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Review Article

Psychological Depression and Cardiac Surgery: A Comprehensive Review

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Abstract: The psychological and neurological impact of cardiac surgery has been of keen empirical interest for more than two decades although reports showing the prognostic influence of depression on adverse outcomes lag behind the evidence documented in heart failure, myocardial infarction, and unstable angina. The paucity of research to date is surprising considering that some pathophysiological mechanisms through which depression is hypothesized to affect coronary heart disease (e.g., platelet activation, the inflammatory system, dysrhythmias) are known to be substantially influenced by the use of cardiopulmonary bypass. As such, cardiac surgery may provide a suitable exemplar to better understand the psychiatric mechanisms of cardiopathogenesis. The extant literature is comprehensively reviewed with respect to the deleterious impact of depression on cardiac and neuropsychological morbidity and mortality. Research to date indicates that depression and major depressive episodes increase major cardiovascular morbidity risk after cardiac surgery. The association between depressive disorders and incident delirium is of particular relevance to cardiac surgery staff. Contemporary treatment intervention studies are also described along with suggestions for future cardiac surgery research. **Keywords:** depression, depressive disorder, coronary artery bypass, coronary artery disease, antidepressive agents. *JECT. 2012;44:224–232*

The impact of psychological depression in the etiology and prognosis of coronary heart disease (CHD) has been empirically described for more than two decades in myocardial infarction literature. Some of the earliest reports of cardiac surgery reported an association between cardiopulmonary bypass use and psychoses related to the stressors of surgery (1) and susceptibility to neurological insult and neurocognitive changes (2). Although the psychological side effects of cardiac surgery have long been of interest, the prevalence and influence of depression on patients undergoing cardiac surgery lag behind the evidence documented in heart failure, myocardial infarction, and acute coronary syndromes (3). Rather, in cardiac surgery, an emphasis has been placed on preserving cognitive function but not mental health function per se. This is surprising considering that approximately 2–3% of patients undergoing cardiac surgery experience a form of psychological depression immediately leading up to and after surgery (4–8). Moreover, some pathophysiological mechanisms through which depression is hypothesized to affect CHD (platelet activation, the inflammatory system, dysrhythmias) are known to be substantially influenced by the use of cardiopulmonary bypass (9). Therefore, cardiac surgery may provide a suitable exemplar to better understand psychiatric mechanisms of cardiopathogenesis. An overview of research documenting a deleterious impact of depression on cardiac and neuropsychological morbidity and mortality is described. Part of the review describes the pathophysiological mechanisms as relevant. Finally, contemporary

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Table 1. Coronary artery bypass graft studies reporting prevalence of depression with structured diagnostic interview.

Reference	Sample Characteristics	Diagnosis	Timing of Assessment	Major Depression (%)	Dysthymia (%)
Kazmierski (44)	563 open-heart surgery with CPB, Poland	MINI	Pre	6.2	—
Connerney (4)	309 CABG, US	NIMH	Pre	20.0	—
Kazmierski (36)	260 CABG, Poland	MINI	Pre	6.2	—
Tully (5,75)	158 CABG ± valve, Australia	MINI	Pre	17.1	—
Mitchell (8)	124 CABG, Canada	MINI	Pre	28.2	—
Fraguas (6)	50 CABG, Brazil	CIS	Pre	8.0	6.0
Rafanelli (7)	47 CABG, Italy	SCID	Post (1 month)	10.6	12.8
Rothenhauseler (76)	34 CABG, Germany	SCID	Pre	2.9	17.6*

*Minor depression and dysthymia.
CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CIS, Clinical Interview Schedule; MINI; MINI International Neuropsychiatric Interview; NIMH, National Institute of Mental Health; Pre, preoperative period; Post, postoperative period; SCID, Structured Clinical Interview for DSM Disorders; US, United States.

treatment intervention studies are described along with suggestions for future cardiac surgery research.

