The importance of depression and alcohol use in coronary artery bypass graft surgery patients: risk factors for delirium and poorer quality of life

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Abstract

Objective To investigate whether depression, anxiety and stress increase the risk for delirium and poor quality of life (QOL) after coronary artery bypass (CABG) surgery. Methods A total of 180 CABG patients (mean age of 63.5 ± 10.1 years, 82.2% males) completed baseline and postoperative self-report questionnaires to assess distress and QOL. Incident delirium was diagnosed postoperatively with a structured clinical interview and patients were monitored every day post-operatively for confusion and disturbance in consciousness. Results Delirium developed in 63 persons (35% of sample). After adjustment for covariates, delirium was significantly associated with depression [odds ratio (OR): 1.08; 95% confidence interval (CI): 1.03–1.13, P = 0.003], anxiety (OR: 1.07; 95% CI: 1.02–1.13, P = 0.01) and stress (OR: 1.05; 95% CI: 1.00–1.09, P = 0.03). Preoperative depression scores were associated with poorer QOL including bodily pain (β = −0.39, P = 0.013), vitality (β = −0.32, P = 0.020), social functioning (β = −0.51, P ≤ 0.001), emotional role function (β = −0.44, P = 0.003) and general health (β = −0.33, P = 0.038). Among the covariates, harmful levels of alcohol use was consistently associated with poorer QOL. Conclusions Depression and harmful levels of alcohol use were consistently associated with poorer QOL whereas depression, anxiety and stress were associated with delirium risk. These findings point to further research examining depression and harmful levels of alcohol use in coronary heart disease populations undergoing coronary revascularization.

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1 Introduction

Coronary artery bypass grafting (CABG) is being performed on an increasingly older population with multiple and severe comorbidities such as chronic kidney disease, respiratory diseases and diabetes. Although many patients experience favorable outcomes in terms of event-free survival, short term cognitive function is often markedly impaired and longer term quality of life (QOL) remains poor. Among the important cognitive outcomes, delirium occurs in 11% to 50% of CABG patients. Delirium is frequently caused by multi-factorial etiologies and may serve as a broad marker of an undetected but emerging post-surgical complications. The high prevalence and poorer longer term outcome of delirium underscores the need to better understand delirium etiology and identify modifiable risk factors. A systematic review of ten studies identified depression as among the most consistent predisposing risk factor for delirium following cardiac surgery. However, geriatric depression can be difficult to detect, and unfortunately less is known regarding other psychiatric symptoms such as anxiety and general stress. Currently, it remains to be clearly explicated whether depression is a risk factor for delirium independent from anxiety and stress, or whether negative emotions generally increase delirium risk. This is an important clinical pursuit since psychological risk factors and health behaviors tend to cluster together.

Like cognitive function, deterioration in QOL after CABG is complex and not completely understood. Emerging research shows that improvement in QOL is not ubiquitous even in the presence of an otherwise favorable

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clinical picture characterized by patent grafts and freedom from symptomatic angina and dyspnea. Unsurprisingly, psychological factors, especially depression, have been heavily implicated in poor QOL after CABG.\textsuperscript{[12,14]} Like depression, although anxiety and stress are common throughout the perioperative period,\textsuperscript{[12,15,16]} their role in longer term QOL has not been clarified even though anxiety is prevalent in 20\% to 40\% of heart disease patients, including CABG patients.\textsuperscript{[17]} Moreover, anxiety confers heightened risk for CABG complications and mortality.\textsuperscript{[16,18]} Nevertheless, the effects of anxiety concurrently with depression and stress remains under-researched.

This study aimed to examine whether depression, anxiety and stress increase the risk for incident delirium after CABG surgery. Secondly, we aimed to evaluate the association between these negative emotional states, and delirium, with longer-term QOL.

2 Methods

2.1 Population

Between April 2003 and May 2011, consecutive patients admitted to our institution for elective CABG surgery and aged 18 years or older were assessed for eligibility criteria. Participants were excluded from the study when: English was not their native language; they had cerebrovascular disease (including cerebrovascular accident, reversible ischemic neurological deficit or transient ischemic attack) or a history of other neurological disease, dementia, a head injury or loss of consciousness; met screening criteria for confusion or disorientation; had previously undergone open heart surgery; did not attend the pre-admission clinic; or resided in a very remote location precluding follow-up. All patients provided informed consent and ethical approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee.

