and EuroSCORE showed significant correlations with cognitive performance: indeed, higher Stroke Index and EuroSCORE were associated with worse memory, attention, and executive functions. The EuroSCORE, not the Stroke Index, was related to short-term memory span as measured with Digit Span Test. Therefore, although both the Stroke Index and the EuroSCORE account for several potential risk factors influenced by cognitive deficits in patients undergoing cardiac surgery, the EuroSCORE may provide a more accurate measure also in relation with memory dysfunction which, in turn, can be easily worsened by intraoperative events such as embolization load, hypoperfusion and neuroinflammatory processes, mostly related to CPB technique.

The present study also aimed at measuring the correlations between the Stroke Index or EuroSCORE and affective variables. Most of the Stroke Index and EuroSCORE variables have been related to anxiety and depression (Kozora et al., 2008; Thomas et al., 2004; Woo et al., 2009), which, in turn, are significant risk factors for subsequent cardiac events and mortality in cardiac surgery patients (Blumenthal et al., 2003; Connerney et al., 2001; Tully et al., 2008). The present results indicate that the EuroSCORE, not the Stroke Index, is significantly associated with anxiety and depression scores. Although the correlations between the EuroSCORE and mood were moderate, the EuroSCORE, not the Stroke Index, may account for the potential risk factors related to state and trait anxiety as well as

depression as measured with STAI Y1, STAI Y2, and CES-D, respectively. Based on these data, the Stroke Index score may underestimate the perioperative risk of patients undergoing cardiac surgery whereas the EuroSCORE may also account for risk factors due to preoperative anxiety and depressive symptoms. In addition, the EuroSCORE seems to represent a useful index to evaluate the association between biomedical risk factors and the state anxiety which, in turn, may affect cognitive performance in patients undergoing cardiac surgery. On the other hand, it can be hypothesized that both the affective and cognitive factors may influence not only the cardiovascular recovery but also the overall health behaviors that are related to good or poor adjustment to everyday life.

It is noteworthy that the EuroSCORE predicts the overall risk of mortality in which the risk of stroke measured by Stroke Index may be included. Therefore, while the EuroSCORE may comprehend a global evaluation of patients undergoing cardiac surgery, the Stroke Index may be considered an index able to specifically predict only stroke risk and cognitive functioning.

The comparison between included and excluded patients showed that, in line with previous literature, the patients who were not able to complete the psychological evaluation were older, with lower education and with higher EuroSCORE. These findings indirectly strengthen the evidence of an association between variables related with cardiac surgery risk as measured with the EuroSCORE (i.e., patient-, cardiac- and operation-related factors) and preoperative cognitive reserve of patients undergoing cardiac surgery. Thus, they also suggest the need for an appropriate psychological evaluation possibly using tests age- and education-corrected providing further useful information concerning the preoperative psychological functioning of cardiac surgery patients. Again, compared to the Stroke Index, the EuroSCORE represents a more suitable risk score able to detect cognitive impairments and mood dysfunctions of high risk patients undergoing cardiac surgery.

The current study had several limitations. First, it did not examine whether preoperative psychological risk factors (e.g., cognitive deficits, anxiety, and depression) may be predictors for early- and long-term adverse clinical and medical outcomes in patients who underwent cardiac surgery. Second, the Experiment I did not investigate the potential role played by *hemodynamic* variables in predicting adverse outcomes after cardiac surgery. To overcome these limitations, a long-term clinical and medical follow-up is still ongoing and the pre and intraoperative hemodynamic risk factors underlying POCD have been examined (Experiment II and III), respectively.

In conclusion, our data suggest that the EuroSCORE may provide a more complete risk score compared to the Stroke Index for patients undergoing cardiac surgery. Thus, the EuroSCORE is recommended as it represents a more accurate mirror of the patient's psychological status compared to the Stroke Index. Moreover, a preoperative age- and education-corrected psychological assessment should be taken into account to evaluate the cognitive functioning, anxiety and depression in patients undergoing cardiac surgery.

3. HEMODYNAMIC RISK FACTORS UNDERLYING COGNITIVE DECLINE AFTER CARDIAC SURGERY

3.1 Study II: Preoperative Cerebral Hypoperfusion and Cognitive Decline after Cardiac Surgery

Cerebral hypoperfusion is one of the major intraoperative risk factor for POCD (Arrowsmith et al., 2000; Fearn et al., 2001; Likoski et al., 2004). The most vulnerable areas of the brain in hypoperfusion are the watershed areas at the junction of the major cerebral arterial territories (Gilman, 1965). During extracorporeal circulation, systemic flow rate is usually based on body surface and the degree of hypothermia and adjusted according to indices of the adequacy of organ perfusion. It is well-established that low pump flow with concurrently arterial hypotension is related to decreased cerebral blood flow velocity. Also, non-pulsatile perfusion has been linked to reduced endothelial shear stress and nitric oxide production which, in turn, may lead to increased vascular resistance and end-organ dysfunction (Macha et al., 1996). Cerebral hypoperfusion seems to be strongly influenced by the duration of extracorporeal circulation. There is converging evidence that patients who have prolonged duration of CPB are at greater risk of cerebral hypoperfusion (and microembolization) and, therefore, are at greater risk of postoperative neurological and cognitive dysfunctions. Indeed, the progressive cerebral vasoconstriction that occurs during prolonged duration of CPB, may lead to a gradual decrease in cerebral blood flow (Prough et al., 1991; Rogers et al., 1988), which, in turn, is associated with adverse cognitive outcome in cardiac surgery patients.

Moreover, given the link between cerebral hypoperfusion, white matter infarctions and damage in prefrontal-basal ganglia network, which, in turn, are related to cognitive

performance, especially to attentional and psychomotor dysfunctions (Roman, 2004), it can be hypothesized that also preoperative reduced cerebral blood flow velocity can be implicated as a physiological risk factor for cognitive impairment after cardiac surgery.

3.1.1 Abstract[2]

Postoperative cognitive decline is a frequent complication after cardiac surgery. Although intraoperative events are risk factors for postoperative cognitive decline, the role played by preoperative hypoperfusion in cognitive decline has not yet been investigated. It is also unknown whether the impact of preoperative hypoperfusion in the left or right middle cerebral arteries can differentially account for postoperative cognitive decline. The main aims of this study were to investigate whether preoperative cerebral hypoperfusion was associated with early postoperative cognitive decline and whether lateralized hypoperfusion would differentially affect postoperative cognitive decline in patients after cardiac surgery. Bilateral middle cerebral arteries continuous transcranial Doppler sonography was preoperatively performed at rest in 31 right-handed patients who underwent cardiac surgery to detect cerebral blood flow velocity. All patients completed a neuropsychological evaluation to assess attention, short-term memory, working memory, and psychomotor function before surgery and at discharge. Postoperative cognitive decline was defined using the standard deviation method. Logistic regression was used to investigate the association between hypoperfusion and postoperative cognitive decline, controlling for common preoperative risk factors. Fourteen patients (45%) exhibited postoperative cognitive decline. Cerebral hypoperfusion in the left middle cerebral artery selectively predicted the incidence of postoperative cognitive decline (*odds ratio* = 0.90, $p < .02$), whereas cerebral blood flow

[2] Abstract published in Messerotti Benvenuti, S., Zanatta, P., Longo C., Mazzarolo, A. P., & Palomba, D. (2012). Preoperative cerebral hypoperfusion in the left, not in the right, hemisphere is associated with cognitive decline after cardiac surgery. *Psychosomatic Medicine, 74*, 73-80.

velocity in the right middle cerebral artery was unrelated to postoperative cognitive decline (*odds ratio* = 1.07, p = .39). Patients who underwent cardiac surgery with reduced cerebral blood flow velocity in the left middle cerebral artery preoperatively are at greater risk for postoperative cognitive decline. Left cerebral hypoperfusion may also represent an independent predictor of postoperative cognitive decline in these patients. Transcranial Doppler evaluation may have substantial clinical benefits for the detection of patients at high risk of postoperative cognitive decline after cardiac surgery.

Keywords: Cardiac surgery patients; Cerebral blood flow velocity; Cognition; Hypoperfusion; Transcranial Doppler

3.1.2 Introduction

The present study was specifically aimed at exploring whether cerebral hypoperfusion could represent a hemodynamic risk factor for POCD in cardiac surgery. Transcranial Doppler studies have recently suggested that hypoperfusion may be the main cause of POCD when cerebral perfusion is decreased in order to minimize intraoperative microembolization (Stump et al., 1996). Moreover, hypoperfusion may also limit the washout of emboli: the watershed cerebral zones represent preferred sites for persistent microemboli in the cerebral circulation. Interestingly, recent evidence indicates that intraoperative microembolization in the left, not in the right middle cerebral artery, is associated with early verbal POCD (Fearn et al., 2001), suggesting a differential impact of lateralized cerebral hypoperfusion on postoperative cognitive dysfunction.

In contrast to the large body of literature on intraoperative events (i.e., microembolization and cerebral hypoperfusion) associated with POCD, the relationship between resting preoperative cerebral blood flow velocity and cognitive dysfunction after

cardiac surgery has been neglected. Indeed, cerebral blood flow velocity may represent a useful and accurate indicator of the preoperative cerebral perfusion underlying cognitive performance (Stroobant & Vingerhoets, 2009) in patients undergoing cardiac surgery, thus contributing to the evaluation of their preoperative risk for POCD. Cerebral hypoperfusion, which often results from cardiovascular dysfunction or hypotension, may cause white matter infarctions and interrupt the prefrontal-basal ganglia networks which, in turn, are associated with working memory, attentional and psychomotor dysfunction, especially in elderly patients (Roman, 2004). Based on these findings, the present study was designed to examine whether preoperative cerebral hypoperfusion could represent a risk factor for cognitive decline in patients who underwent cardiac surgery.

Moreover, it is widely acknowledged in the neuropsychological literature, and also confirmed by studies using transcranial Doppler, functional magnetic resonance or positron emission tomography, that the left hemisphere is specialized for language (Markus & Boland, 1992; Njemanze, 1991; Rihs, Gutbrod, Steiger, Sturzenegger, & Mattle, 1995; Stroobant & Vingerhoets, 2000), verbal working memory (Paulesu, Frith, & Frackowiak, 1993) and psychomotor function (Haaland, Elsinger, Mayer, Durgerian, & Rao, 2004; Rushworth, Krams, & Passingham, 2000; Schluter, Rushworth, Passingham, & Mills, 1998), whereas the right hemisphere is specialized for visuospatial functions, such as spatial memory and orienting (Coull & Nobre, 1998; Droste, Harders, & Rastogi, 1998; Garavan, Ross, & Stein, 1999; Ghilardi et al., 2000; Jonides et al., 1993). Several lines of evidence have shown that the right hemisphere is also specialized for inhibitory functions as revealed by studies on healthy individuals (Garavan et al., 1999) and studies on patients with disinhibition syndromes and elevation of mood or secondary mania associated with depression (Shulman, 1997; Starkstein & Robinson, 1997). Therefore, it may be expected that lateralized preoperative hypoperfusion could differentially affect POCD. However, to our knowledge,

the differential impact of hypoperfusion in the left and right middle cerebral arteries on POCD has not yet been investigated. Accordingly, the current study aimed to investigate whether preoperative lateralized cerebral hypoperfusion differentially affected POCD in cardiac surgery patients.

3.1.3 Methods

Participants

Following local ethics committee approval, 31 right-handed patients admitted for cardiac surgery were sequentially enrolled in the study after giving written informed consent. Each patient was scheduled for first-time cardiac surgery. All patients underwent cardiac surgery at an Italian north-eastern regional hospital from June 2009 to September 2010. Inability to read or understand Italian, visual or auditory impairments, left-hand dominance, use of psychotropic drugs, and prior cerebrovascular and/or neurological diseases were the exclusion criteria. Patients were mostly males (N = 26, 84%), with a mean age of 62.7 years (SD = 12.7) and a mean education of 9.7 years (SD = 4.5). Mean percentage of left ventricular ejection fraction was 64% (SD = 10%). The risk of mortality associated with cardiac surgery was calculated for each patient approximately a week prior to first-time cardiac surgery using the EuroSCORE (Nashef et al., 1999) (for the details of EuroSCORE see p. 69). The mean logistic EuroSCORE was 3.7% (SD = 2.7%) which represents a moderate risk for mortality in cardiac surgery (i.e., EuroSCORE ranges from 3% to 5%) (Nashef et al., 1999).

Twenty patients underwent heart valve surgery (11 patients underwent aortic valve replacement, 9 patients mitral valve replacement), four patients underwent coronary artery bypass graft (two off-pump and two on-pump), and the remaining seven patients underwent combined cardiac surgery (e.g., heart valve surgery plus coronary artery bypass graft).

Independently of original cardiovascular disease, each patient had the same protocol of cardioplegia and a mild hypothermic CPB except for the two patients who had off-pump coronary bypass grafting. CPB lasted 120 min on average (*SD* = 47 min); the mean aortic cross-clamping duration was 80 min (*SD* = 30 min). The mean lengths of postoperative mechanical ventilation and intensive care stay were 7 h (*SD* = 5 h) and 28 h (*SD* = 16 h), respectively. The mean duration of postsurgical stay in the ward was 107 h (*SD*= 43 h), as reported in Table 3.1. All the demographic, biomedical and surgical details are reported in Table 3.1.

Table 3.1 *Characteristics of Patients Enrolled in the Study*

Variable	**Patients (*N* = 31)**
Sex, male (%)	84
Age (years)	62.7 (12.7)
Education (years)	9.7 (4.5)
Weight (Kg)	80 (15)
Height (cm)	170 (9)
Types of cardiac surgery	
- Coronary artery bypass graft (%)	13
- Heart valve replacement (%)	64
- Combined procedures (%)	23
EuroSCORE (%)	3.7 (2.7)
Blood Pressure (mmHg)	78.7 (12)
Heart Rate (bpm)	61.8 (11.3)
Left Ventricular Ejection Fraction (%)	64 (10)
Angina (%)	32
Hypertension (%)	42
Diabetes (%)	23
Atrial fibrillation (%)	16
Duration of Aortic Cross-Clamping (min)	80 (30)
Duration of Extracorporeal Circulation (min)	120 (47)
Duration of Mechanical Ventilation (h)	7 (5)
Duration of Intensive Care (h)	28 (16)
Duration of Hospital Stay (h)	107 (43)
CBF velocity (cm/s)	49.4 (13.3)
- CBF velocity, left MCA (cm/s)	49.3 (17.9)
- CBF velocity, right MCA (cm/s)	49.4 (15.4)

Note: Data are *M* (*SD*) of continuous and *N* (%) of categorical variables. EuroSCORE: European system for cardiac operative risk evaluation; Bpm: Beats per minute; CBF: Cerebral blood flow; MCA: Middle cerebral artery

Transcranial Doppler Recording, Intraoperative Management and Postoperative Values

The week before surgery all patients had a neurosonology evaluation, which consisted of a bilateral middle cerebral arteries cerebral blood flow velocity monitoring at rest with a multifrequency (2.5 – 2 MHz) transcranial Doppler (Doppler box-DWL/Compumedics, Singen, Germany). The two ultrasound probes were fixed on the transtemporal windows by the Lam rack helmet (DWL/Compumedics, Singen Germany) (Figure 3.1).

Prior to surgery all patients were premedicated in the ward with an intramuscular injection of fentanil 100 µg and midazolam 5 mg. The anesthesia induction was established with fentanil 5 µg/Kg, midazolam 0.2 mg/Kg, propofol 1 mg/Kg, and cisatracurium 0.1 mg/Kg before performing the tracheal intubation. The maintenance of anesthesia was performed with propofol 3–5 mg/Kg/min and remifentanil 0.2–0.4 µg/Kg/min just to maintain the bispectral index value lower than 40.

Figure 3.1 The transcranial Doppler apparatus (see also the Lam rack helmet; DWL/Compumedics, Singen Germany).

Cognitive Evaluation

The cognitive evaluation was performed approximately 15 days before cardiac surgery approximately 7 days after cardiac surgery, before discharge from hospital. The evaluation included tests aimed at assessing cognitive functions, including short-term memory, working memory, psychomotor and executive functions. All cognitive tests were administered individually by a trained psychologist blind to the patient's preoperative transcranial Doppler recording in a quiet and isolated room at the hospital. The cognitive tests were as follows:

1- TMT A and B;

2- Memory with interference 10 s / 30 s is a dual task test;

3- Digit Span Test;

4- Phonemic Verbal Fluency.

For the details of each cognitive test used see pp. 70-71.

Statistical Analysis

Clinically significant POCD has been defined as a decline of 1 *SD* in performance in at least one test (Aberg et al., 1984; Calabrese et al., 1987; Elsass & Henriksen, 1984; Fish, Helms, Sarnquist, Tinklenberg, & Miller, 1982; Gill & Murkin, 1996; Klonoff, Clark, Kavanagh-Gray, Mizgala, & Munro, 1989; Sotaniemi et al., 1986). Paired T-tests were performed to compare the preoperative and postoperative scores of each cognitive test overall and separately for the groups with or without POCD. Effect sizes were calculated using Cohen's *d* with values of 0.2, 0.5, and 0.8 corresponding to small medium and large effects, respectively. Hierarchical logistic regression was used to predict POCD (coded: absent = 0, present = 1) from cerebral blood flow velocity, controlling for education and EuroSCORE (which includes sex, age, cardiac- and operation-related factors). Specifically, education and EuroSCORE were entered in step 1 and, then, cerebral blood flow velocity in the left and

right hemispheres were entered in step 2. The odds ratio (*OR*) and 95% confidence intervals (*95% CI*) for each predictor variable are reported.

Spearman's correlation coefficients were calculated between preoperative cerebral blood flow velocity in both the left and right middle cerebral arteries, and each preoperative and postoperative cognitive score. Correlation coefficients were also computed between cerebral blood flow velocity in left or right middle cerebral artery and the residualized change scores for each cognitive test. A *p-value* of < .05 was considered statistically significant. STATISTICA 6.1 (Stat Soft Inc., Tulsa, OK, USA) software was used for all the statistical analyses.

3.1.4 Results

Preoperative and Postoperative Cognitive Functions

The descriptive statistics and the incidence of POCD (i.e., a change from preoperative to postoperative score of greater than 1 *SD*) for each cognitive test are reported in Table 3.2. Fourteen patients (45%) showed a clinically significant cognitive decline after cardiac surgery.