DEPRESSION AMONG PATIENTS UNDERGOING CARDIAC SURGERY

The term major depressive episode is used to refer to a psychiatric diagnosis of unipolar depression episode as distinct from bipolar depression, adjustment disorders, and other types of mood disorders. The cardinal symptoms of major depressive episode include depressed mood and/or loss of interest or pleasure among other cognitive and somatic symptoms described subsequently. The prevalence of major depressive episode is 15–20% among patients undergoing coronary artery bypass graft (CABG) surgery. Comparatively, prevalence estimates among the general population is 5–9% for females and 2–3% among males (10). Collectively, research to date indicates that the number of patients affected by any depression (i.e., major, minor or dysthymia) approximates between 20% and 30% of patients undergoing CABG surgery depending on concurrent comorbidity rates, and a summary is provided in Table 1. A notable limitation of these studies, however, is the low sample size, highlighting a need for further research.

Studies using self-report depression measures suggest up to 50% of patients experience depressive symptoms (9,11–13). Studies using self-report measures do not reflect a clinical diagnosis of depression but, rather, depression symptoms. Peterson and colleagues (14) explain that newly developed depressive symptoms result from the stressors of surgery that can produce an adjustment reaction or reactive-type depression. In any case, as described further subsequently, identifying depression in the patient undergoing CABG surgery is complicated by the somatic symptoms experienced in CHD and the physical stressors of surgery.

IDENTIFYING DEPRESSION

The American Heart Association (15) recommended the Patient Health Questionnaire (PHQ) (16) to screen for depressive symptoms. In its expanded form, the PHQ-9 covers the full spectrum of symptoms reflective of a major depressive episode, depicted in Table 2. As Carney and Freedland point out (17), many different combinations of symptoms fulfill criteria for a major depressive episode. The American Heart Association and American College of Cardiology Foundation (18) stated that a reasonable level of evidence exists for depression screening, stating it is reasonable in instances in which patients have access to case management in collaboration with their primary care physician and a mental health specialist. As such, not every cardiac surgery unit or medical center could feasibly adopt a routine depression screening and follow-up protocol. Indeed, close monitoring and follow-up for patients describing thoughts of death or self-harm are strongly recommended. Shemesh et al. (19) reported that >12% of cardiovascular patients require immediate evaluation of suicidal thought and intent, reiterating the practical requirements for referral pathways after assessment.

It has been suggested that a positive response to either of the PHQ-2 questions should be followed up with

Table 2. Core depression symptoms assessed by the PHQ-9.

Over the past 2 weeks, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed or the opposite—being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead of or hurting yourself in some way

Questions are scored: not at all = 0; several days = 1; more than half the days = 2; nearly every day = 3. Refer to references (16,22).
PHQ, Patient Health Questionnaire.

Table 3. Association between depression and mortality or cardiac outcome after cardiac surgery.