2.2 Patient assessment

Medical comorbidities were evaluated by cardiac surgery registrars according to the standardized definitions of the Australian Society of Cardiac and Thoracic Surgeons.\textsuperscript{[19]} Alcohol use and number of standard drinks was based on the National Health and Medical Research Council guidelines for harmful drinking;\textsuperscript{[20]} 2 versus ≥ 3 standard drinks per day. Self-report questionnaires were administered during the week prior to surgery, on the fourth postoperative day, and again at six months. The Depression, Anxiety and Stress Scales (DASS) is a 42-item self-report inventory measuring the three distress types in our study.\textsuperscript{[21]} Respondents endorse 42 statements on a Likert-type scale ranging between 0 (“does not apply to me at all”) to 3 (“applies to me very much, or most of the time”) and a score is derived for each sub-scale of depression, anxiety and stress (higher scores indicating greater distress). The DASS has excellent reliability and validity,\textsuperscript{[21,22]} and has been widely used with CABG patients.\textsuperscript{[16,23,24]}

The Short-Form Health Survey (SF-36) is a valid and reliable self-report questionnaire of QOL.\textsuperscript{[25]} The SF-36 measures eight subjective health domains; physical functioning, role limitations to physical health, role limitations due to emotional problems, bodily pain, vitality, mental health, social role functioning and general health perceptions. Scores are standardized into continuous variables and range from 0 to 100, with higher scores representing better quality of life. The SF-36 is the most common measure of QOL in the CABG surgery population,\textsuperscript{[26,27]} and has been utilized to document longer term cardiac surgery outcomes and distress.\textsuperscript{[14]}

Delirium was assessed post-operatively using the Delirium Symptom Interview (DSI) which combines structured interview questions with behavioral observations.\textsuperscript{[28]} The DSI measures symptom domains defined by Diagnostic and Statistical Manual of Mental Disorders–III criteria: disorientation, disturbance of consciousness, sleep/wake disturbance, perceptual disturbances, altered psychomotor activity, incoherent speech and fluctuating behavior. The DSI has shown to have good sensitivity (0.90) and specificity (0.80) and strong inter-rater reliability (0.90),\textsuperscript{[29]} including in the post-CABG population.\textsuperscript{[10]} We also assessed disorientation and disturbance in consciousness on a daily basis until hospital discharge with the Short Portable Mental Status Questionnaire\textsuperscript{[30]} as described elsewhere.\textsuperscript{[31]}

2.3 Surgical procedure

Comprehensive descriptions of the CABG surgical and cardiopulmonary bypass (CPB) procedures at our institution can be found elsewhere.\textsuperscript{[32,33]} Briefly, general anaesthesia was induced with fentanyl (10–30 g/kg) and supplemented with sevoflurane and/or propofol. All patients underwent cardiac surgery with CPB using a S3 roller pump (Stockert, Munich, Germany). Cardiopulmonary bypass was instituted after positioning of either a single 36/51 Fr two-stage atrial cannula (SarnsTM, Terumo Corporation, Tokyo, Japan), or 32–36 Fr bicaval cannulation (SarnsTM), and a 22 Fr ascending aortic cannula (DLP, Medtronic, Minneapolis, MN), or 20 Fr FemFlex used in the ascending aortic position (Edwards Lifesciences, Irvine, CA). The CPB circuit included a hard-shell membrane oxygenator (Capiox® SX25RX, Terumo Corporation, Japan), biopassive tubing (SMARxT®, Cobe Cardiovascular, Arvada, CO) a 40 m arterial line filter.
D703, Dideco, Mirandola, Italy) and a 0.2 m prebypass filter (Prebypass Plus®, Pall Corporation, Port Washington, USA). Packed red blood cells were added if required to provide a predicted haemoglobin level of > 7 g/dL on initiation of CPB. Routine CPB protocol included arterial non-pulsatile target flow rate of 1.8–2.4 L/min per m², alpha-stat pH management with target Po2 100–250 mmHg, gravity venous drainage, and tepid systemic temperature management (nasopharyngeal temperature 34–35°C). Mean CPB arterial pressure was controlled using metaraminol, phentolamine or isoflurane to achieve a target of 40–80 mmHg. Target nasopharyngeal temperatures for separation from bypass was > 36°C with rewarming rate < 1°C per min. Blood glucose concentration was targeted at < 10 mmol/L during CPB, with an intravenous insulin [(Actrapid) Novo Nordisk Pharmaceuticals, Baulkham Hills, NSW, Australia] bolus and/or infusion if glucose exceeded this value. After surgery patients were transferred to the intensive care unit and managed according to unit protocol.