Overall, scores declined for TMT A ($t(30) = -2.71$, $p < .01$, $d = .63$) and TMT B ($t(30) = -1.95$, $p = .06$, $d = .41$) and improved for memory with 30 s interference ($t(30) = -2.33$, $p < .03$, $d = .43$). None of the other neuropsychological scores changed significantly after surgery (p's > .69).

Patients with POCD exhibited significant declines in TMT A ($t(13) = -2.57$, $p < .03$, $d = 0.8$) and TMT B ($t(13) = -2.71$, $p < .02$, $d = .75$) but not in the other cognitive tests (p's > .16). In the group without POCD, performance on the TMT B improved from the preoperative to postoperative period ($t(16) = 2.13$, $p < .05$, $d = .53$).

Table 3.2 *Mean (SD) Scores and Incidence of Postoperative Cognitive Decline for each Cognitive Test*

	Full sample (*N* = 31)		**Group without POCD (*N* = 17)**		**Group with POCD (*N* = 14)**		
Measure	**Preoperative Mean (*SD*)**	**Postoperative Mean (*SD*)**	**Preoperative Mean (SD)**	**Postoperative Mean (*SD*)**	**Preoperative Mean (*SD*)**	**Postoperative Mean (*SD*)**	**Incidence of POCD (*SD* method, %)**
Trail Making Test A[‡]	47 (23)	62 (43)[*]	34 (9)	38 (10)	64 (24)	92 (49)[*]	29
Trail Making Test B[‡]	176 (126)	199 (158)[§]	99 (29)	91 (28)[*]	269 (136)	330 (152)[*]	19
Memory with 10 s int.[†]	6 (2.7)	6.1 (2.8)	7.4 (1.6)	7.9 (1.5)	4.4 (2.8)	3.9 (2.6)	26
Memory with 30 s int.[†]	5.3 (3)	6 (2.8)[*]	6.9 (2.6)	7.5 (2)	3.4 (2.2)	4.1 (2.4)	13
Digit Span Test (forward)[†]	5.1 (1)	5.1 (1.2)	5.7 (0.8)	5.8 (1.1)	4.4 (0.6)	4.3 (0.7)	26
Phonemic Fluency[†]	9 (4)	9.2 (4.3)	10.6 (3.9)	11.3 (3.5)	7.1 (3.3)	6.7 (3.9)	19

Note: [*]Paired T-test, $p < .05$; [§]Paired T-test, $p < 0.1$; [†]Higher scores indicate better functions; [‡]Higher scores indicate worse functions. SD = Standard deviation; POCD = Postoperative cognitive decline

Relationship between Preoperative Cerebral Blood Flow Velocity and Postoperative Cognitive Decline

The multiple logistic regression model showed that POCD was predicted by education (*OR* = 0.69, *95% CI* = 0.50–0.96, $p < .03$), EuroSCORE (*OR* = 2.21, *95% CI* = 1.09–4.47, $p < .03$), and left cerebral blood flow velocity (*OR* = 0.90, *95% CI* = 0.82–0.98, $p < .02$), but not right cerebral blood flow velocity (*OR* = 1.07, *95% CI* = 0.99–1.16, $p = .39$). In brief, POCD was associated with fewer years in formal education, elevated biomedical risk for mortality following cardiac surgery, and, most importantly, reduced blood flow velocity in the left middle cerebral artery. It is worth noting that supplementary analyses indicated that mean cerebral blood flow velocity did not predict POCD.

Relationship between Preoperative Cerebral Blood Flow Velocity and Cognitive Scores

Correlational analyses revealed marginally significant associations between preoperative cerebral blood flow velocity in left middle cerebral artery and preoperative scores of TMT B ($p = .07$), memory with 10 s ($p = .07$) and 30 s ($p = .06$) interference. No significant correlations between left cerebral blood flow velocity and TMT A, Digit Span Test, and Phonemic Fluency were noted. Preoperative cerebral blood flow velocity in right middle cerebral artery was not related to any preoperative cognitive score.

Significant correlations were found between preoperative cerebral blood flow velocity in left middle cerebral artery and postoperative scores of both memory with 10 s interference and memory with 30 s interference. Preoperative cerebral blood flow velocity in left middle cerebral artery was also correlated with postoperative score of TMT B. No significant correlations between cerebral blood flow velocity in left middle cerebral artery and TMT A, Digit Span Test and Phonemic Fluency were detected. Preoperative cerebral blood flow velocity in right middle cerebral artery was unrelated to any postoperative cognitive score.

Residualized change scores for memory with 10 s interference significantly correlated with cerebral blood flow velocity in left middle cerebral artery while no significant correlations were found between other cognitive scores and left cerebral blood flow velocity. Cerebral blood flow velocity in right middle cerebral artery was again unrelated to residualized change in any cognitive scores. All the correlations are reported in Table 3.3.

Table 3.3 *Spearman's (ρ) Correlation Coefficients between Preoperative Cerebral Blood Flow Velocity in the Left or Right Middle Cerebral Artery and Preoperative, Postoperative, and Residualized Change Scores for each Cognitive Test*

Measure	Preoperative		Postoperative		Residualized change	
	CBF velocity		CBF velocity		CBF velocity	
	Left MCA	Right MCA	Left MCA	Right MCA	Left MCA	Right MCA
	ρ	*ρ*	*ρ*	*ρ*	*ρ*	*ρ*
Trail Making Test A‡	-0.18	0.11	-0.23	-0.06	-0.01	-0.13
Trail Making Test B‡	-0.33§	0.0	-0.35*	-0.14	-0.12	-0.25
Memory with 10 s int.†	0.32§	0.23	0.45*	0.20	0.35*	0.10
Memory with 30 s int.†	0.34§	0.19	0.36*	0.21	0.19	0.05
Digit Span Test (forward)†	0.1	-0.05	0.30	-0.21	0.25	-0.12
Phonemic Fluency†	0.23	0.05	0.21	0.09	0.07	0.07

Note: *Spearman's correlation, $p < .05$; §Spearman's correlation, $p < 0.1$; †Higher scores indicate better functions; ‡Higher scores indicate worse functions. CBF = Cerebral blood flow; MCA = Middle cerebral artery

3.1.5 Discussion

The present study investigated the association between preoperative resting cerebral hypoperfusion and postoperative attention, short-term memory, working memory, and psychomotor function. It also aimed to elucidate whether the preoperative reduction of cerebral blood flow velocity in the left or right middle cerebral artery would be selectively related to POCD. Although the overall preoperative cerebral hypoperfusion was not associated with cognitive decline after cardiac surgery, POCD was predicted by reduced preoperative cerebral perfusion in the left (but not in the right) middle cerebral artery. Moreover, this association between hypoperfusion in the left middle cerebral artery and POCD was independent of years of education and EuroSCORE, which includes patient-related factors (e.g., sex, and age), cardiac-related factors (e.g., unstable angina, and pulmonary hypertension) and operation-related factors (e.g., emergency operation, and ventricular septal rupture). Correlation analyses showed an association between preoperative cerebral blood flow velocity in the left, not in the right middle cerebral artery and preoperative and postoperative scores on the executive function tests (i.e., TMT B, memory 10 s, memory 30 s). However, with the exception of reduced left cerebral blood flow velocity being associated with relatively poorer pre-to-post scores on the working memory task, cerebral blood flow velocity was not significantly related to changes in cognitive test performance.

The literature investigating cognitive decline after cardiac surgery has focused on the impact of intraoperative hypoperfusion on POCD (McKhann et al., 2002; Scarborough et al., 2003) showing that it is related to postoperative cognitive performance (Likosky et al., 2004), especially in tests requiring attention (Fearn et al., 2001). During surgery ischemic damage to small vessels in watershed areas of frontoparietal-subcortical regions may selectively impair attention, psychomotor and executive function (Longstreth et al., 1996). Indeed, the

watershed areas at the junction of the major cerebral arterial territories are the most vulnerable to the intraoperative hypoperfusion (Fearn et al., 2001). It is therefore reasonable to assume that this vulnerability may be enhanced in patients whose cerebral perfusion is already impaired before surgery. It has previously been demonstrated that cerebral hypoperfusion resulting from cardiovascular disease causes incomplete white matter infarctions similar to the penumbra of large infarcts (Pantoni, Garcia, & Gutierrez, 1996). Also, elderly patients with cardiovascular diseases and impaired circulation due to atheromatous stenosis of the cerebral arteries are susceptible to watershed infarcts, neuronal loss and ischemic neuronal damage in basal ganglia, cerebellar and cerebral cortex which are highly sensitive to hypoperfusion (Moody, Bell, & Challa, 1990; Roman, 2004). Thus, preoperative hypoperfusion along with subsequent cerebral dysfunctions may represent a relevant risk factor for POCD by reducing the preoperative brain reserve of patients undergoing cardiac surgery (Stroobant & Vingerhoets, 2009). Specifically, the *brain reserve capacity* (Katzman, 1993) or *threshold model* (for a review see Stern, 2002) assume that when synapses are depleted beyond some critical point, the depletion will result in symptoms of sufficient severity to diagnose cognitive impairment. In patients with less reserve, symptoms would appear earlier whereas, conversely, in patients with more reserve, synapses loss must be more severe before symptoms appear. Brain reserve mediates between the clinical outcome and the pathology, and the level of reserve can also influence the severity of symptoms after the threshold for their appearance has occurred. Our findings suggest that preoperative hypoperfusive brain lesions can reduce the brain reserve capacity and, therefore, predispose patients to adverse neurological and cognitive dysfunctions, postoperatively. Along the same line of reasoning, cerebral hypoperfusion may also be the mechanism underlying the *"cardiogenic dementia"* that is the cognitive deterioration observed following recurrent episodes of heart disease or cardiac arrhythmias (see the editorial, *Lancet*, 1981).

Among the neuropsychological tests used here to assess cognitive function, the overall changes from preoperative to postoperative evaluation showed that TMT A and TMT B had a high level of sensitivity for detecting POCD. Several lines of evidence suggest that the cognitive set shifting evaluated with TMT B involves functionally convergent neuroanatomical areas, especially basal ganglia, dorsolateral and medial prefrontal cortices (Zakzanis, Mraz, & Graham, 2005), which, in turn, are particularly susceptible to ischemic hypoperfusive brain lesions (Moody et al., 1990; Roman, 2004). Moreover, the correlational analyses showed that TMT B and memory with interference were sensitive cognitive tests related to preoperative hypoperfusive brain lesions. It is noteworthy that functional neuroimaging studies with healthy human participants have demonstrated increased activity in the medial dorsolateral prefrontal cortex (D'Esposito et al., 1998) during tasks aimed at assessing working memory which may be affected by preoperative cerebral hypoperfusion (Moody et al., 1990; Roman, 2004). Taken together, our findings suggest that executive functions (i.e., set shifting, inhibitory control and working memory assessed with TMT B and memory with 10 and 30 s interference, respectively) are more sensitive to reduced cerebral blood flow velocity in left middle cerebral artery compared to other cognitive functions, such as psychomotor speed and short-term memory (assessed with TMT A and Digit Span Test, respectively).

Our study also showed that cerebral hypoperfusion in left middle cerebral artery was selectively related to POCD in cardiac surgery patients whereas cerebral blood flow velocity in right middle cerebral artery did not predict the incidence of POCD. Indeed, hypoperfusion in the left hemisphere was an independent risk factor for POCD. These results are also consistent with the correlational data showing associations between preoperative cerebral blood flow velocity in the left, not in the right middle cerebral artery, on the one hand, and

preoperative, postoperative, and the change from pre-to-post (memory 10 s) in working memory and executive function, on the other hand.

Previous studies have suggested that the right hemisphere is likely to be more affected by intraoperative events than left hemisphere given that the brachiocephalic artery has a more direct origin from the aortic arch which in turn may enhance microembolization from the heart or CPB circuit (Coffey et al., 1983; Sotaniemi, Juolasmaa, & Hokkanen, 1981). Thus, our findings suggest that factors other than neuroanatomical pathways should be taken into account to help minimize POCD due to cerebral hypoperfusion. Indeed, a recent study has reported that postoperative cognitive dysfunction mainly occurs when intraoperatively hypoperfusion and/or microembolization is greater in the left middle cerebral artery compared to the right middle cerebral artery (Fearn et al., 2001). Our findings also extend the literature by showing that not only intraoperative but also preoperative hypoperfusion in the left middle cerebral artery represents a significant risk factor for POCD compared to hypoperfusion in the right middle cerebral artery. This suggests that the left hemisphere may be more sensitive to preoperative hypoperfusive brain lesions (reduced blood flow) than the right hemisphere or, alternatively, that cognitive functions commonly impaired after cardiac surgery are more sensitive to preoperative hypoperfusion in the left hemisphere than in the right hemisphere. Specifically, functional magnetic resonance studies have observed activation of the left dorsolateral prefrontal cortex and supplementary motor area when contrasting Part B versus Part A of a verbal adaptation of the TMT, a format which reduces the visuomotor and visuospatial components of the written TMT (Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002). These findings are consistent with other neuroimaging data that implicate the bilateral intraparietal sulci as well as the left dorsolateral and medial prefrontal cortices in tasks that evaluate set shifting, cognitive flexibility and, to a certain extent, working memory. In line with these neuroimaging findings, Zakzanis and colleagues

(2005) have recently shown a distinct left-sided and medial prefrontal activity using a functional magnetic resonance-compatible virtual stylus which simulated the traditional paper and pencil version of the classic TMT. Therefore, the hypothesis that, compared to the right hemisphere, the left hemisphere is more susceptible to preoperative hypoperfusive brain lesion, which, in turn, is associated with generalized POCD, seems to be tenable. It is noteworthy that handedness may also provide a further explanation of our data. While left-handers seem to show a more variable pattern of hemispheric dominance (Stroobant & Vingerhoets, 2000) and a minor degree of hemispheric dominance (Gur et al., 1982), most right-handed patients have a left hemisphere specialization for language and verbal tasks. Given that the current study controlled for possible handedness bias by selecting a homogenous group of right-handed patients, the enhanced sensitivity of POCD to preoperative hypoperfusive brain lesions in the left hemisphere may be associated with right-handed dominance.

Nonetheless, this alternative interpretation of the results should be viewed with caution. Although POCD is usually evaluated with cognitive tests that may be more sensitive to left than right hemisphere cognitive dysfunction, e.g., lexical access (Gazzaniga, 2005), verbal working memory (Paulesu et al., 1993) and psychomotor skills (Haaland et al., 2004; Serrien, Ivry, & Swinnen, 2006; Zwinkels, Geusgens, van de Sande, & van Heugten, 2004), the strongest connectivity in the brain may be between homologous regions in both hemispheres, and it seems unlikely that cognitive tests activate the left hemisphere in isolation. Indeed, tasks investigating executive functions, especially TMT which involves visuospatial and visuomotor skills, seem to require coordinated neural activity among several cortical and subcortical regions. Although several studies have described TMT as one of the most sensitive tests to detect brain dysfunction (Crawford, Parker, & McKinlay, 1992; Lezak et al., 2004; Spreen & Strauss, 1991), hemispheric lesions cannot be determined using TMT

because it involves activation of different brain regions in both right and left hemispheres (Heillbronner, Henry, Buck, & Adams, 1991; Reitan & Wolfson, 1995). More importantly, Garavan and colleagues. (1999) have suggested that response inhibition, a primary component of TMT B, is performed by a distributed collection of primarily frontal, especially dorsolateral prefrontal cortex, and largely right hemisphere regions. Previous studies of healthy individuals and patients provided evidence of right hemisphere activation during tasks involving an inhibitory component (Klingberg & Roland, 1997; Ponesse et al., 1998; Shulman, 1997; Starkstein & Robinson, 1997). Interestingly, Monchi and colleagues (Monchi, Petrides, Petre, Worsley, & Dagher, 2001) have also shown activation of the basal ganglia cortical loop involving caudate nucleus, mediodorsal thalamus and mid ventrolateral prefrontal cortex during a set shifting task (i.e., Wisconsin Card Sorting Test). Taken together, these studies suggest an activation of some convergent cerebral areas involved in the regulation of set shifting and inhibition assessed with executive function tasks similar to TMT (Garavan et al., 1999; Monchi et al., 2001). It may be argued that our cognitive tests battery evaluated the overall integrity of several cortical and subcortical brain networks, especially the dorsolateral prefrontal cortex and basal ganglia in both the left and right hemisphere.

In conclusion, in addition to intraoperative cerebral hypoperfusion, a preoperative reduced cerebral blood flow velocity at rest in the left middle cerebral artery may represent a further risk factor for short-term and working memory, attention and psychomotor function after cardiac surgery. Therefore, the preoperative cerebral monitoring through transcranial Doppler, especially in the left middle cerebral artery, may represent an important instrument to preoperatively detect patients at high-risk of POCD; it could also provide useful information to guide intraoperative management of patients undergoing cardiac surgery.

3.2 Study III: The Role of Intraoperative Microembolization in Cognitive Decline after Heart Valve Surgery

There are several lines of evidence that, along with cerebral hypoperfusion, intraoperative microembolization causes cognitive impairment if emboli enter the cerebral circulation in significant numbers (Pugsley et al., 1994). Transcranial Doppler studies have recently confirmed that intraoperative microembolization is directly related to POCD (Hogue et al., 2008; Russel, 2002), especially with attentional (Borger, Peniston, et al., 2001; Deklunder, Prat, et al., 1998; Deklunder, Roussel, et al., 1998; Fearn et al., 2001; Pugsley et al., 1994; Stump et al., 1996), short-term and episodic memory (Borger, Peniston, et al., 2001, Pugsley et al., 1994; Stump et al., 1996), working memory (Deklunder, Prat, et al., 1998; Deklunder, Roussel, et al., 1998; Fearn et al., 2001), and psychomotor dysfunctions (Borger, Peniston, et al., 2001; Deklunder, Roussel, et al., 1998; Pugsley et al., 1994) after cardiac surgery.