Reference	Sample	Age (% female)	Follow-up	Outcome, *N* (%)	Depression Measures	Prevalence Preoperative/ Postoperative	Adjustment	Critical Value HR/OR/RR (95% CI)
Baker (9)	158 CAG ± valve, AUS	64.6 (25.3)	Median 2 years	All-cause mortality, *n* = 6 (3.8)	DASS ≥ 10	1 day preoperative, 15.2%	—	Unadjusted OR 6.24; 95% CI = 1.18–32.98, $p < .05$
Blumenthal (24)	817 CAG, US	61 (27)	Mean 5.2 years	All-cause mortality, *n* = 122 (15)	CES-D 16–26 (mild)	1 day preoperative, 26.1% mild preoperative	Cigarette smoking, LVEF, sex, age, grafts 4 vs 2, DM, previous MI,	Moderate–severe adjusted HR 2.37 (1.40–4.00), $p = .001$;
					CES-D ≥ 27 (moderate to severe)	11.9% moderate to severe preoperative,		mild adjusted HR 1.08 (.70–1.67), $p = .723$
Burg (33)	89 CAG, US	66.3 (0)	2 years	Cardiovascular mortality, *n* = 5 (5.6)	BDI > 10	<1 week preoperative 28.1%	Tu score (age, gender, LV function, urgency, redo)	Adjusted OR = 23.16 (95% CI = 1.38–389.08, $p = .03$
Burg (25)	89 CAG, US	65.9 (0)	6 months	Hospitalization for MI or unstable angina, *n* = 8 (9)	BDI ≥ 10	<1 week 28.1% preoperative	History of MI, chronic renal insufficiency	$\chi^2 = 4.24$, $p = .039$
Connerney (4)	309 CAG, US	63.1 (33)	12 months	MI, PCTA, redo, cardiac arrest, death resulting from cardiac causes, rehospitalization for angina, CHF, *n* = 42 (14)	BDI ≥ 10	4–10 days postoperative, 28%	MDD, LVEF, sex, living alone, LOS, NYHA class, CAG/valve, vessels	Adjusted RR = 1.62 (.83–3.16), p = NR
Connerney (4)	309 CAG, US	63.1 (33)	12 months	MI, PCTA, redo, cardiac arrest, death resulting from cardiac causes, rehospitalization for angina, CHF, *n* = 42 (14)	DIS	4–10 days postoperative, 20.4%	LVEF, sex, living alone, LOS, NYHA class, CAG/valve, vessels	Adjusted RR 2.31 (1.17–4.56) $p = .01$
Connerney (28)	309 CAG, US	63.1 (33)	Median 9.3 years	Cardiac mortality, *n* = 62 (20.1)	DIS	4–10 days postoperative, 20.4%	Female sex, age, LVEF, DM	Adjusted HR 1.78 (1.04–3.04), $p = .04$
Connerney (28)	309 CAG, US	63.1 (33)	Median 9.3 years	All-cause mortality, *n* = 117 (37.9)	DIS	4–10 days postoperative, 20.4%	Female sex, age, LVEF, DM	Adjusted HR 1.19 (.78–1.82), $p = .42$
Oxlad (26)	119 CAG ± valve, AUS	63.3 (16.0)	6 months	CHD or surgery related readmission, *n* = 21 (17.9)	DASS-D ≥ 10	5–6 days postoperative, 15.7%	CPB time	Adjusted preoperative HR 5.15 (1.45–18.28), $p = .01$ Adjusted postoperative HR = .97 (.25–3.79), $p = .96$

Continued

Table 3. *Continued.*

Reference	Sample	Age (% female)	Follow-up	Outcome, *N* (%)	Depression Measures	Prevalence Preoperative/ Postoperative	Adjustment	Critical Value HR/OR/RR (95% CI)
Oxman (77)	232 CAG, AVR, CAG ± AVR, US	¥(28)	6 months	In-hospital and postoperative all-cause mortality, *n* = 21 (9.1)	HAM-D ≥ 9	1–2 weeks preoperative 21.6%	—	χ^2, $p = .07$
Phillips-Bute (78)	427 CAG, US	61 (30)	2 years	Repeat CAG, PCI, MI, cardiac arrest, all-cause mortality, *n* = not stated	CES-D >16	1 day preoperative 36.8%	None	Unadjusted OR = 2.6; 95% CI = 1.6–4.3, $p < .05$
Szekley (79)	180 CAG/valve, HUN	57.9 (33.9)	4 years	All-cause mortality, *n* = 17 (9.4)	BDI > 10	1–5 days preoperative 44%	—	NS, not reported
Szekley (79)	180 CAG/valve, HUN	57.9 (33.9)	4 years	Cardiac death, hospitalization for angina, CHF, MI, PTCA, cardiac arrest, *n* = 48 (26.2)	BDI > 10	1–5 days preoperative 44%	DM, postoperative infection, ICU days, preoperative and post discharge 6th month STAI-T, 6 month BDI scores	Adjusted HR = .980 (95% CI = .917–1.047, $p = .544$)
Tully (61)	440 CAG ± valve, AUS	64 (20)	Median 5 years 10 months	All-cause mortality, *n* = 67 (15.2)	DASS-D ≥ 10	<1 week preoperative 20%	Age, renal disease, valve procedure, CVD, PVD	Adjusted HR = 1.61 (95% CI = .91–2.85), $p = .10$
Tully (11)	226 CAG, AUS	63 (17)	6 months	Cardiovascular/ surgery readmission, *n* = 72 (32)	DASS-D ≥ 10	<1 week preoperative 20.1% 4 days postoperative 23.5%	Anxiety, stress, age, sex, LVEF, urgency, lung disease, CHF, DM, PVD, renal disease, MI < 90 days, HTN, CCS, psychoactive medication use	Adjusted preoperative HR = .80 (.38–1.68), $p = .56$ Adjusted postoperative HR = 2.06 (.97–4.40), $p = .06$
Tully (32)	226 CAG, AUS	63 (17)	Median 4.9 years	MI, unstable angina, revascularization, CHF, sustained arrhythmia, stroke/CVA, LV failure, cardiac mortality, *n* = 65 (28.8)	BDI-II Cognitive factor	4 days postoperative	LVEF, age, respiratory disease, CHF, renal disease, DM	Adjusted HR = 1.36 (1.02–1.82), $p = .04$