It is well-established that heart valve surgery represents a major risk factor for intraoperative microembolization in comparison with CABG (Abu-Omar et al., 2004; Braekken et al., 1998; Hermann et al., 1998; Thiel et al., 1997). Specifically, Abu-Omar et al. (2004) found that, compared to off-pump CABG (i.e., without CPB), there is a 7-fold increase in microemboli in on-pump CABG (i.e., with CPB) and a 22-fold increase in open procedures (e.g., heart valve surgery, and combined procedure). The total median of microemboli in off-pump CABG (i.e., without extracorporeal circulation) procedure was 40 (interquartile range: 28-80), whereas it was 275 (interquartile range: 199-472) and 860 (interquartile 393-1321) during on-pump CABG (i.e., with extracorporeal circulation) and heart valve surgery (i.e., open procedures), respectively. Figures 3.2 and 3.3 show the percentages of gaseous and solid microembolization during the course of on-pump CABG

and open procedures (i.e., heart valve surgery), respectively. In particular, in heart valve surgery, gaseous microemboli may enter the circulation during the bypass circuit after blood sampling and injection of drugs, and during cardiac ejection (Blauth, 1995). Moreover, the increase in numbers of gaseous microembolization in heart valve surgery is in line with transesophageal echocardiographic findings even after de-airing procedures (Tingleff, Joyce, & Pettersson, 1995). Based on these considerations, the present study was designed to investigate the impact of intraoperative microembolization in patients who underwent heart valve surgery.

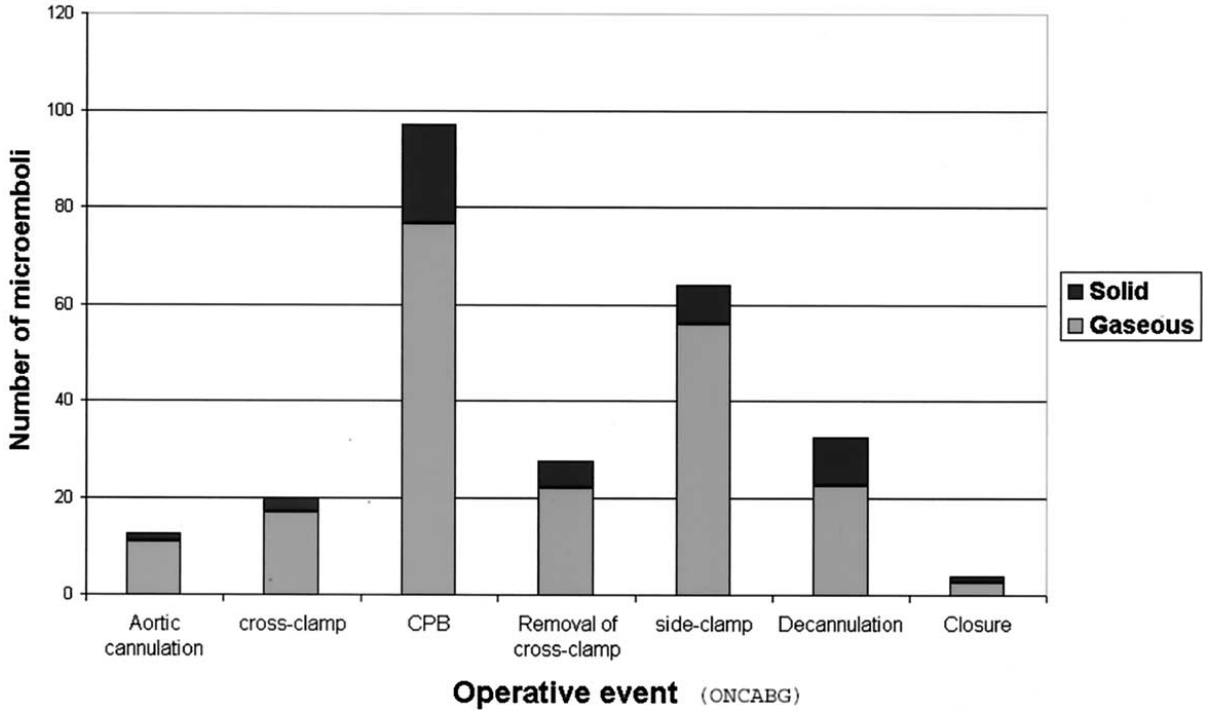

Figure 3.2 Gaseous and solid microembolization during the course of ONCABG. ONCABG = on-pump coronary artery bypass graft; CPB = cardiopulmonary bypass. From Abu-Omar et al., 2004

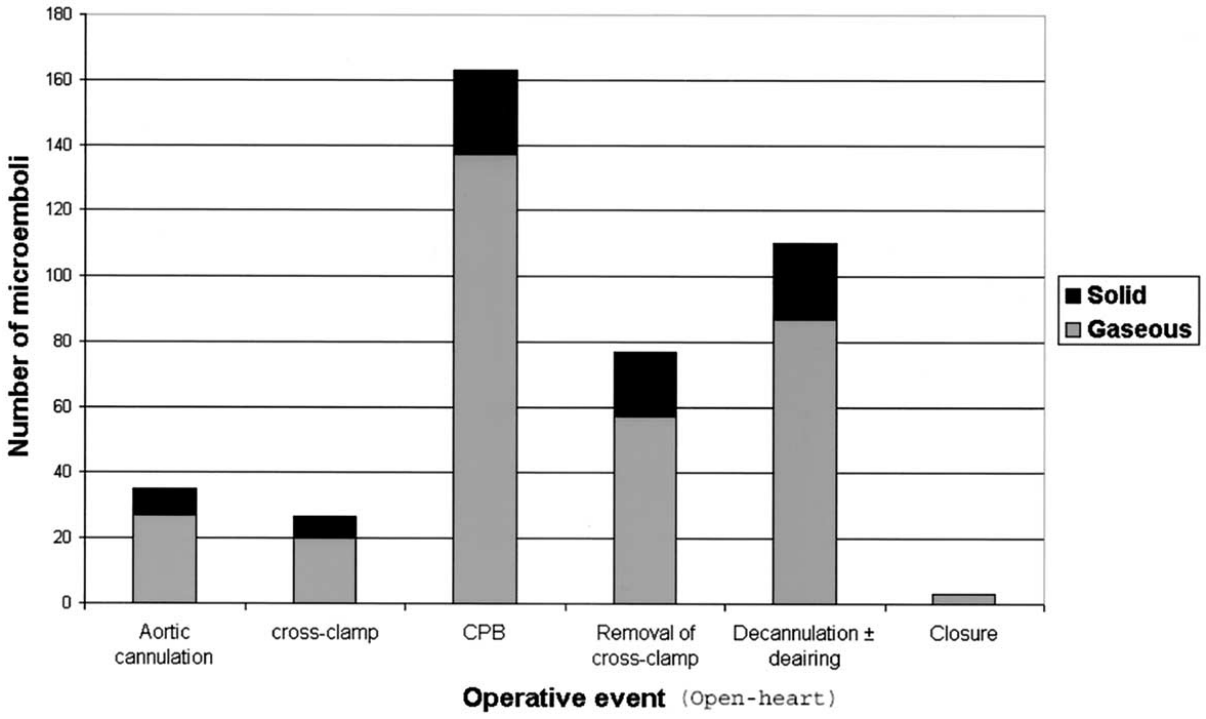

Figure 3.3 Gaseous and solid microembolization during the course of an open procedure. CPB = cardiopulmonary bypass. From Abu-Omar et al., 2004

3.2.1 Abstract[3]

Our objective was to determine the role of asymmetry and the nature of microembolization on postoperative cognitive decline in patients who had undergone heart valve surgery. Continuous transcranial Doppler ultrasound was intraoperatively used for both middle cerebral arteries in 13 right-handed heart valve surgery patients to detect microembolization. Trail Making Test A and B, Memory with 10/30 s interference, Digit Span Test and Phonemic Fluency were performed preoperatively, at discharge and three months after surgery. Our data suggests that early and late postoperative psychomotor and executive functions might be sensitive to microemboli in the left but not the right middle cerebral artery. Moreover solid and gaseous microemboli are both similarly associated with early postoperative cognitive decline while, surprisingly, late postoperative cognitive decline is more likely to be caused by gaseous than solid microemboli.

Keywords: Cardiac surgery; Cognition; Heart valve surgery; Microembolization; Transcranial Doppler

[3] Abstract in press in Zanatta, P., Messerotti Benvenuti, S., Valfrè, C., Baldanzi, F., & Palomba, D. (in press). The role of asymmetry and the nature of microembolization in cognitive decline after heart valve surgery: a pilot study. *Perfusion*.

3.2.2 Introduction

The present study specifically aimed at exploring whether cerebral microembolization could represent a risk factor for POCD in heart valve surgery patients. Several studies using intraoperative transcranial Doppler monitoring have recently shown that the number of microemboli is directly associated with early POCD (Deklunder, Roussel, et al., 1998; Fearn et al., 2001). A few studies have also investigated the potential role of asymmetric intraoperative microembolization on cognitive decline (Bokeriia et al., 2007; Fearn et al., 2001; Jacobs et al., 1998; Lee et al., 2003). These studies have shown that microembolization may induce specific cognitive impairment in accordance to the brain region to which they are delivered.

Memory, psychomotor and executive functions seem to be affected more than other cognitive domains by intraoperative microemboli during both CABG (Fearn et al., 2001; Pugsley et al., 1994) and heart valve surgery (Deklunder, Roussel, et al., 1998). Although a few studies did not find an association between intraoperative microemboli and POCD in heart valve surgery patients (Neville, Butterworth, James, Hammon, & Stump, 2001), it is widely acknowledged that heart valve surgery represents a major risk factor for intraoperative microembolization in comparison with CABG (Abu-Omar et al., 2004; Thiel et al., 1997) and, therefore, for cognitive deficits after cardiac surgery (Braekken et al., 1998; Hermann et al., 1998). However, the differential impact of asymmetric microembolization on POCD was examined only in CABG patients (Fearn et al., 2001; Jacobs et al., 1998; Lee et al., 2003) or, at best, in both CABG and open heart surgery patients without differentiating between aortic and valve surgery (Bokeriia et al., 2007).

More recently, transcranial Doppler technology has allowed the discrimination of solid from gaseous intraoperative microemboli (Russel & Brucher, 2002). It has been hypothesized that POCD is more likely to be associated with solid than gaseous

microembolization (Abu-Omar et al., 2004). However, the literature is still lacking with regard to the potentially different roles played by both solid and gaseous intraoperative microemboli in early and late cognitive decline after cardiac surgery, especially in patients underwent heart valve surgery.

Accordingly, the current study examined the differential impact of asymmetry (i.e. left or right middle cerebral artery) and the nature (i.e. solid or gaseous) of intraoperative microembolization on attention, short-term memory, working memory, and psychomotor function in patients who underwent heart valve surgery. Our analyses explored whether microembolization in the left or right middle cerebral artery had a differential impact on early (i.e. at discharge) or late (i.e. at a three-month follow-up) POCD. Whether solid or gaseous microemboli have a differential impact on early or late POCD was also considered.

3.2.3 Methods

Participants

Following the local ethics committee's approval, 13 right-handed patients were asked to give their written informed consent and were enrolled in the study. All of the patients underwent a comprehensive cognitive evaluation preoperatively, before the patients were discharged from hospital and three months after surgery. They underwent aortic or mitral valve replacement because of aortic valve stenosis or mitral valve insufficiency, respectively. CABG or combined heart surgery, the inability to read or understand the Italian language, visual or auditory impairments and the use of psychotropic drugs were the criteria for exclusion. The patients were predominantly male (N = 11, 84.6%), with a mean age of 63.2 years (SD = 11.1) and a mean level of education of 10.5 years (SD = 5.2). The mean percentage of left ventricular ejection fraction was 64.5 % (SD = 11) that falls into the normal range (Paulus et al., 2007). The risk of mortality associated with cardiac surgery was

calculated using the logistic EuroSCORE (Nashef et al., 1999; for the details of EuroSCORE see p. 69). The mean logistic EuroSCORE rating was 4.1% (*SD* = 4.7%) which represents a moderate risk for mortality in cardiac surgery (i.e., EuroSCORE ranges from 3% to 5%) (Nashef et al., 1999).

Anesthesia, Surgical Management and Transcranial Doppler Monitoring

The patients were premedicated in the ward with an intramuscular injection of fentanil 100 mcg and midazolam 5 mg. The anesthesia induction was established with fentanil 5 mcg/Kg, midazolam 0.2 mg/Kg, propofol 1 mg/Kg, and cisatracurium 0.1 mg/Kg before the tracheal intubation was performed. The maintenance of anesthesia was performed with propofol 4 mg/Kg/min and remifentanil 0.4 mcg/Kg/min, in order to maintain a bispectral index value lower than 40. All of the patients were anesthetized by the same physician. Before the skin incision, the patient's bilateral middle cerebral arteries cerebral blood flow velocity was monitored and any emboli were detected and differentiated with a multifrequency (2.5-2 MHz) transcranial Doppler (DWL/Compumedics, Singen Germany). The double ultrasound emission allowed the detection of solid microemboli because they reflect more high frequency ultrasound than the gaseous microemboli which, in turn, reflect more low frequency ultrasound (Figure 3.4).

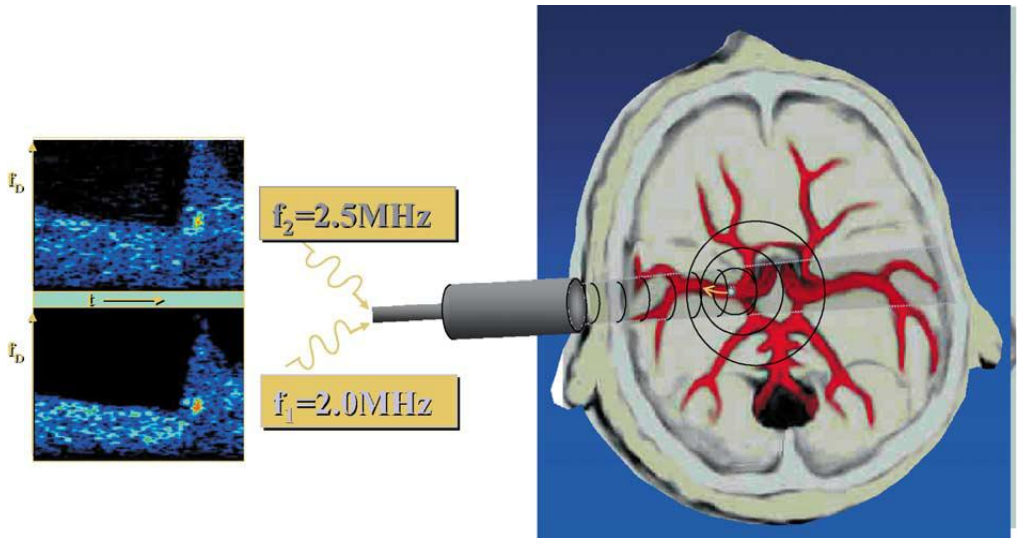

Figure 3.4 Multifrequency Doppler with insonation of the middle cerebral arteries using 2.0 and 2.5 MHz frequencies. From Russel, 2002

The two ultrasound probes were fixed on the transtemporal windows by the Lam rack helmet (Doppler box-DWL/Compumedics, Singen, Germany). The cerebral blood flow velocity spectra and the emboli differentiation count were calculated offline by the same intraoperative neurophysiologist-anesthesiologist who had previously performed the anesthesia and the transcranial Doppler monitoring.

Nine patients underwent an aortic valve replacement, while the others (*N* = 4) underwent a mitral valve replacement. They all had the same protocol of cardioplegia and a mild hypothermic CPB. The CPB lasted for an average of 106 min (*SD* = 30 min), while the average duration of the aortic cross-clamping procedure was 79 min (*SD* = 29 min). The mean durations of postoperative mechanical ventilation and the patients' stay in intensive care were 8 h (*SD* = 6 h) and 28 h (*SD* = 15 h), respectively. The average length of the patients' postsurgical stay in the ward was 102 h (*SD* = 34 h).

Cognitive Evaluation

A cognitive evaluation was performed two weeks prior to surgery, approximately one week after surgery when the patient was discharged from the hospital, and at a three-month follow-up. It included tests aimed at assessing cognitive performances such as memory, psychomotor and executive functions. The cognitive tests were as follows:

1- TMT A and B;

2- Memory with interference 10 s / 30 s is a dual task test;

3- Digit Span Test;

4- Phonemic Verbal Fluency.

For the details of each cognitive test used see pp. 70-71.

All of the cognitive tests were administered on an individual basis by a trained psychologist who was blind to the patients' transcranial Doppler emboli detection procedure in a quiet and isolated room at the Cardiovascular Department of Treviso Regional Hospital.

Statistical Analysis

The total number of microemboli which occurred in the left or right middle cerebral artery was calculated. The total number of solid or gaseous microemboli regardless of their localization and cognitive scores were also calculated for each patient. Paired t-test analyses were conducted for the total number of microemboli in the left and right middle cerebral arteries. The difference between solid and gaseous microemboli was analysed as well. Unpaired t-test analyses were also performed in order to investigate whether the patients who had undergone aortic or mitral valve replacement were homogenous for the total number of left or right middle cerebral artery microembolization as well as for the total number of solid or gaseous microemboli.

Both early and late POCD were respectively calculated as the preoperative raw scores - raw scores at discharge or the preoperative raw scores - raw scores at a three-month follow-up for each cognitive test. Statistical correlations were calculated between the number of microemboli which occurred during intraoperative heart valve surgery in the left or right middle cerebral arteries and early and late postoperative changes in score on each of the cognitive tests. Statistical correlations were also studied between the number of solid or gaseous microemboli and early and late postoperative changes in score on each of the cognitive tests. All statistical correlations were conducted using non-parametric Spearman's correlation coefficients. A *p-value* of $< .05$ was considered as being statistically significant. STATISTICA 6.1 (Stat Soft Inc., Tulsa, OK, USA) software was used for each statistical analysis.

3.2.4 Results

No patients had major neurologic postoperative events such as transient ischemic attack, stroke, coma, seizures or delirium. No significant difference was found between the total number of microemboli in the left and right middle cerebral arteries ($t(9) = -1.30$, $p = .23$). The number of gaseous microemboli was significantly larger than the number of solid ones ($t(10) = -3.75$, $p < .004$). Moreover, no significant differences were found between patients who had undergone aortic or mitral valve replacement in the total number of microemboli in the left ($t(10) = 1.08$, $p = .31$) and right middle cerebral artery ($t(9) = -0.80$, $p = 0.44$) as well as in the total number of solid ($t(11) = 1.37$, $p = .20$) and gaseous microemboli ($t(11) = -0.57$, $p = .58$).

Asymmetric Microembolization and Early Postoperative Cognitive Decline

Significant correlations were found between the total number of left microemboli and early POCD in TMT A (ρ = -.67, p < .02) and TMT B (ρ = -0.61, p < .05), but not for Memory with 10 (ρ = .35, p = .26) and 30 s Interference (ρ = .00, p = .99), Phonemic Fluency (ρ = -.07, p = .83) and Digit Span Test (ρ = .46, p = .13). The right microemboli failed to show significant correlations with TMT A (ρ = -.31, p = .35), TMT B (ρ = -.59, p = .06), memory with 10 (ρ = .35, p = .30) and 30 s Interference (ρ = .54, p = .08), Phonemic Fluency (ρ = -.02, p = .96) and Digit Span Test (ρ = .32, p = .33). All details of correlation analyses are reported in Table 3.4. Correlations between the left or right and early postoperative decline in TMT A or TMT B are shown in Figure 3.5.

Asymmetric Microembolization and Late Postoperative Cognitive Decline

Left microembolization showed significant correlations with cognitive decline at a three-month follow-up in TMT A (ρ = -0.63, p < .05) and Digit Span Test (ρ = .65, p < .03), but not in TMT B (ρ = -.07, p = .82), Memory with 10 (ρ = .08, p = .81) or 30 s Interference (ρ = .13, p = .68) and Phonemic Fluency (ρ = -.02, p = .96). No significant correlations were observed between right microembolization and cognitive decline at three months in TMT A (ρ = -.27, p = .45), TMT B (ρ = -.32, p = .36), Memory with 10 (ρ = .22, p = .51) and 30 s Interference (ρ = -.15, p = .66), Phonemic Fluency (ρ = -.11, p = .74), and Digit Span Test (ρ = .52, p = .10). All details of correlation analyses are reported in Table 3.4. Correlations between left or right and late postoperative decline in TMT A or Digit Span Test are shown in Figure 3.6.

Table 3.4 *Spearman's (ρ) Correlation Coefficients between Left or Right Microemboli and Postoperative Cognitive Decline at Discharge and Three-Month Follow-up*

Measure	Discharge		Follow-up	
	Left microemboli	**Right microemboli**	**Left microemboli**	**Right microemboli**
	ρ	***ρ***	***ρ***	***ρ***
Change in Trail Making Test A[‡]	-.67[*]	-.31	-.63[*]	-.27
Change in Trail Making Test B[‡]	-.61[*]	-.59	-.07	-.32
Change in Memory with 10 s Interference[§]	.35	.35	.08	.22
Change in Memory with 30 s Interference[§]	.00	.54	.13	-.15
Change in Phonemic Fluency[§]	-.07	-.02	-.02	-.11
Change in Digit Span Test (forward)[§]	.46	.32	.65[*]	.52

Note: [*] $p < .05$; [‡]Higher scores indicate better functioning; [§]Higher scores indicate worse functioning.

Microemboli in the Left or Right Middle Cerebral Artery and Early Postoperative Cognitive Decline

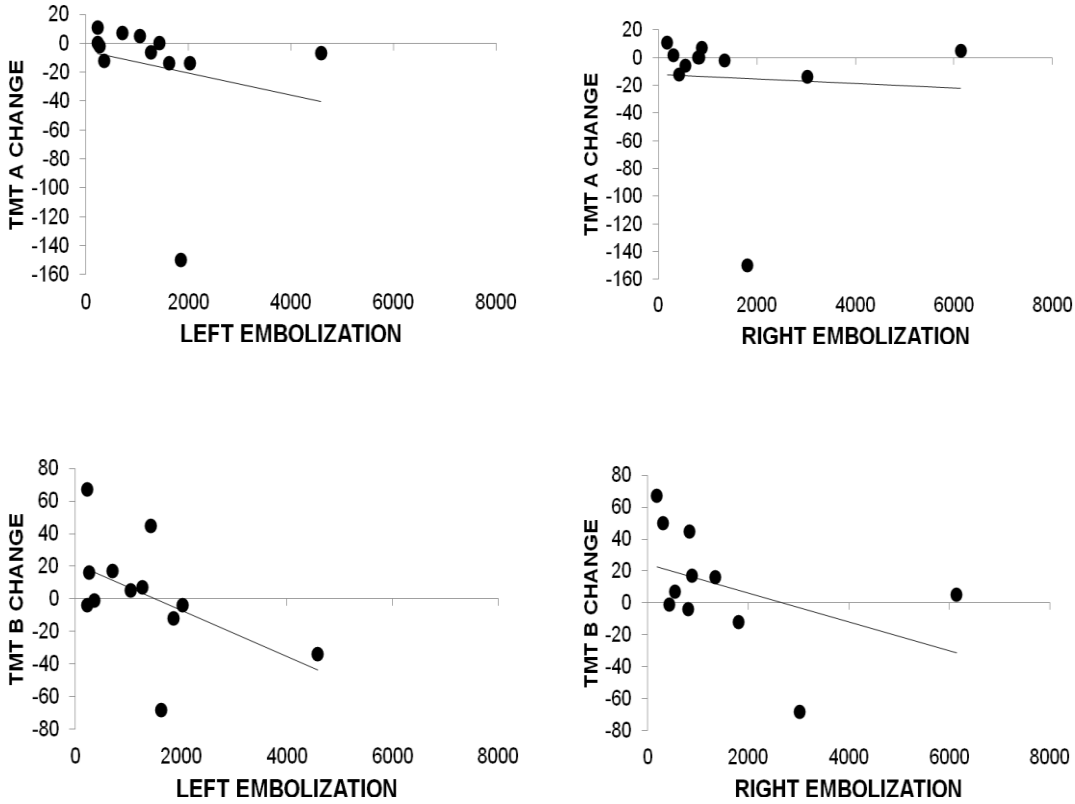

Figure 3.5 Correlations between microemboli in both the left and right middle cerebral arteries and changes in the Trail Making Test part A (TMT A) and part B (TMT B) scores at discharge. Change in TMT A/B: higher scores indicate better functioning.

Microemboli in the Left or Right Middle Cerebral Artery and Late Postoperative Cognitive Decline

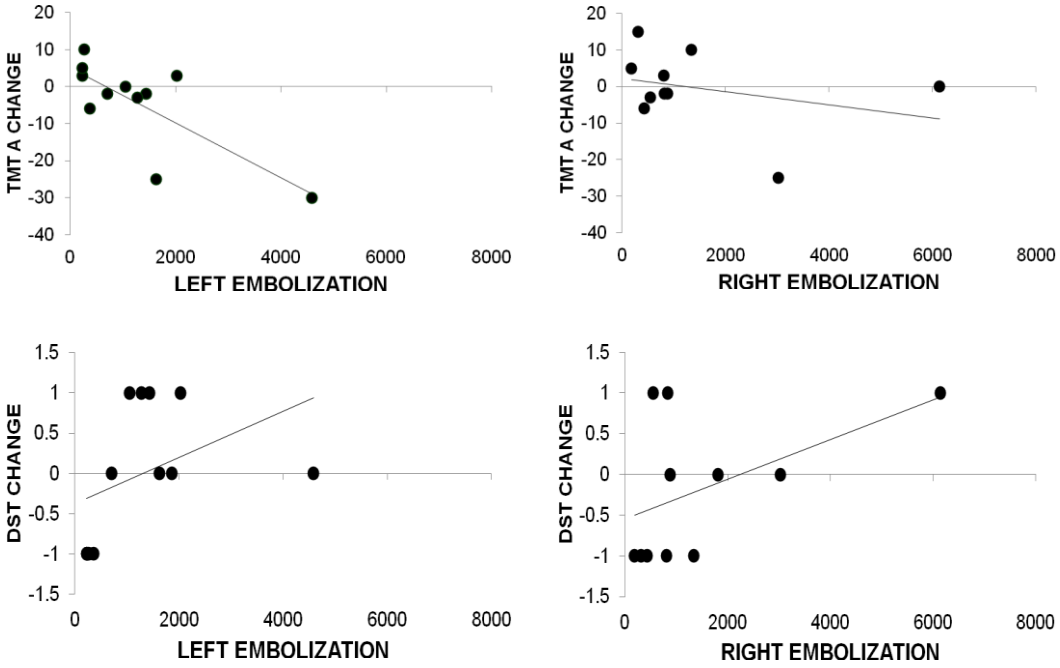

Figure 3.6 Correlations between microemboli in both the left and right middle cerebral arteries and changes in the Trail Making Test part A (TMT A) and the Digit Span Test (DST) scores at three months after surgery. Change in TMT A: higher scores indicate better functioning; Change in Digit Span Test: higher scores indicate worse functioning.

Solid or Gaseous Microembolization and Early Postoperative Cognitive Decline

Moreover, significant correlations were found between solid microemboli and early POCD in TMT A (ρ = -.78, p < .003) and TMT B (ρ = -.79, p < .002), but not with Memory with 10 (ρ = .25, p = .40) and 30 s periods of interference (ρ = .10, p = .74), Phonemic Fluency (ρ = .19, p = .54) and Digit Span Test (ρ = .20, p = .51). Gaseous microemboli were significantly correlated with early POCD in TMT B (ρ = -.62, p < .03) but not with TMT A (ρ = -.39, p = .18), Memory with 10 (ρ = .42, p = .15) and 30 s Interference (ρ = .46, p = .11), Phonemic Fluency (ρ = -.15, p = .62) and Digit Span Test (ρ = .39, p = .18) (Table 3.5).

Solid or Gaseous Microembolization and Late Postoperative Cognitive Decline

No significant correlations were found between solid microemboli and late POCD in TMT A (ρ = -.45, p = .15), TMT B (ρ = -.24, p = .46), Memory with 10 (ρ = -.09, p = .77) and 30 s Interference (ρ = -.18, p = .55), Phonemic Fluency (ρ = .10, p = .75) and Digit Span Test (ρ = .26, p = .39), gaseous microemboli showed significant correlations with late cognitive decline in TMT A (ρ = -.58, p < .05) and Digit Span Test (ρ = .73, p < .005). Gaseous microemboli did not significantly correlate with TMT B (ρ = -.08, p = .79), Memory with 10 (ρ = .28, p = .35) and 30 s Interference (ρ = .04, p = .89) or Phonemic Fluency (ρ = -.10, p = .74). All of the statistical correlations between solid or gaseous microemboli and early and late POCD are reported in Table 3.5.

Table 3.5 *Spearman's (ρ) Correlation Coefficients between Solid or Gaseous Microemboli and Postoperative Cognitive Decline at Discharge and Three-Month Follow-up*

Measure	Discharge		Follow-up	
	Solid microemboli	**Gaseous microemboli**	**Solid microemboli**	**Gaseous microemboli**
	ρ	***ρ***	***ρ***	***ρ***
Change in Trail Making Test A[‡]	-.78[**]	-.39	-.45	-.58[*]
Change in Trail Making Test B[‡]	-.79[**]	-.62[*]	-.24	-.08
Change in Memory with 10 s Interference[§]	.25	.42	-.09	.28
Change in Memory with 30 s Interference[§]	.10	.46	-.18	.04
Change in Phonemic Fluency[§]	.19	-.15	.10	-.10
Change in Digit Span Test (forward)[§]	.20	.39	.26	.73[**]

Note: [*] $p < .05$; [**] $p < .001$; [‡]Higher scores indicate better functioning; [§]Higher scores indicate worse functioning.

3.2.5 Discussion

The present study is a report on the relationship between the number of intraoperative microemboli detected by transcranial Doppler on the left or right with changes in early and late postoperative cognitive scores assessing memory, psychomotor and executive functions. Given that the total number of microemboli did not show a significant difference between the left and right middle cerebral arteries, the findings obtained in the present study have several implications.

Our data are in line with previous studies which have shown a relationship between intraoperative microembolization in the left middle cerebral artery and early POCD (Bokeriia et al., 2007; Fearn et al., 2001; Lee et al., 2003). Interestingly, our findings showed that early POCD in psychomotor and executive functions as measured by validated instruments such as TMT A and TMT B was associated with microembolization in the left, not the right, hemisphere.

An association between late POCD in psychomotor functioning and verbal memory and microembolization in the left, not in the right, hemisphere was also observed. Hence, it was shown that microembolization in the left middle cerebral artery that occurs during heart valve surgery may involve not only a POCD in verbal memory but also in psychomotor and executive functions both at discharge and after three months. Indeed, it is known that the parietal and temporal regions of the brain in the left hemisphere are dominant in terms of both psychomotor skills and verbal memory performances as assessed by TMT A/B and Digit Span Test, respectively (Haaland et al., 2004; Serrien et al., 2006).

Our results extend the previous data by showing that TMT A and TMT B have a high level of sensitivity to microembolization in the left middle cerebral artery during heart valve surgery as well as Digit Span Test forward (Bokeriia et al., 2007). On the other hand, Memory tests with 10 and 30 s of Interference and Phonemic Fluency tests did not show an

adequate level of sensitivity to intraoperative brain damage in the left or the right middle cerebral artery. It may be also suggested that complex tasks evaluating higher cerebral processes (i.e. psychomotor and executive functions) such as TMT A and TMT B may be more sensitive to brain damage due to intraoperative microemboli when compared to simple tasks, namely memory with 10 and 30 s of Interference or Phonemic Fluency.

The differential impact of the nature of intraoperative microembolization was investigated as well. In agreement with previous studies, the majority of intraoperative microemboli which occurred during heart valve surgery was gaseous (Abu-Omar et al., 2004; Russel & Brucher, 2002; Telman, Kouperberg, Sprecher, & Yarnitsky, 2002). However, both solid and gaseous microemboli which were detected in the left or right middle cerebral artery were similarly related with early POCD. Indeed, even if only solid microembolization may affect early POCD in psychomotor functioning, both solid and gaseous microemboli were equally associated with changes in executive functions. This suggests that lateralized early cognitive decline was partially independent of the nature of microembolization.

Surprisingly, cognitive decline after three months in psychomotor functioning and verbal memory in heart valve surgery patients was more likely to be associated with gaseous than solid microembolization. It may be suggested that gas microbubbles can induce brain ischemia due to both an occlusive mechanism, exactly what a solid particulate does, and a humoral immune reaction; furthermore, this inflammatory response can lead to local injuries and increase the chance of ischemic results which, in turn, can affect both early and late postoperative cognitive performance (Muth & Shank, 2000). Thus, our data also seem to extend the findings in the existing literature by showing that intraoperative solid microemboli were potentially no more damaging than gaseous ones in terms of early POCD; furthermore, it was shown that POCD detected after three months is more likely to be associated with gaseous than solid microembolization.

As a major strength, we investigated the relationship between the impact of asymmetric intraoperative microembolization and early or three-month POCD in a group with homogenous demographic, clinical and intraoperative characteristics. Indeed, no differences between patients who had undergone aortic or mitral valve surgery occurred in both the total number of left or right middle cerebral artery and solid or gaseous microembolization. The current study not only provides the evidence that intraoperative microemboli are strongly related with early postoperative cognitive dysfunction, but also may extend the previous literature indicating that microembolization in the left but not in the right middle cerebral artery is associated with late postoperative cognitive impairment in psychomotor functioning and verbal memory. Finally, our findings provide further evidence for the long-term effects of microembolization on cognitive functions and also suggest that intraoperative microembolization may induce specific POCD in accordance with the brain region in which they are formed, namely the left temporal and parietal regions of the brain.

4. DEPRESSION, EMOTION REGULATION, AND COGNITIVE DYSFUNCTIONS AFTER CARDIAC SURGERY

Depression is commonly reported in patients after cardiac surgery. Preoperative incidence of depression varies between 27% and 36% (Langeluddecke et al., 1989; McKhann et al., 1997). Importantly, it is well-recognized that depressive symptoms persist postoperatively for most patients undergone cardiac surgery and, therefore, are the major predictor of postoperative depression (Magni et al., 1987; McKhann et al., 1997; Strauss et al., 1992). Indeed, Magni et al. (1987) found that 34% of the variation in postoperative depressed mood was significantly predicted by preoperative depression scores. McKhann et al. (1997) found that, compared to 13% of patients not depressed prior to surgery, more than 50% of patients with preoperative depression were depressed 1 month after surgery. In turn, there is converging evidence that depression is an important and independent risk factor for subsequent cardiac events and/or mortality in patients after cardiac surgery (Blumenthal et al., 2003; Burg et al., 2003; Connerney et al., 2001; Gardner & Worwood, 1997).

Depression has been considered a disorder of emotion regulation characterized by persistent negative affect and/or lack of positive affect (for a review see, Davidson, Pizzagalli, Nitschke, & Putnam, 2002). There is evidence that depression alters the commonly used strategies to down-regulate emotions, namely reappraisal and suppression. Reappraisal, on the one hand, consists of changing the way a situation is construed in order to decrease its emotional impact. On the other hand, suppression comes later in the emotion regulation and consists of inhibiting the outward signs of inner feelings (Gross, 2002).

Cognitive deficits are commonly observed in depressed patients (Lezak et al., 2004). Indeed, it is well-recognized that depression is related to impaired cognitive performances, especially to memory (Burt, Zembar, & Niederche, 1995), attentional (Kizilbash,

Vanderploeg, & Curtiss, 2002), and executive dysfunctions (Lockwood, Alexopoulos, & Van Gorp, 2002), and some psychological models of depression underline the role of altered cognitive processes in the pathogenesis of the disorder (for a review see Beck, 2008). Depression is commonly associated to impaired cognitive performances also in cardiac surgery patients (Andrew et al., 2000; Stroobant and Vingerhoets, 2008), and this association has been proved to further contribute to postoperative adverse clinical outcomes (Phillips-Bute et al., 2006).

Among cognitive processes, emotional information processing is particularly impaired in depressed patients (for a review see Leppänen, 2006). Indeed, several studies indicate that affective processing of emotional stimuli, mostly faces, is altered in depressed patients (Leppänen, 2006), suggesting that cognitive impairment in general and, particularly, an altered affective processing may contribute to the above-mentioned impaired emotion regulation observed in depressed patients (Davidson et al., 2002).