AUS, Australia; BDI, Beck Depression Inventory; CAG, coronary artery graft; CCS, Canadian Cardiovascular Society; CES-D, Center for Epidemiological Studies-Depression; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CPB, cardiopulmonary bypass time; CVA, cerebrovascular accident; DASS, depression, anxiety and stress scales; DIS, diagnostic interview schedule; DM, diabetes mellitus; HAM-D, Hamilton Rating Scale for Depression; HR, hazard ratio; HUN, Hungary; HTN, hypertension; ICU, intensive care unit; LOS, length of stay; LV, left ventricular; LVEF, left ventricular ejection fraction; MDD, major depressive disorder; MI, myocardial infarction; NYHA, New York heart Association; OR, odds ratio; PCI, percutaneous coronary intervention; PCTA, percutaneous coronary transluminal angioplasty; PVD, peripheral vascular disease; RR, risk ratio; STAI-T, State Trait Anxiety Inventory-Trait; US, United States.

administration of the PHQ-9 with scores ≥10 on the PHQ-9 requiring an even more comprehensive assessment such as by a psychiatrist or psychologist (15). As previously mentioned, the somatic-laden depression diagnostic criteria overlap CHD symptoms. Specifically fatigue, loss of appetite, psychomotor retardation, insomnia, and difficulty concentrating can be the direct physiological response to a medical illness and hospitalization (20) and have been documented to significantly increase in the first month after CABG surgery (21). Important risk factors associated with a major depression episode among patients undergoing CABG surgery include female gender, younger age, a previous depression episode, and evidence of a family history of depression (8). Patients at high risk might warrant closer monitoring during the perioperative period with respect to depression and related psychiatric sequelae such as delirium, as described subsequently. Brief psychological reactions to the impending stressors of surgery and the postoperative recovery period may spontaneously remit over time, thus requiring no further intervention. Watchful waiting, monitoring, and brief support of suspected depressed cases might serve as a useful strategy before implementing psychological intervention. The developers of the PHQ-9 describe recommendations for what constitutes depression remission and treatment efficacy in primary care populations (22). With respect to identification of a major depressive episode, the only study to use receiver operating characteristics in patients undergoing CABG surgery showed that a self-report measure of depression yielded an area under the curve of .811 and 70.4% sensitivity and 77.1% specificity (23). Without more research, the use of self-report measures to identify depression in CABG populations remains largely unknown.