The reciprocal interaction between cognitive and affective dysfunctions in depression is supported by the underlying neural circuits. The strongest evidence from functional magnetic resonance and positron emission tomography studies implicates a reduced activation in dorsolateral and dorsomedial prefrontal cortex, especially on the left side (Figure 4.1), as well as the in the left subgenual portion of the anterior cingulate gyrus (subgenual prefrontal cortex) in individuals with depression (for a review see Drevets, 1998) (Figure 4.2).

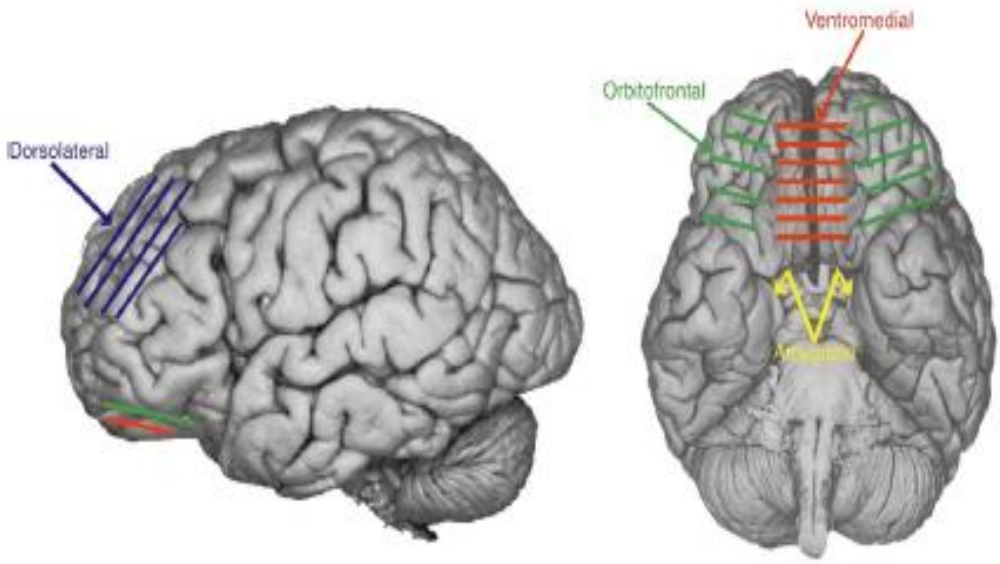

Figure 4.1 Sectors of human prefrontal cortex. Left: lateral view indicating dorsolateral (blue), ventromedial (red), and orbitofrontal (green) cortical territories. Right: ventral view indicating ventromedial (red), and orbitofrontal (green) cortical territories. The amygdalae are also indicated on the medial margin of temporal lobes, just dorsal to the unci which are identified in the tips of the arrowhead (yellow). From Davidson & Irwin, 1999; from DeArmond, Fusco, & Dewy, 1989 (modified)

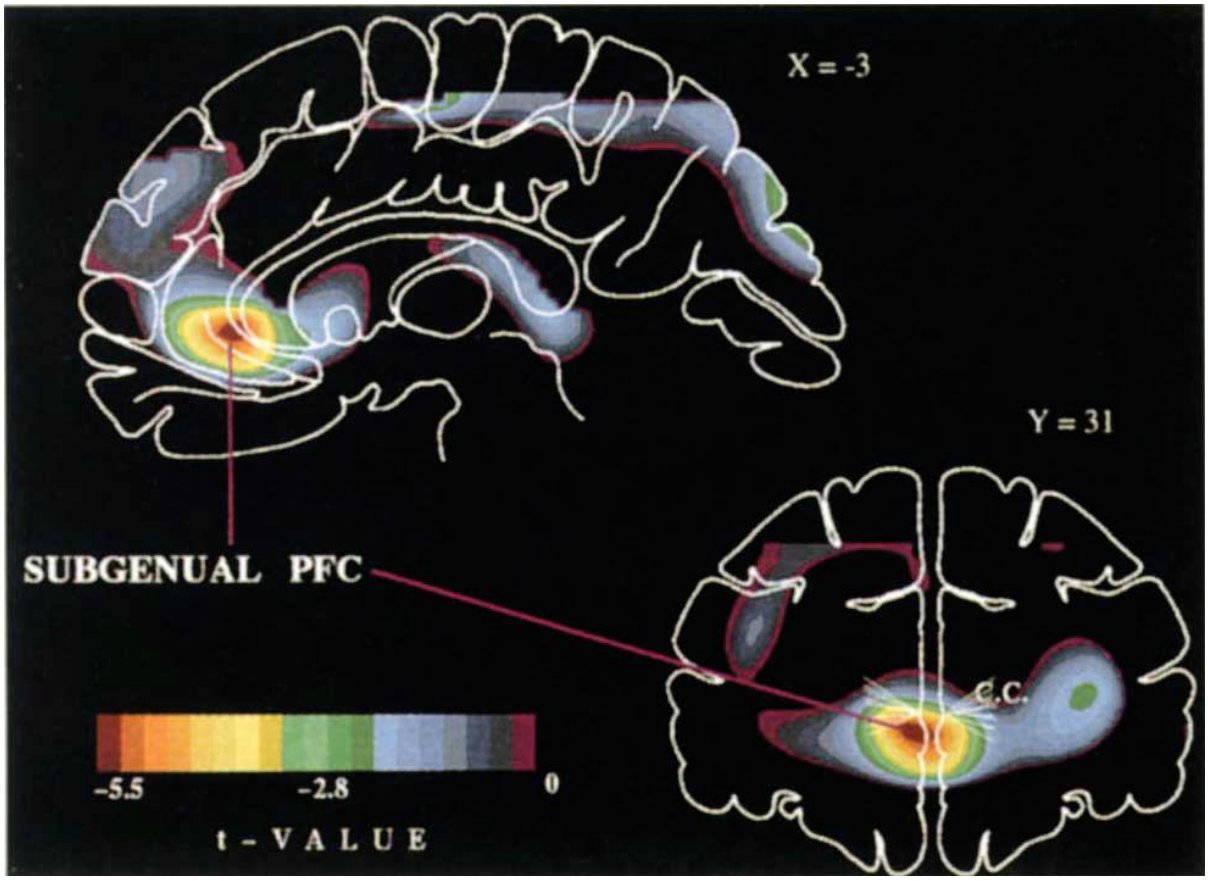

Figure 4.2 Coronal (y = 31 mm) and sagittal (x = -3mm) sections showing negative voxel t-values where glucose metabolism is decreased in patients with depression (N = 17) compared to those without depression (N = 12). The figure shows abnormality in subgenual portion of anterior cingulate gyrus (subgenual prefrontal cortex), which is at least partly accounted for by a corresponding reduction in gray matter volume in the left subgenual prefrontal cortex, as magnetic resonance imaging revealed (Drevets et al., 1997). From Drevets, 1998 (modified); from Drevets et al., 1997

Dorsolateral, dorsomedial and ventromedial prefrontal cortex, especially on the left side, are mainly involved in cognitive functions such as verbal working memory (D'Esposito et al., 1998), and set shifting evaluated with TMT B (Zakzanis et al., 2005). The same areas are also involved in approach- and withdrawal-related emotion and mood (Davidson & Irwin, 1999). Indeed, affect-guided planning and anticipation that involves the experience of emotion related to an anticipated choice, namely the emotion-based decision making, has been found to become impaired in patients with lesions of ventromedial prefrontal cortex

(Damasio, 1994). The failure to anticipate positive incentives and behavior toward the acquisition of appetitive goals are symptoms of depression that may be associated with neural abnormalities in the circuitry that implements positive affect-guided anticipation (Davidson et al., 2002). Specifically, the left-sided prefrontal cortex has been frequently considered to be involved in the approach-related, appetitive goals. Conversely, the right-sided prefrontal cortex has been frequently linked to behavioral inhibition and withdrawal in situations that involve alternative response options to approach (Garavan et al., 1999; Konishi et al., 1999). Therefore, the hypoactivation in left-sided prefrontal cortex and/or the activation in right-sided prefrontal cortex have been linked to depression (for a review see Davidson et al., 2002).

Reduced anterior cingulate cortex activation has been also implicated as a potential neural mechanism underlying depression, emotion dysregulation and cognitive deficits (Curran et al., 1993; Davidson et al., 2002; Ito et al., 1996) (Figure 4.3). The anterior cingulate cortex is assumed to be largely involved in emotional processing as well as attention, motor and autonomic control (Bush, Luu, & Posner, 2000; Critchley, Mathias, & Dolan, 2003). Indeed, the anterior cingulate cortex can be divided in at least two subdivisions, namely the affect and cognitive subdivisions (Devinsky, Morrell, & Vogt, 1995; Vogt, Finch, & Olson, 1992; Vogt, Nimchinsky, Vogt, & Hof, 1995). The first, affect subdivision, comprises the ventral and rostral areas of the anterior cingulate cortex. The second, cognitive subdivision encompasses dorsal regions of the anterior cingulate cortex. The affect subdivision of the anterior cingulate cortex is a part of the limbic system (Mega, Cummings, Salloway, & Malloy, 1997) and has extensive connections with prefrontal cortex, amygdala, hippocampus and parahippocampal gyrus (Devinsky, et al., 1995; Paus et al., 2001). Conversely, the cognitive subdivision is connected with the dorsolateral prefrontal cortex, parietal cortex, posterior cingulate, supplementary motor area, and spinal cord.

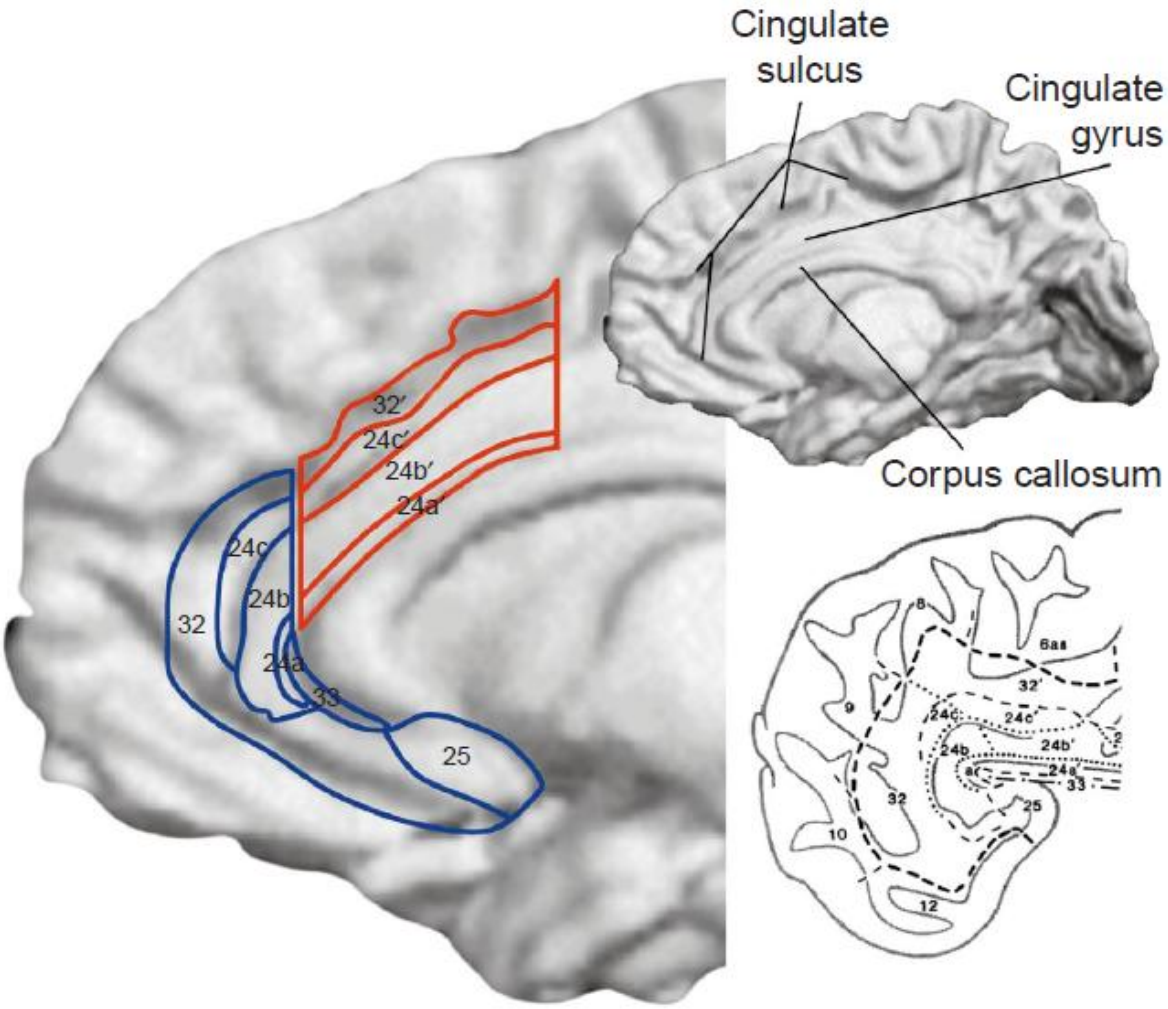

Figure 4.3 The upper right part of the figure shows a reconstructed magnetic resonance imaging of the medial surface of the right hemisphere of a single human brain (posterior towards the right, anterior towards the left). The cortical surface has been "partially inflated" to allow simultaneous viewing of gyri and sulci. The enlarged section (left) shows a schematic representation of cytoarchitectural areas of anterior cingulate cortex. Affective division areas are outlined in blue and cognitive division areas are outlined in red. These simplified localizations are only approximations for illustrative purposes. A schematized flat map of actual anterior cingulate cortical areas is shown in the bottom right panel. The combination of broken and dotted lines outlines cingulate areas whereas the borders of each sulcus appear as thin unbroken black lines. From Bush et al., 2000; from Vogt et al., 1995 (modified)

Finally, given that the affect subdivision of anterior cingulate cortex has extensive connections with nucleus accumbens, orbitofrontal cortex, preiaqueductal grey, amygdala, anterior insula, and autonomic brainstem motor nuclei, it has been assumed to be involved in visceral and autonomic regulation (Davidson et al., 2002).

4.1 Study IV: EEG Activity during an Emotional Imagery Task is Modulated by Depression in Patients after Cardiac Surgery

4.1.1 Abstract

Depression is a common risk factor for adverse psychological outcomes in patients after cardiac surgery. Indeed, it is well-established that depression can alter cognitive functions and emotion regulation, postoperatively. There is converging evidence that frontal midline theta power is related to both emotional status and cognitive performance in non-cardiac individuals. However, it is still unknown whether depression may alter electroencephalographic activity at rest and/or during an imagery task requiring both cognitive and emotional processing in patients after cardiac surgery. For this purpose, all the patients recruited (N = 35) completed a psychological evaluation to assess emotional reappraisal and suppression, and depression, postoperatively. Electroencephalography was recorded over midline sites (Fz, Cz, and Pz) at rest and during the emotional imagery task in patients without depression (N = 23) and in patients with depression (N = 12) after cardiac surgery. Analyses of variance showed that, compared to non depressed patients, those with depression had lower reappraisal scores. While no significant effects were noted in cortical activity at rest, patients with depression showed significant lower increase in frontal theta power during the emotional imagery task than those without depression. Moreover, frontal theta power was selectively related to reappraisal score. In contrast, alpha and beta power during the emotional imagery task were unrelated to depression and reappraisal. The current findings may extend previous data by showing an association between frontal theta activity, cognitive functions, and emotional reappraisal in patients after cardiac surgery. This study also suggests that depression may alter cortical activity underlying emotional and cognitive

processing postoperatively, further contributing to adverse psychological and clinical outcomes in cardiac surgery patients.

Keywords: Cognition; Depression; Electroencephalography; Emotion regulation; Frontal midline theta

4.1.2 Introduction

Most of EEG studies on depression have focused on lateralized activation related to negative or positive mood (for a review see Davidson et al., 2002). Indeed, several EEG studies reported an altered pattern of asymmetric activation in prefrontal cortex in the direction of reduced left relative to right cortical activation in individuals with depression (Bell, Schwartz, Hardin, Baldwin, & Kline, 1998; Bruder et al., 1997; Debener et al., 2000; Gotlib, Ranganath, & Rosenfeld, 1998; Pauli, Wiedemann, & Nickola, 1999; Reid, Duke, & Allen, 1998). In particular, EEG asymmetries in alpha power (8-12 Hz), which is negatively associated with cortical activation, have been related to depression (Davidson et al., 2002).

In contrast with the relatively large body of literature on lateralized EEG activity, especially on alpha or beta activity, few studies have examined EEG patterns selectively related to cognitive and emotional processes in depressed patients. In line with brain imaging data, there is converging evidence that dipoles within the anterior cingulate cortex (Brodman's areas 24/32) can account for frontal midline theta activity. Moreover, EEG and positron emission tomography studies have documented an association between frontal midline theta and rostral anterior cingulate cortex metabolism (Brodman's areas 24/32) (Pizzagalli, Oakes, & Davidson, 2003).

Interestingly, Mizuki, Kajimura, Nishikori, Imaizumi, & Yamada (1984) have shown that frontal midline theta activity was more marked in subjects who were less anxious, less

neurotic and more extroverted compared to anxious, neurotic and introverted individuals. Also, increased frontal midline theta power has been linked to feelings of relief from anxiety in humans during performance of a mental cognitive task (Suetsugy et al., 2000). In recent years, Sammler, Grigutsch, Fritz, & Koelsch (2007) have found a relationship between frontal midline theta activity and emotional processing. In particular, frontal midline theta power was greater during the pleasant than unpleasant stimuli music pieces.

It is also important to note that enhanced frontal midline theta activity has been observed during several cognitive tasks (for overviews see Inanaga, 1998; Schacter, 1977) such as working memory and learning (e.g. Jensen & Tesche, 2002; Klimesch, Schack, & Sauseng, 2005; Onton, Delorme, & Makeig, 2005), and mental calculation (e.g., Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Sasaki, Tsujimoto, Nambu, Matsuzaki, & Kyuhou, 1994). Therefore, frontal midline theta seems to be related to emotional status and heightened mental effort and sustained attention required during a multitude of cognitive tasks.

Although these findings provide the evidence for an association between frontal midline theta, emotional and cognitive processing, to our knowledge, the potential influence of depression on EEG theta activity during an emotional and cognitive task has not been yet investigated in patients after cardiac surgery. Accordingly, the primary aim of the present study was to examine in postoperative cardiac patients the relationship between depression and EEG theta activity at rest and during an imagery task requiring emotional processing. It was hypothesized that depressed patients would show attenuated frontal midline theta power at rest and during the imagery task compared to non depressed patients. It was further hypothesized that reduced theta activity would be associated with reduced emotional reappraisal and/or enhanced emotional suppression strategies in patients after cardiac surgery.

4.1.3 Methods

Participants

After local ethics committee approval, 35 patients (mean age = 60.2, *SD* = 8.1; male sex, *N* = 30, 86%) who had undergone first-time cardiac surgery were sequentially enrolled in the study after obtaining their written informed consent. All patients underwent cardiac surgery at an Italian north-eastern regional hospital and were admitted for rehabilitation in Motta di Livenza Hospital between November 2010 and July 2011. Age 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 hospital with beta-blocker and/or angiotensin-converting enzyme inhibitor medication. Patients were classified into one of two groups, based on the presence of clinically significant depression measured as a score greater than 16 on the Center for Epidemiological Studies Depression Scale (CES-D) (Fava, 1982; Radloff, 1977): patients with depression (*N* = 12) and without depression (*N* = 23).

Physiological Recording

Quantitative electroencephalogram (QEEG) was obtained employing ProComp Infiniti (Thought Technology Ltd, Montreal, QC) hardware and software. Gold electrodes were applied with paste on three midline sites (Fz, Cz, Pz) according to the International 10–20 System (Jasper, 1958), with reference on the left earlobe and ground on the right one. Impedance was kept below 5 KOhm. The EEG signal was bandpass filtered (0.5 – 40 Hz) and sampled at 256 Hz and. In order to remove eye movements, gold cup electrodes were placed below and at the outer canthus of the left eye to detect vertical and horizontal eye movements. The electroculogram (EOG) was sampled at 256 Hz. The EEG digitized waveforms were edited off-line in order to remove segments containing eye movements

artifacts. Using the BioGraph Infiniti software (Thought Technology Ltd, Montreal, QC), a series of digital filters were applied to the recorded signal to extract frequency-domain information. After passing data through a Hanning window, spectral power estimates were calculated for each active site on raw 1-s EEG segments (1-Hz frequency resolution). Then, power values within the theta (4–7.5 Hz), alpha (8–12 Hz), and beta (13–30 Hz) bandwidths were averaged across consecutive 10-s segments.

Psychological Measures and Emotional Imagery Task

The psychological evaluation included a short clinical interview and two self-report questionnaires aimed at assessing depression and emotion regulation. The depression and emotion regulation questionnaires consisted of:

1- Center for Epidemiological Studies Depression Scale (CES-D) (Fava, 1982; Radloff, 1977), which consists of 20 items representing the more common symptoms of depression. The scores range from 0 to 60, with higher scores indicating higher depressive symptoms. A clinically significant depression was defined as a score greater than 16 on the CES-D (Fava, 1982; Radloff, 1977);

2- 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 and expressive suppression. The questionnaire includes six items for cognitive reappraisal and four items for expressive suppression. Scores range from 6 to 42 and from 4 to 28 for reappraisal and suppression scales, respectively.

The emotional imagery test is a common psychological test widely used in psychophysiological assessment in order to evaluate the subject's physiological arousal during the retrieval and mental representation of emotional events (e.g., Bradley & Lang,

2006; Jones & Johnson, 1978; Lang, 1978; Lang, Kozak, Miller, Levin, & McLean., 1980; Miller et al., 1987). The test requires the subject being involved in a cognitive task (retrieval and imagery), which is emotionally laden (Bradley & Lang, 2006; Lang, 1978). Therefore, physiological arousal induced by the task, reflects both the cognitive effort and the affective impact of the imagined situation. While in most psychophysiological studies the imagery test has included autonomic responses (e.g., Bradley & Lang, 2006; Jones & Johnson, 1978; Lang, 1978; Lang et al., 1980; Miller et al., 1987), very few studies have also assessed EEG activation during the task (e.g., De Pascalis, Ray, Tranquillo, & D'amico, 1998; Oathes et al., 2008; Sebastiani, Simoni, Gemignani, Ghelarducci, & Santarcangelo, 2003).

Compared to more standardized cognitive or emotional tests (e.g. memory with interference or affective picture viewing, respectively), it has the advantage to address individual ability to mentally represent emotional events and even personally relevant emotional events (when personal scenes are used instead of a-priori selected scenes). This feature is particularly important with clinical subjects (Keane et al., 1998; McTeague, Lang, Laplante, & Bradley, 2011; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987), and, particularly, in depression, where abnormalities in cognitive processes of retrieval, imagery, and emotional processing have been reported (for a review see Leppänen, 2006).

In the present study, the emotional imagery task required each patient to retrieve and image a scene that he/she had reported as anxiety-provoking during the initial assessment interview. Although not required by instructions, almost all patients referred to stressful life events such as the day before cardiac surgery or myocardial infarction. Each patient was instructed to imagine the scene as fully as possible and to continue to visualize the scene for 1-min (according to the procedure used by Watkins, Clum, Borden, Broyles, & Hayes, 1990). QEEG was recorded during the emotional imagery task and during 1-min preceding baseline as well as 1-min following imagery (i.e., rest).

Procedure

Each evaluation was performed the same time of the day after the admission for rehabilitation (i.e., approximately 10 days after cardiac surgery). Patients were provided with instructions on the study and were first interviewed in order to collect demographic information. Patient's medical report was used to obtain clinically relevant information. Patients were then seated in a comfortable armchair and CES-D and ERQ questionnaires were administered individually by a trained psychologist blind to the patient's EEG recording. After questionnaires completion, EEG electrodes were applied. Eyes-open QEEG was recorded for a 4-min at rest. Each patient then performed the emotional imagery task. In order to avoid distraction during the emotional imagery, patients were told that they would be later requested to describe the event they had imagined. This part of the test was not analyzed. QEEG was recorded for 1-min baseline before imagery task as well as for 1-min during and after (i.e., rest) the emotional imagery (Figure 4.4).

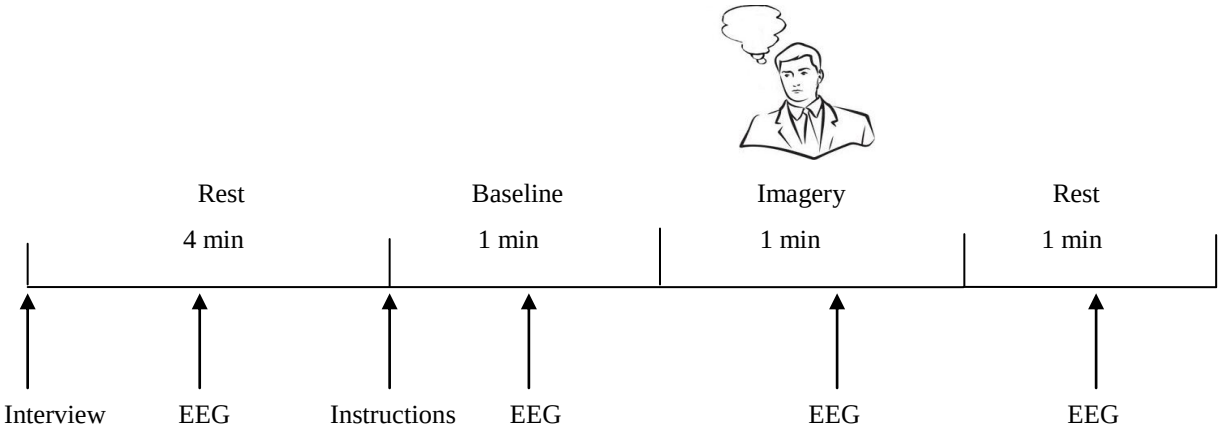

Figure 4.4 Procedure of psychophysiological assessment at rest and during emotional imagery task.

Statistical Analysis

Analyses of variance (ANOVAs), with Group (patients with depression, patients without depression) as the between-subject factor, were used to compare the age, education, and ERQ scores of the two groups. Fisher's exact test or chi-square analyses were conducted to compare the two groups in terms of sex, surgical procedures, diabetes, hypertension, dyslipidemia, and smoking. Separate mixed ANOVAs with Group (patients with depression, patients without depression) as the between-subject factor, and Electrode (Fz, Cz, Pz) were conducted for 4-min resting EEG on theta (4–7.5 Hz), alpha (8–12 Hz), and beta (13–30 Hz) power. To analyze differences between groups in EEG cortical activity during the emotional imagery task, separate mixed ANOVAs, with Group (patients with depression, patients without depression) as a between-subject factor, Electrode (Fz, Cz, Pz) and Condition (1-min baseline, 1-min imagery, 1-min rest) as a within subject factor, were also conducted on theta (4–7.5 Hz), alpha (8–12 Hz), and beta (13–30 Hz) power. The significance of main effects and interactions was adjusted where appropriate using the Greenhouse-Geisser method to correct for violations of sphericity. 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). Bonferroni test was used for post-hoc analysis.

Moreover, Spearman's correlation coefficients were calculated between ERQ Reappraisal and Suppression scores and theta, alpha, and beta power for each electrode (Fz, Cz, Pz) and condition (1-min baseline, imagery, and rest). A p value of $< .05$ was considered statistically significant. All statistical analyses were performed using STATISTICA 6.1 (StatSoft Inc, Tulsa, OK, USA).

4.1.4 Results

Demographic, Biomedical and Emotion Regulation Characteristics of Patients with Depression and without Depression

Chi-square or Fisher's exact test analysis revealed no group differences for sex, (p = .31), surgical procedures, (p = .23), diabetes, (p = .39), hypertension (p = .48), dyslipidemia (p = .99), and smoking (p = .69). Similarly, ANOVA yielded no group differences for age, $F(1, 33) = 0.62$, $p = .44$, $\eta_p^2 = .02$, and education, $F(1, 33) = 2.73$, $p = .11$, $\eta_p^2 = .08$. Patients with depression exhibited significantly lower ERQ Reappraisal scores compared to patients without depression $F(1, 33) = 9.03$, $p < .006$, $\eta_p^2 = .21$, whereas no significant difference between groups was found in ERQ Suppression scores, $F(1, 33) = 0.08$, $p = .78$, $\eta_p^2 = .00$. The descriptive statistics for each group are reported in Table 4.1.

Table 4.1 *A Comparison of the Demographic, Biomedical and Emotion Regulation Characteristics of the Groups*

Variable	Patients with depression (*N* = 12)	Patients without depression (*N* = 23)	*p*
Age (years)	61.7 (10.2)	59.3 (6.9)	.44
Education (years)	9.1 (3.8)	11.0 (3.0)	.11
Male Sex (*N*, %)	9 (26)	21 (60)	.31
Surgical Procedure			.23
CABG (*N*, %)	5 (14)	9 (26)	
Heart Valve (*N*, %)	3 (8)	9 (26)	
Combined (*N*, %)	4 (11)	2 (6)	
Diabetes (*N*, %)	3 (8)	3 (8)	.39
Hypertension (*N*, %)	8 (23)	11 (31)	.48
Dyslipidemia (*N*, %)	5 (14)	11 (31)	.99
Smoking			.69
Actual (*N*, %)	1 (3)	4 (11)	
Past (*N*, %)	5 (14)	6 (17)	
No (*N*, %)	6 (17)	13 (37)	
ERQ Reappraisal	24.5 (7.2)	31.0 (5.4)	<.006
ERQ Suppression	16.0 (5.3)	15.4 (5.8)	.78

Note: Data are *M* (*SD*) of continuous and *N* (%) of categorical variables. CABG = coronary artery bypass graft; ERQ = Emotion regulation questionnaire

EEG Activity at Rest in Patients with Depression and without Depression

The Group by Electrode ANOVA on 4-min resting theta power did not show a significant main effect for Group $F(1, 33) = 0.06$, $p = .81$, $\eta_p^2 = .00$ nor Electrode $F(2, 66) = 0.15$, $p = .86$, $\eta_p^2 = .00$, and neither a Group × Electrode interaction effect $F(2, 66) = 0.95$, $p = .39$, $\eta_p^2 = .03$. The Group by Electrode ANOVA on 4-min resting alpha power did not reveal a significant main effect for Group $F(1, 33) = 1.02$, $p = .32$, $\eta_p^2 = .03$, nor a Group × Electrode interaction effect $F(2, 66) = 0.64$, $p = .53$, $\eta_p^2 = .02$, whereas a significant main effect for Electrode was found $F(2, 66) = 28.77$, $p < .001$, $\eta_p^2 = .47$. Similarly, the Group by Electrode ANOVA on 4-min resting beta power did not yield a significant main effect for Group $F(1, 33) = 0.68$, $p = .41$, $\eta_p^2 = .02$, nor a Group × Electrode interaction $F(2, 66) = 1.13$, $p = .33$, $\eta_p^2 = .03$, whereas a significant main effect for Electrode was found $F(2, 66) = 7.63$, $p < .002$, $\eta_p^2 = .19$. Bonferroni Post-Hoc comparisons revealed greater alpha power over Pz compared to Fz ($p < .001$) and Cz ($p < .001$) and greater beta power over Cz compared to Fz ($p < .001$) and Pz ($p < .004$) (Table 4.2).

Table 4.2 *Mean (SD) EEG Activity at Rest in Patients with Depression and without Depression*

Variable	Patients with depression (*N* = 12)			Patients without depression (*N* = 23)		
	Fz	**Cz**	**Pz**	**Fz**	**Cz**	**Pz**
Alpha (μV^2/Hz)	3.78 (3.53)	4.78 (4.59)	6.94 (5.78)	3.86 (3.36)	4.82 (4.34)	6.95 (5.64)
Beta (μV^2/Hz)	0.54 (0.24)	0.66 (0.30)	0.57 (0.22)	0.53 (0.25)	0.65 (0.32)	0.55 (0.23)
Theta (μV^2/Hz)	2.83 (1.89)	2.80 (1.99)	2.77 (1.93)	2.76 (1.73)	2.79 (1.81)	2.61 (1.54)

EEG Activity in Patients with Depression and without Depression during the Emotional Imagery Task

The Group by Electrode by Condition ANOVA on theta power during the emotional imagery task yielded a significant main effect for Electrode $F(2, 66) = 22.55$, $p < .001$, $\varepsilon = .58$, $\eta_p^2 = .41$, and Condition $F(2, 66) = 4.07$, $p < .03$, $\varepsilon = .89$, $\eta_p^2 = .11$, and a Group × Electrode × Condition interaction effect $F(4, 132) = 4.32$, $p < .02$, $\varepsilon = .49$, $\eta_p^2 = .12$. This interaction is depicted in Figure 4.5. Specifically, in patients without depression, frontal theta power significantly increased from 1-min baseline to 1-min emotional imagery ($p < .001$) and decreased after imagery during 1-min rest ($p < .001$). In contrast, patients with depression showed a significant increase of frontal theta power from baseline and imagery to rest ($p < .001$ and $p < .03$, respectively) but not from baseline to imagery ($p = .99$). Bonferroni Post-Hoc comparisons did not yield significant differences within groups over Cz and Pz. Moreover, during imagery condition, patients without depression revealed a significant greater theta power over Fz than Cz ($p < .001$) and Pz ($p < .001$) sites, whereas patients with depression had greater theta power in Fz compared to Pz ($p < .001$) but not to Cz ($p = .44$). During 1-min rest, patients with depression had greater theta power over Fz than Cz ($p <$

.001) and Pz ($p < .001$) sites, while patients without depression showed greater theta power in Fz compared to Pz ($p < .03$) but not to Cz ($p = .99$). Finally, no main effect for Group, $F(1, 33) = 0.03$, $p = .87$, $\eta_p^2 = .00$, Group × Electrode, $F(2, 66) = 0.53$, $p = .49$, $\varepsilon = .58$, $\eta_p^2 = .02$, and Group × Condition interaction effects, $F(2, 66) = 2.77$, $p = .08$, $\varepsilon = .89$, $\eta_p^2 = .08$ were found.

The Group by Electrode by Condition ANOVA on alpha power yielded a significant main effect for Electrode $F(2, 66) = 4.05$, $p < .05$, $\varepsilon = .62$, $\eta_p^2 = .11$, but not for Group, $F(1, 33) = 0.29$, $p = .59$, $\eta_p^2 = .01$, and Group × Electrode × Condition interaction effect, $F(4, 132) = 0.22$, $p = .72$, $\varepsilon = .35$, $\eta_p^2 = .01$. Similarly, the Group by Electrode by Condition ANOVA beta power revealed a significant main effect for Electrode $F(2, 66) = 11.13$, $p < .001$, $\varepsilon = .92$, $\eta_p^2 = .25$, but not for Group, $F(1, 33) = 0.37$, $p = .55$, $\eta_p^2 = .01$, Group × Electrode × Condition interaction effect, $F(4, 132) = 0.76$, $p = .49$, $\varepsilon = .62$, $\eta_p^2 = .02$.