DEPRESSION AND MORBIDITY AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

The recent depression research among patients undergoing CABG surgery is described in Table 3. The association between depressive symptoms at the time of CABG surgery and late mortality has been corroborated by several studies (4,9,24). In a study of 309 patients undergoing CABG surgery, Connerney et al. (4) reported that a major depressive episode, but not depressive symptoms, was associated with cardiac events at 1-year follow-up (risk ratio, 2.31; 95% confidence interval [CI], 1.17–4.56) adjusted for ejection fraction, female sex, extended length of hospital stay, New York Heart Association class, number of vessels revascularized, and living alone. Blumenthal et al. (24) reported a similar finding for person with moderate to severe depression symptoms and increased mortality risk (hazard ratio, 2.4; 95% CI, 1.2–4.2). Evidence implicating depression in nonfatal morbidity outcomes has been reported for hospital readmissions (11,25–27), major cardiac events (4,28), and poorer quality of life (29). For example, patients reporting depressive symptoms 1 month after cardiac surgery were found to have a greater proportion of arrhythmias and return of angina symptoms at 5-year follow-up (12). Scheier et al. (30) reported that depressive symptoms were associated with surgery, CHD, and wound infection hospital readmissions among 309 patients at 6-month follow-up. In a study of 963 patients undergoing CABG, improvement in physical health at 6-month follow-up was lower among patients with depressive symptoms after adjustment for cardiac severity and baseline health (31). A systematic comparison of depression, anxiety, and stress suggested that only depression was consistently associated with quality-of-life measures of vitality, social role functioning, and physical and general health (29).

With respect to specific clusters of depression symptoms, two recent studies support a prognostic association between cognitive depression symptoms (e.g., pessimism, past-failure, self-criticalness, worthlessness) with nearly twofold greater risk of cardiac morbidity and mortality after CABG surgery (28,32). These findings suggest that the adverse effects of depression after CABG surgery are independent of any somatic depressive symptoms or medical comorbidity and diverge from findings with patients with myocardial infarction. However, Carney and Freedland's recent review (17) generally does not support that any particular subtype of depression confers greater CHD morbidity risk.

Studies to date are not without their limitations such as the low number of morbidity events experienced and lack of control for conventional risk factors (28). Unfortunately, these practices tend to bias the results in favor of rejecting the null hypothesis and the resultant wide CIs (e.g., 9,26,33) obscure the effect sizes and biological plausibility of an effect for depression.

DEPRESSION AND NEUROPSYCHOLOGICAL MORBIDITY AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

The cognitive outcomes from cardiac surgery and the role for the perfusionist and cardiopulmonary bypass circuit continue to be of empirical interest. A major depressive episode also increases the risk for delirium among cardiac surgery populations (34), which is the most common psychiatric disorder observed on admission to healthcare settings (35). A fluctuating delirious state is characterized by disorientation to time, place, and persons; perceptual disturbances; and hallucinations. The incidence of delirium after cardiac surgery varies widely between 3.1% and 50% (36–42). McAvay and colleagues (43) showed that dysphoric mood and hopelessness depressive symptoms were

associated with incident delirium after hospitalization. Kazmierski et al. (44) screened patients undergoing open heart surgery for major depression episodes before surgery and found more than a fourfold greater risk for delirium after surgery (adjusted odds ratio [OR], 4.69; 95% CI, 1.84–11.93). Our prognostic study with 158 patients undergoing CABG (5) modified the diagnostic criteria for delirium to reduce potential bias from overlapping delirium–depression symptoms (e.g., concentration difficulties). Even with more stringent delirium criteria, preoperative major depression remained associated with incident delirium after CABG surgery (5) (adjusted OR, 3.86; 95% CI, 1.42–10.52). Surprisingly, parallel research concerning post-CABG neuropsychological function has produced predominantly null findings or weak correlations between depression and cognitive function in the short term (18,45) and long term (13,46,47). At 6-month and 5-year follow-up, depression, anxiety, and stress were not consistently associated with neuropsychological dysfunction in regression analysis among 75 patients undergoing CABG surgery and 36 control subjects (47). These results suggest that although depression poses a risk for delirium, there is not a consistent association with neuropsychological function.

MECHANISMS OF CARDIOPATHOGENESIS

An increased risk in CHD morbidity attributable to emotional distress is explained by behavioral and biological mechanisms. Epidemiological surveys suggest that affective disorders are associated with larger body mass index, hypertension, hypercholesterolemia, diabetes (48), physical inactivity (49), and regular smoking and nicotine dependence (50,51). Psychological distress has also been associated with less concordance to exercise regimens and smoking cessation 4 months after myocardial infarction (52). The biological mechanisms of cardiopathogenesis attributable to depression are multifactorial and include the dysregulation of the hypothalamic–pituitary–adrenal axis (53–55), reduced heart rate variability (56–58), altered serotonergic pathways, inflammatory response (59), and altered platelet aggregability (60). Reports among patients undergoing CABG show that depression symptoms are associated with peripheral vascular disease and diabetes (14), impairment in left ventricular function (61), and lower use of the left internal mammary artery (9).

INTERVENTION AND TREATMENT

With respect to pharmacological management, clinicians should be aware of the possible proarrhythmic and cardiotoxic effects of tricyclic antidepressants in cardiac patients and the common use of tricyclics such as amitriptyline for pain management (62,63). Selective serotonin reuptake inhibitors (SSRIs) on the other hand have been hypothesized as safe among cardiac patients as a result of the serotonin transporter affinity and attenuation of platelet functioning. Safety, tolerability and efficacy of SSRIs among cardiac patients have been reported in some studies (45,64) but not others (65–67). Possible risks for patients undergoing CABG surgery specifically include increased bleeding attributable to SSRIs; however, this has not been consistently supported (68–70). One study suggested an increased mortality and readmission risk after CABG surgery attributable to SSRIs (71) and others have indicated greater morbidity but not mortality risk (70). The largest study from a Swedish registry of 10,884 CABG procedures reported a 40–45% increased hazard ratio in adjusted analyses for rehospitalization and death respectively (72). Two recent systematic reviews of randomized, controlled trials (RCTs) in patients with CHD both corroborated SSRI and placebo were not associated with reductions, or increased risk, in mortality (50,51).

A diverse range of behavioral and psychological RCT interventions have been reported and cognitive–behavioral therapy or collaborative care constitutes Class IIa evidence (i.e., additional studies with focused objectives are needed, and it is reasonable to administer treatment) (73). Freedland et al. (74) compared cognitive behavior (n = 41) or supportive stress management (n = 42) vs. usual care (n = 40) and found significant 3-month depression remission rates in the treatment arms (71%, 57%, and 33%, respectively; p = .002). Group differences were sustained at 9-month follow-up, whereas cognitive–behavioral therapy intervention was found to be superior with respect to measures of anxiety, hopelessness, stress, and quality of life. Four sessions of psychoeducation and skills training in a RCT treatment group (n = 48) were associated with reduced depressive symptoms 4 weeks after surgery by comparison to a usual care group (n = 48) (53). A biweekly, nurse-led telephone-delivered intervention for depressed patients over 8 months reported modest effect sizes (.30; 95% CI, .17–.52) for mental health quality of life (54), and a trend toward favorable cardiac hospital readmission rates. One disconcerting finding for mental health professionals was the low mental health service visits (4% intervention vs. 6% usual care), suggesting that patients undergoing CABG surgery may not be suited to this particular form of psychological support (55). Together with the findings of lower cardiac events in patients randomized to a stress intervention over 12 months in Finland (56), these studies suggest that sustained depression remission can be achieved with a diverse range of interventions. However, more comprehensive psychological interventions appear to be required for clinically significant reductions in cardiovascular complications. Also, as the developers of the PHQ-9 point out (22), severe depression episodes require combinations of antidepressants and psychotherapy; thus, neither treatment modality can be recommended over the other.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Although a concerted effort has been made to improve patient cognitive outcomes after cardiac surgery, far less intervention has been invested in improving the mental health outcomes of patients undergoing cardiac surgery. Indeed, the interaction between depression pathophysiology and effects of cardiopulmonary bypass is a potentially fruitful avenue of research in cardiac surgery to better understand mechanisms of psychiatric cardiopathogenesis. Naturally, the rates of depression after cardiac surgery highlight a requirement for appropriate identification, support, and intervention efforts. One suggestion for future depression focused research in CABG surgery would be to investigate the impact of closely related psychological constructs, particularly anxiety (57,58). Collaboration between psychologists and psychiatrist specialists with cardiac surgeons, cardiologists, and cardiac nurses may enhance the research basis for improved patient outcomes. It is commonly hoped that intervention might mitigate the deleterious impact of depression on subsequent morbidity and mortality.

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