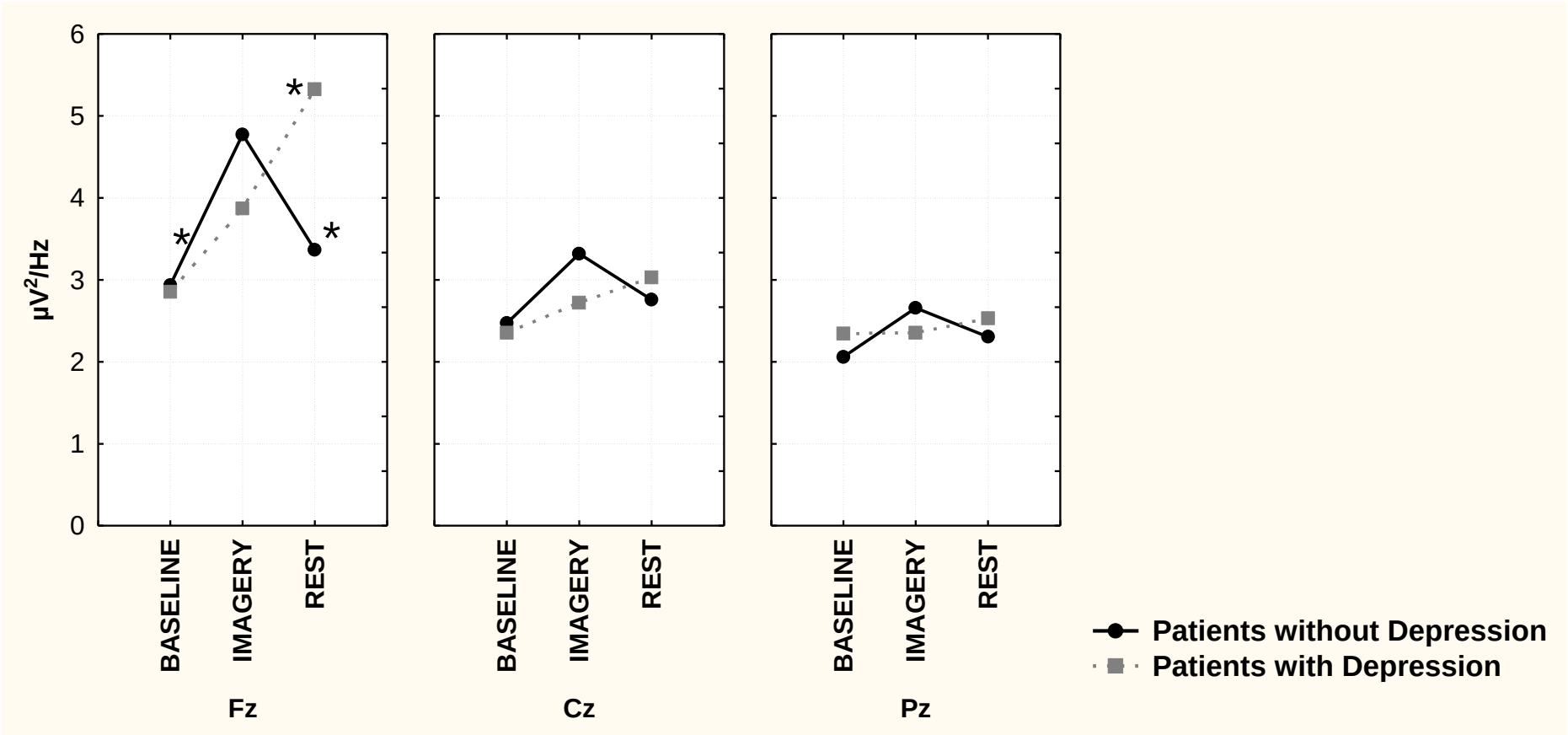

Figure 4.5 Mean theta power (μV^2/Hz) at Fz, Cz, and Pz during each phase of the emotional imagery task (Baseline, Imagery, Rest) in patients with depression and in patients without depression. *Bonferroni Post-Hoc comparisons, $p < .05$

Relationship between EEG Activity and Reappraisal and Suppression

Correlation analyses revealed no significant associations between ERQ Reappraisal scores, and alpha and beta power over all midline sites (Fz, Cz, Pz) during 1-min baseline, emotional imagery and 1-min rest periods (p's > .19). Although central and parietal theta power was unrelated to ERQ Reappraisal scores during each phase of emotional imagery task (p's > .31), frontal theta power during imagery (but not during 1-min baseline and 1-min rest) was significantly associated with ERQ Reappraisal (ρ = .33, p < .05). This correlation is depicted in Figure 4.6. No significant correlations between ERQ Suppression, theta, alpha and beta power over all midline sites during baseline, emotional imagery and 1-min rest periods were noted (p's > .09).

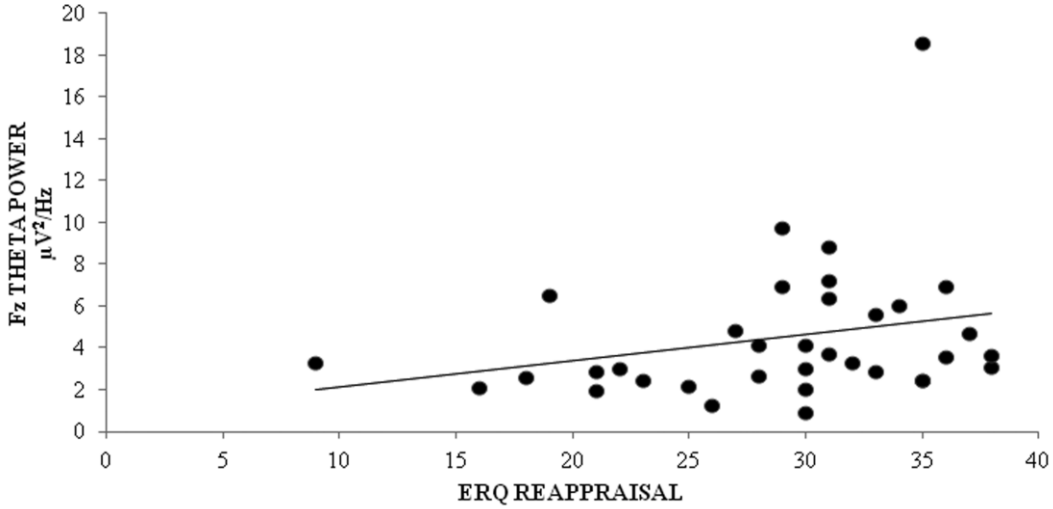

Figure 4.6 Correlations between scores on ERQ Reappraisal and frontal (Fz) theta power ($\mu V^2/Hz$). ERQ = emotion regulation questionnaire.

4.1.5 Discussion

The present study investigated whether cortical activity at rest and during an emotional imagery task would be influenced by depression in patients who had undergone cardiac surgery. The relationship between emotion regulation and EEG activity was also considered. Patients with depression had lower scores in ERQ Reappraisal, but not in ERQ Suppression, scale than patients without depression. Although depression did not modulate resting EEG activity, patients with depression were characterized by reduced increase of frontal theta power from baseline to emotional imagery than those without depression. Moreover, compared to patients without depression, a significant increase of frontal theta power was found in patients with depression from emotional imagery to 1-min rest. Correlation analyses revealed that frontal theta power during the imagery condition was selectively associated with ERQ Reappraisal scores, whereas ERQ Suppression scores were unrelated to EEG activity in patients after cardiac surgery.

These novel findings add to the literature on cognitive and emotional dysfunctions in depression by showing that reduced frontal theta power may be an index of impaired cognitive and emotional processing, which, in turn, may be related to poor emotion regulation. It is noteworthy that depression was selectively associated with reduced reappraisal which, in turn, was directly related to frontal theta power during the imagery condition. Reappraisal involves cognitive strategies aimed at changing the way a situation is construed in order to decrease its emotional impact. Also, reappraisal has been linked to more positive and less negative mood states (for a review see Gross, 2002). In agreement with previous EEG data (Sammler et al., 2007), our findings suggests a possible relationship between positive mood and frontal theta power. The current findings are in line with previous literature showing that increase in frontal theta power is linked to reduced anxiety and neuroticism as well as increased extroversion and feelings of relief (Mizuki et al., 1984; Suetsugy et al., 2000). Taken together these observations argue that frontal theta power may be directly related to emotion regulation and reduced depression other than reduced anxiety.

By using a cognitive-emotional test, the present findings add further information to the relationship among depression, cognitive processes, and frontal theta power. Indeed, it is well-established that depression can affect cognitive performance (Lezak et al., 2004), especially attention and executive functions. Moreover, evidence from EEG studies shows that frontal theta power is linked to sustained attention and heightened mental effort required in a large variety of cognitive tasks (for an overview see Inanaga, 1998; Schacter, 1977). In particular, frontal theta power can be observed during tasks requiring working memory and learning (e.g., Jensen & Tesche, 2002; Klimesch et al., 2005; Onton et al., 2005), and mental calculation (e.g., Asada et al., 1999; Sasaki et al., 1994). Therefore, it can be suggested that reduced frontal theta activity may be implicated as neural mechanism underlying the influence of depression on cognitive performance.

The finding that frontal theta power is associated to depression-related cognitive and emotional dysfunctions during the emotional imagery task may be explained by reduced anterior cingulate cortex activity. Indeed, frontal theta power and brain metabolism in the rostral anterior cingulate cortex have been recently linked by means of combined positron emission tomography and EEG (Pizzagalli et al., 2003) and intracranial recordings (Nishida et al., 2004; Uchida, Maehara, Hirai, Kawai, & Shimizu, 2003), thus suggesting that rostral anterior cingulate cortex can be implicated as a cerebral substrate of frontal theta power. Moreover, the anterior cingulate cortex is assumed to be largely involved in emotional processing as well as attention, motor and autonomic control (Bush et al., 2000; Critchley et al., 2003). Specifically, the anterior cingulate cortex can be divided in at least two subdivisions, namely the affect and cognitive subdivisions (Devinsky et al., 1995; Vogt et al., 1992; Vogt et al., 1995): the affect subdivision encompasses rostral and ventral of the anterior cingulate cortex; conversely, the cognitive subdivision is intimately connected with dorsolateral prefrontal cortex, posterior cingulate and parietal cortex (Devinsky et al. 1995, Vogt et al., 1992; Vogt et al., 1995). Given that the rostral anterior cingulate cortex possesses strong connections with limbic and paralimbic cerebral regions such as the nucleus accumbens, amygdala, anterior insula, it has been considered a key area in connecting cognition, emotional processing and the regulation of emotional states in psychopathology (for a review see Davidson et al., 2002). Taken together, these observations suggest that reduced frontal theta activity may represent the link between reduced anterior cingulate cortex activation and depression-related cognitive deficits and emotional dysregulation in patients after cardiac surgery.

The results of the present study suggests that, compared to patients without depression, those with depression had poorer cognitive-emotional processing which, in turn, was related to their greatly attenuated frontal theta activity during the emotional imagery task.

Moreover, the direct relationship between ERQ reappraisal scores and frontal theta power during the imagery condition is consistent with cognitive-affective processes involved in reappraisal. Indeed, reappraisal, which consists of construing a potentially emotion-eliciting situation in nonemotional terms, can be defined as a type of cognitive-emotional change (Gross, 2002).

In conclusion, the present study examined how EEG activity is modulated by depression during cognitive-emotional task in patients who had undergone cardiac surgery. The current findings show that depression can influence EEG activity during an imagery task requiring both cognitive and emotional processing. This study reveals that depression is selectively related to a reduced frontal theta power that may be interpreted as a sign of poor cognitive and emotional processing, which, in turn, can be associated with emotion dysregulation, despite the exact ratio of contribution of cognitive and emotional processes remains to be clarified.

5. GENERAL DISCUSSION

5.1 A Summary of Aims and Findings

In this thesis four studies have been described that were primarily meant to investigate the extent of cognitive decline along with depression after cardiac surgery, and, secondarily, to identify some psychobiological factors potentially underlying the above-mentioned phenomena. Specifically, the main aim of the Experiment I was to examine whether increased biomedical risk as measured by the Stroke Index and EuroSCORE was associated with impaired cognitive performance, anxiety and depression in patients undergoing cardiac surgery. It was found that both the Stroke Index and EuroSCORE were related to cognitive performance, whereas only the EuroSCORE was significantly associated also with anxiety and depression scores. Therefore, compared to the Stroke Index, the EuroSCORE seems to represent a more comprehensive and accurate index to evaluate the association between biomedical risk factors and psychological dysfunctions such as cognitive deficits, anxiety and depression in patients undergoing cardiac surgery.

The principal factors influencing brain dysfunctions and cognitive decline after cardiac surgery are the hemodynamic changes associated with the cardiopulmonary bypass that is used in most of the cardiac surgery procedures. These intraoperative effects can be potentiated by pre-existing hemodynamic brain dysfunctions. Therefore, to examine potential hemodynamic mechanisms underlying postoperative cognitive decline, the experiments described in chapter three were designed. The Experiment II was designed to examine whether preoperative hypoperfusion in middle cerebral arteries could be related to cognitive decline after cardiac surgery. Moreover, it was examined whether cerebral hypoperfusion in left or right middle cerebral artery would differentially account for cognitive decline in patients undergoing cardiac surgery. The Experiment II showed that hypoperfusion in the left

middle cerebral artery selectively predicted the incidence of cognitive decline after surgery, whereas blood flow velocity in the right middle cerebral artery was unrelated to postoperative cognitive decline. Hence, the Experiment II revealed that left cerebral hypoperfusion may represent an independent predictor of cognitive decline in cardiac surgery patients.

The second experiment reported in chapter three was designed to determine the role of asymmetry and the nature of microembolization on postoperative cognitive decline in patients who had undergone heart valve surgery. Along with reduced blood flow, the occurrence of microemboli during surgery is a major risk factor for postoperative cognitive functions in patients undergone cardiac surgery. The Experiment III showed that microembolization in the left middle cerebral artery was significantly related to early and late (i.e., 3-month follow-up) postoperative cognitive decline, whereas microembolization in the right middle cerebral artery was unrelated to early and late cognitive decline. This experiment suggests that microemboli during cardiac surgery induce specific cognitive impairment in accordance to the brain region to which they are delivered. Moreover, gaseous microembolization was significantly related to both early and late cognitive decline, whereas solid microemboli were significantly related to early but not to late postoperative cognitive decline.

Finally, the research was focused on depression that is the principal affective disorder commonly observed in cardiac surgery patients. Depression has been linked to morbidity and mortality in patients after cardiac surgery, thus contributing to adverse medical and clinical outcomes, postoperatively. It has been recently shown that depression can be also considered a risk factor for cognitive dysfunctions after cardiac surgery. Therefore, to investigate the potential relationship between depression and cognitive performance in patients who had undergone cardiac surgery, the experiment in chapter four was carried out. Specifically, the Experiment IV was carried out to investigate whether EEG activity could reflect the influence

of depression during an emotional imagery task requiring the subject being involved in a cognitive task (retrieval and imagery), which is emotionally laden. Although depression did not influence resting EEG activity, compared to non depressed controls, a reduced frontal theta (4-7.5 Hz) activity was observed in patients with depression during the emotional imagery task. Also, reduced frontal theta activity was selectively associated with reduced emotional reappraisal. These findings suggest that reduced frontal theta power may be interpreted as a sign of cognitive dysfunctions and/or emotion dysregulation in depressed patients after cardiac surgery.

Overall, these findings provide a better understanding of the psychological and psychophysiological mechanisms underlying postoperative cognitive decline and depression in cardiac surgery patients.

5.2. Cognitive Decline in Cardiac Surgery Patients: Insights from Psychophysiological Measures

The current thesis provides further evidence for the role played by pre, intra and postoperative biomedical and psychological risk factors in cognitive deficits after cardiac surgery. Preoperatively, it has been shown the need for the inclusion of psychological evaluation aimed at assessing cognitive and emotional states along with the most common demographic (e.g., age, and gender) and biomedical (e.g., hypertension, and diabetes) risk factors (Experiment I). While biomedical risk-stratification scores, namely the Stroke Index and EuroSCORE, help surgical decision-making by predicting the perioperative medical outcome with the evaluation of real, measurable and easily available risk factors (e.g., age, hypertension, and angina), the inclusion of psychological assessment of cognitive and emotional states can help surgical decision-making by predicting the short- and long-term postoperative clinical and psychological outcomes of patients undergoing cardiac surgery. Indeed, the inclusion of preoperative psychological evaluation, along with biomedical risk-stratification scores, can provide surgeons (and patients) with additional and relevant information about postoperative outcomes, and, therefore, reduce psychological dysfunctions as well as mortality and medical morbidity after cardiac surgery. It is well-established that preoperative cognitive (e.g., memory, attention, and executive dysfunctions) and emotional dysfunctions (e.g., anxiety, and depression) are independent and important predictors for adverse clinical and psychological outcomes after cardiac surgery (Andrew et al., 2000; Blumenthal et al., 2003; Connerney et al., 2001; Phillips-Bute et al., 2006; Stroobant & Vingerhoets, 2008). It is noteworthy that as compared with patients without adverse psychological outcomes, patients with postoperative cognitive dysfunctions and/or depression are more likely to have a longer stay in intensive care unit and on the ward (Roach et al., 1996). Furthermore, 90% of patients without adverse psychological outcomes are discharged

to their home as compared to 60% of patients with cognitive and/or emotional dysfunctions (Roach et al., 1996). Based on these findings, cardiac surgery teams may consider the development of new, integrated risk-stratifications scores, including psychological risk factors in the preoperative demographic and biomedical evaluation.

While preoperative psychological evaluation may allow a better identification of patients at high risk for psychological and clinical adverse outcomes after cardiac surgery, preoperative hemodynamic measures can provide further information on the cerebrovascular reserve of patients undergoing cardiac surgery. A more comprehensive risk-stratification score accounting for the conjunction between psychological risk factors, namely cognitive deficits, anxiety and/or depression (Experiment I), and hemodynamic risk factors, namely the cerebral hypoperfusion (Experiment II), may provide useful criteria for predicting patients at high risk for subtle psychological and clinical adverse outcomes after cardiac surgery. It is noteworthy that the detection of preoperative cerebral hypoperfusion in patients undergoing cardiac surgery may also provide further indications and warnings to the surgical team, especially to the anesthesiologist, perfusionist, and surgeon, when planning intraoperative management and cardiopulmonary bypass. Preoperatively, an integrated biomedical, psychological and hemodynamic evaluation can guide the anesthesiologist in the choice of intraoperative management, for example, suggesting the need for employing a careful intraoperative monitoring of brain through transcranial Doppler, EEG and somatosensory evoked potentials (Zanatta et al., 2011).

Intraoperatively, there is evidence for the effectiveness of transcranial Doppler monitoring for detecting microembolization (Experiment III). Based on recent findings showing that intraoperative brain monitoring through transcranial Doppler, EEG, and somatosensory evoked potentials, can reduce perioperative major neurological complications in cardiac surgery (Zanatta et al., 2011), monitoring brain metabolism, blood flow velocity

and brain function simultaneously may also reduce cognitive decline after cardiac surgery. Indeed, multimodal brain monitoring can guide the entire surgical team in maintaining brain homeostasis and the functional integrity that can improve postsurgical cognitive outcomes and the quality of life in patients who underwent cardiac surgery. The intraoperative continuous monitoring of these neurophysiologic variables and brain hemodynamics data would also provide a better understanding of brain physiology during extracorporeal circulation. Neuroprotective interventions based on multimodal monitoring potentially could eliminate postoperative complications and prevent cognitive decline, especially in patients with preoperative risk factors for cerebral ischemia, lower cerebrovascular reserves and/or those undergoing complex surgical interventions (Zanatta et al., 2011). Transcranial Doppler monitoring along with EEG and somatosensory evoked potentials may allow the possibility of changes in the operative strategy if specific intraoperative warning events are detected. Multimodal brain monitoring can also indentify those patients who had intraoperative warnings and, therefore, indicate the need for psychological and/or psychophysiological rehabilitation program, postoperatively.

Moreover, cognitive dysfunctions caused by intraoperative microembolization detected through transcranial Doppler (Experiment III) were in line with previous data showing that the events such as cerebral microemboli and hypoxia during heart valve surgery may selectively impair the integrity of medial temporal lobe structures and frontal lobe underlying memory and executive dysfunctions, respectively (Ebert, Walzer, Huth, & Herrmann, 2002).

Postoperative depression may alter cognitive processing and emotion regulation (Experiment IV). The preliminary findings of Experiment IV may also help in identifying the underlying cortical activity of depression-related cognitive and emotion dysfunctions as revealed by reduced frontal theta activity during the emotional imagery task. Frontal theta

activity has been related to emotional processing (Sammler et al., 2007) and feelings of relief from anxiety (Suetsugy et al., 2000). On the other hand, frontal theta activity has been observed during several cognitive tasks (for overviews see Inanaga, 1998; Schacter, 1977) such as working memory and learning (e.g. Jensen & Tesche, 2002; Klimesch et al., 2005; Onton et al., 2005), and mental calculation (e.g., Asada, et al., 1999; Sasaki et al., 1994). Based on these findings and given that depression is linked to postoperative cognitive dysfunctions (Andrew et al., 2000; Stroobant & Vingerhoets, 2008), emotion information processing (Leppänen, 2006) and emotion dysregulation (Davidson et al., 2002; Gross, 2002), the current study suggests frontal theta activity as a possible neural substrate underlying the influence of depression on cognitive functions and emotion regulation.

Moreover, the finding that depression may reduce frontal theta activity, which, in turn, reflects impaired cognitive and emotional processing, is in line with brain imaging studies implicating reduced anterior cingulate cortex activation as a neural mechanism underlying frontal theta activity, on the one hand, and depression, cognitive deficits, and emotion dysregulation, on the other hand (Curran et al., 1993; Davidson et al., 2002; Ito et al., 1996). Indeed, there is converging evidence that dipoles within the rostral anterior cingulate cortex (Brodman's areas 24/32) can account for frontal midline theta activity (Pizzagalli et al., 2003). Moreover, the anterior cingulate cortex is assumed to be largely involved in emotional processing as well as attention, motor and autonomic control (Bush et al., 2000; Critchley et al., 2003). Specifically, the anterior cingulate cortex can be divided in at least two subdivisions, namely the affect and cognitive subdivisions (Devinsky et al., 1995; Vogt et al., 1992; Vogt et al., 1995): the affect subdivision comprises the ventral and rostral areas of the anterior cingulate cortex, whereas the cognitive subdivision encompasses dorsal regions of the anterior cingulate cortex. Taken together, these observations suggest that reduced frontal theta activity may represent the link between reduced anterior cingulate cortex activation and

depression-related cognitive deficits and emotional dysregulation in patients after cardiac surgery.

The Experiment IV also suggests the potential scientific contribution of an idiographic task, namely the emotional imagery task. It is important to note that the imagery task involved an idiographic approach to assess individual emotional and cognitive processing and, therefore, can be more far-reaching than some more obviously nomothetic approaches such as neuropsychological tests or psychological questionnaires, which, in turn, may not adequately capture individual differences in psychological processing.

Finally, it is important to consider the implications of the current findings for rehabilitation programs. Given the link between cerebral dysfunctions (e.g., EEG and/or hemodynamic) underlying postoperative adverse psychological outcomes, the potential efficacy of biobehavioral interventions such as biofeedback has to be taken into account. Biofeedback is a psychophysiological procedure in which patients learn to gain self-control over physiological functions (e.g., heart rate variability). Neurofeedback is a sophisticated form of biofeedback based on specific aspects of EEG. Specifically, neurofeedback is a procedure whereby individuals learn to self-regulate specific EEG parameters and/or patterns, e.g., the amplitude or coherence of a distinct frequency component of the EEG. The parameter(s) extracted from the EEG is (are) converted into visual, acoustic or audio-visual signals which are continuously feedback to the individual in real time. The individual is trained to change abnormal cortical activity and is usually rewarded when changes occur in the desired direction. Through downtraining (reduction) or uptraining (enhancement) of the altered EEG parameter, the individual learns how to voluntarily regulate it (Heinrich, Gevensleben, & Strehl, 2007). Neurofeedback technique has been used to improve performance on specific cognitive task in healthy (for a review see Vernon, 2005) or in clinical populations with specific EEG abnormalities such as patients with attention deficit

and hyperactivity disorder (i.e., neurofeedback intervention aimed at reducing theta and increasing beta or sensorimotor rhythm) (for a review see Monastra et al., 2005), or with Gilles de la Tourette syndrome (i.e., neurofeedback intervention aimed at reducing theta and increasing sensorimotor rhythm) (Messerotti Benvenuti et al., 2011). Importantly, neurofeedback interventions have been also employed for treating patients with anxiety and/or depression (Gotlib et al., 1998; Rosenfeld, 2000), or with post-traumatic stress disorder (Raymond, Varney, Parkinson, & Gruzelier, 2005).

Postoperatively, neurofeedback technique may be performed along with neuropsychological rehabilitation programs to reduce psychological dysfunctions in patients undergone cardiac surgery. Given the growing knowledge on neural mechanisms underlying postoperative cognitive dysfunctions, anxiety and depression, neurofeedback may be considered in rehabilitative program. For example, based on findings of Experiment IV, it can be hypothesized that neurofeedback intervention aimed at enhancing frontal theta activity may have beneficial effects on depression-related cognitive deficits and/or emotional dysregulation in patients after cardiac surgery.

Based on findings implicating preoperative EEG abnormalities as a potential risk factor for postoperative adverse cognitive outcome, pre-habilitation programs may be taken into account to reduce risk factors *prior to surgery*. While *neuropsychological* rehabilitation program has focused only on *remediation* and/or *compensation* of *postoperative* cognitive deficits, conversely, *neurofeedback*, along with cognitive-behavioral therapy (Furze et al., 2009), may be more effective in reducing *preoperative psychological and cerebral risk factors* for postoperative adverse outcomes in patients *undergoing* cardiac surgery. For example, given that, as compared to age-matched controls, cardiac surgery patients had more preoperative EEG abnormalities (i.e., enhanced δ power, reduced θ and α power), which, in turn, were related to cognitive deficits (Toner et al., 1998), neurofeedback may be effective in

reducing such EEG abnormalities, further potentiating preoperative cognitive functions. Moreover, neurofeedback may also reduce depressive symptoms by reducing EEG abnormalities, e.g., frontal alpha asymmetry (Davidson et al., 2002), selectively related to the preoperative depression. In other words, it may be suggested that neurofeedback intervention aimed at reducing or, at best, eliminating EEG abnormalities related to cognitive or emotional dysfunctions may add to the efficacy of preoperative risk reduction programs as well as postoperative cardiac rehabilitation protocols in cardiac surgery patients.

5.3 Limitations of the Research

The current findings should be interpreted in light of a number of possible methodological issues. First, the Experiment I did not investigate the additive contribution of each variable to the Stroke Index and EuroSCORE preoperative risk scores and their potential predicting values on short- and long-term postoperative psychological dysfunctions. Also, the association between the EuroSCORE and Stroke Index scores with state and trait anxiety and depression as measured with other well-validated questionnaires (e.g., Beck Anxiety Inventory, Beck Depression Inventory, Depression, Anxiety, Stress Scale) was not examined.

Second, despite the absence of a consensus as to what represents cognitive decline after cardiac surgery, in the Experiment II postoperative cognitive decline was defined as a change greater than 1 *SD* of the baseline mean in at least one cognitive test (Gill & Murkin, 1996). However, the incidence analysis (i.e., *SD* method) involves an arbitrary convention to define postoperative cognitive decline. Its 'floor effect' and the risk of overestimating postoperative cognitive decline represent other disadvantages of the 1 *SD* criterion (Keizer, Hijman, Kalkman, Khan, & van Dijk, 2005; Lewis, Maruff, Silbert, Evered, & Scott, 2006; Rasmussen et al., 2001). Alternative methods (e.g., 20% - 20%) suffer from limitations as well. Indeed, the 20% - 20% method has the disadvantage of an extremely high false positive rate (Keizer et al., 2005; Lewis et al., 2006). Furthermore, the 20% - 20% method is based on two arbitrary conventions (i.e., it requires the postoperative performance be 20% worse than the preoperative performance, taken as baseline, in 20% of neuropsychological tasks used). Given that the 1 *SD* and 20% - 20% may not represent accurate methods to detect clinically significant cognitive dysfunction after cardiac surgery, the definition of postoperative cognitive decline remains still controversial.

Third, although the postoperative cognitive decline is a well-established phenomenon (Borger, Peniston, et al., 2001; Deklunder, Prat, et al., 1998; Deklunder, Roussel, et al., 1998;

Fearn et al., 2001; Gill & Murkin, 1996; Hogue et al., 2008; Murkin et al., 1995; Pugsley et al., 1994; Russel, 2002; Stump et al., 1996), whether or not the statistically significant differences between groups are also clinically relevant appears to be a matter of controversy in the literature (Rasmussen et al., 2001). Indeed, a difference in the performance of cognitive tests may be statistically but not clinically significant.

Fourth, the Experiments II and III employed a relatively small sample size; therefore, the present results need to be extended and replicated in order to better understand the pathophysiological mechanisms of preoperative cerebral hypoperfusion and intraoperative microembolization underlying postoperative cognitive decline. Nonetheless, logistic regression analysis showed that a reduction in left-sided blood flow velocity of 1 cm per second was associated with roughly 10% greater likelihood of exhibiting cognitive decline after cardiac surgery, independently of traditional risk factors (Experiment II). Moreover, the correlations in the Experiment III are consistent with previous literature indicating the impact of the total number of microemboli detected by transcranial Doppler on cognitive functions. Fifth, both the Experiments II and III did not include specific and well-validated visuospatial tasks, predominantly involving the right hemisphere, such as the Corsi block task (Spinnler & Tognoni, 1987), in order to investigate the potential relationship with preoperative hypoperfusion and intraoperative microembolization detected in the right middle cerebral artery.

Sixth, in the Experiment IV, all patients were treated in hospital with beta-blocker and/or angiotensin-converting enzyme inhibitor medication. Given evidence that peripherally acting anti-hypertensive medication can modify the electrical activity of the central nervous system (Nicholson, Wright, Zetlein, Currie, & McDevitt., 1988) and cause subjectively sedation and reduced alertness (Croog et al., 1986), it would have been preferable for the patients to be drug free. However, the treatment was part of these cardiac patients' standard

clinical care in this surgical context. It would, therefore, be interesting to examine the EEG activity of other (i.e., drug free) non-cardiac patients undergoing the similar emotional imagery task. Seventh, the Experiment IV did not include a task specifically aimed at evaluating cognitive processing and, therefore, did not examine the potential influence of depression on frontal theta activity during a cognitive task. Finally, the emotional imagery task did not comprise either neutral and/or pleasant conditions or the self-report evaluation of the unpleasantness of the event retrieved. These latter limitations make it somewhat difficult to understand whether the frontal theta power during the emotional imagery task may reflect more a depression-related emotional dysregulation than cognitive dysfunctions, or vice versa, and whether frontal theta activity could reflect the unpleasantness of the event retrieved. Given these limitations, the findings of Experiment IV should be considered as preliminary until they are confirmed by more rigorous studies.

5.4 Directions for Future Research

In order to overcome the above-mentioned limitations and to extend the current findings, future studies should investigate the additive contribution of psychological and physiological measures to the preoperative biomedical risk-stratification scores and their potential predicting values for postoperative psychological and medical outcomes. Specifically, P300 cognitive auditory-evoked potential, that is a highly sensitive and reproducible tool for the evaluation of cognitive function, could be included in the preoperative evaluation in order to better identify patients at high risk for postoperative cognitive decline.

Future research should include a non-surgical control group in order to use measures such as the reliable change index (RCI) to define postoperative cognitive decline (Jacobson & Truax, 1991; Kneebone, Andrew, Baker, & Knight, 1998). Compared to the *SD* method, RCI has recently demonstrated superior sensitivity and specificity in defining postoperative cognitive decline (Keizer et al., 2005; Lewis et al., 2006; Rasmussen et al., 2001). RCI seems to have the advantage of incorporating estimates of the practice effects as well. A follow-up should also be carried out to estimate the relationship between preoperative psychological (e.g., anxiety, and depression) and physiological (e.g., cerebral hypoperfusion) risk factors and long-term psychological and medical outcomes in patients after cardiac surgery.

In order to examine whether or not the statistically significant differences between groups are also clinically relevant, it seems advantageous to include objective physiological measures, such as ERPs (Zimpfer et al., 2004) or cerebral blood flow pre as well as postoperatively. Based on this consideration, future studies could add relevant and objective information concerning the preoperative and postoperative electrophysiological and hemodynamic mechanisms underlying cognitive dysfunctions after cardiac surgery. Sensitive electrocortical (i.e., EEG, ERPs) and hemodynamic (i.e., cerebral blood flow) measures are

important correlates of subtle cognitive decline, which is clinically relevant for cardiac surgery patients. To inform this controversy, research should also include clinically relevant scoring scales and questionnaires assessing the engagement in daily activities, physical limitations and the occupational functioning which, in turn, should be associated with cognitive scores and physiological measures.

Moreover, future research is warranted to consider the potential associations among psychological dysfunctions (cognitive deficits, anxiety and depression), the amplitude and latency of cognitive P300 auditory-evoked potential and cerebral blood flow velocity with respect to cerebral asymmetries pre and postoperatively. Indeed, there is evidence that cerebral hypoperfusion and microembolization caused by CPB technique may induce irreversible damage to brain tissue resulting in cognitive dysfunctions as reflected by prolonged cognitive P300 latencies. Along the same line of reasoning, specific visuospatial tasks, predominantly involving the right hemisphere, such as mental rotation tests (Vandenberg & Kuse, 1978) or Corsi block (Spinnler & Tognoni, 1987) should be included to examine their relationship with pre and postoperative electrocortical activity and cerebral blood flow velocity as well as with intraoperative microembolization detected in the right hemisphere. Researchers should also investigate how preoperative hypoperfusion and intraoperative microembolization in the left or right middle cerebral artery would differentially account for postoperative cognitive decline in left-handed patients.

The role played by intraoperative microemboli according to their asymmetry and nature should be further considered to investigate the cause of silent strokes or transient ischemic attack in relation to short- and long-term psychological dysfunctions. Indeed, intraoperative microemboli represent one of the most relevant causes of adverse neurological and psychological outcome in patients undergoing cardiac surgery, especially when the CPB technique is used. Indeed, brain ischemia due to cardiac surgery may predispose patients to

the development of neurodegeneration disorders which, in turn, are associated with early and late postoperative cognitive decline, anxiety and depression. Medical professionals should aim to reduce intraoperative brain damage to improve short- and long-term postoperative outcomes of patients undergoing cardiac surgery. Hence, the potential effectiveness of intraoperative cerebral monitoring through transcranial Doppler, especially in the left middle cerebral artery, in implementing various prevention strategies and reducing POCD should be also investigated.

Finally, it is important to note that psychobiological mechanisms underlying postoperative cognitive deficits, anxiety, depression and emotion dysregulation should be further considered in order to fully understand their potential relationship. Specifically, with respect to the limitation of the Experiment IV, it should be varied the valence of emotional imagery conditions in order to distinguish whether reduced theta activity mainly reflects depression–related emotional dysregulation or cognitive dysfunctions, or vice versa. The self-report evaluation of the valence (i.e., unpleasantness, neutral, and pleasantness) should be collected after the imagery task to examine whether frontal theta activity may be related to the valence of each event retrieved. Moreover, future research is warranted to include tasks specifically aimed at evaluating cognitive processing in order to examine the potential relationship between frontal theta activity and cognitive functioning.

5.5 Conclusions

Taken together these experiments provide a better understanding of the psychological and psychobiological mechanisms underlying postoperative cognitive decline phenomenon and depression in cardiac surgery patients. Overall, the present findings suggest that preoperative psychological status (Experiment I) and hemodynamic measures (Experiment II, III) should be taken into account to improve the diagnosis and treatment of postoperative psychological (i.e., cognitive and affective) outcome in cardiac surgery patients. Moreover, implicit measures of depression and cognition after surgery should be also considered (Experiment IV). In conclusion, the present thesis suggests the need for including preoperative and postoperative evaluation of cognitive and affective status as well as objective easy-to-use psychophysiological measures to accurately predict and/or treat patient's dysfunctional psychological outcomes. Specifically, preoperative psychological and neurosonological (i.e., with transcranial Doppler) evaluations can indicate patients at high risk for postoperative cognitive decline and, therefore, suggest the need for psychophysiological pre-habilitation programs and/or for careful intraoperative management of patients through brain monitoring. Intraoperatively, the use of brain monitoring with transcranial Doppler for the detection of cerebral microembolization and hypoperfusion can guide the cardiac surgery equipe in the operating theatre. Also, intraoperative brain monitoring can guide the psychophysiological rehabilitation by indicating those patients at high risk for postoperative cognitive dysfunctions. Finally, in order to reduce postoperative electroencephalographic deficits reflecting depression-related cognitive and emotional dysfunctions, the use of neurofeedback intervention could be taken into account. Overall, these findings also provide suggestions or implications for improving patient's well-being and health care interventions after cardiac surgery.

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