2.4 Statistical analysis

To examine the relationship between covariates and delirium, a series of univariable logistic regression analyses was performed utilizing demographic and medical variables (see Table 1). To avoid regression model over-fitting we utilized demographic and medical variables. We examined the pre-operative DASS sub-scales in relation to delirium firstly in isolation (e.g., anxiety only), and then contemporaneously (i.e., depression, anxiety and stress).

To identify the associations between distress and postoperative delirium with QOL, a series of multivariate linear regressions was performed. Negative beta values are indicative of higher distress being associated with lower QOL scores. We forced relevant covariates into the models including; male gender, indigenous and Australian peoples, alcohol use, chronic lung disease, congestive heart failure, hypertension, hypercholesterolemia, diabetes mellitus, peripheral vascular disease, cardiovascular disease, urgent surgery and left ventricular ejection fraction. History of tobacco smoking and recent myocardial infarction were not associated with any QOL measure and therefore were not included in further analyses. Age and time spent on the aortic cross-clamp (minutes) were assessed as continuous variables. We concomitantly adjusted for baseline QOL using the appropriate SF-36 domain. Statistical analyses were performed with SPSS 20.0 software (SPSS Inc., Chicago, IL): a P-value < 0.05 was considered significant and the threshold for multicollinearity was the same as defined previously.[14]

Table 1. Descriptive characteristics of the sample and the association with incident delirium risk.

| Demographic variables | n (%) | OR  | 95% CI | P  |
|-----------------------|-------|-----|--------|----|
| Male gender           | 148 (82.2%) | 0.55 | 0.23–1.33 | 0.19* |
| Age                   | 63.47 ± 10.1 | 0.99 | 0.96–1.02 | 0.63 |
| Indigenous Australian | 5 (2.8%)    | 0.37 | 0.06–2.26 | 0.28 |
| Hypercholesterolemia  | 151 (83.9%) | 2.56 | 0.91–7.21 | 0.08* |
| Diabetes              | 51 (28.3%)  | 2.21 | 1.11–4.4  | 0.03* |
| Hypertension          | 133 (73.9%) | 0.75 | 0.37–1.49 | 0.41 |
| Chronic lung disease  | 37 (20.6%)  | 0.99 | 0.46–2.13 | 0.98 |
| Congestive heart failure | 26 (14.4%) | 0.99 | 0.41–2.39 | 0.98 |
| Peripheral vascular disease | 19 (10.6%) | 1.13 | 0.42–3.09 | 0.81 |
| Myocardial infarction previous < 30 days | 53 (29.4%) | 0.94 | 0.48–1.87 | 0.86 |
| Substance abuse       | 2 (1.1%)    | 1.77 | 0.11–28.81 | 0.69 |
| History of tobacco smoking | 125 (69.4%) | 1.11 | 0.56–2.19 | 0.77 |
| History of alcohol use (> 3 standard drinks per day) | 13 (7.2%) | 1.28 | 0.39–4.21 | 0.69 |
| Renal disease         | 13 (7.2%)   | 1.01 | 0.28–3.58 | 0.99 |

Table shows univariate logistic regression ORs for incident delirium risk and are presented as mean ± SD or n (%). *Standardized definitions of the Australian Society of Cardiac and Thoracic Surgeons. CPB: cardiopulmonary bypass.

3 Results

3.1 Descriptives

Of the 180 volunteers for this study, seven were not evaluated for delirium due to death, extended ICU stays or withdrawal from the study. The remaining 173 participants were predominantly males (82.2%) with a mean age of 63.5 ± 10.1 years. The most common comorbidities were hypercholesterolemia (83.9%) and hypertension (73.9%).

3.2 Incident delirium

Delirium developed in 63 participants (35% of the sample). Univariable regressions identified male gender, hypercholesterolemia, diabetes and urgent surgery as the covariates associated with delirium. The multivariable analyses adjusted for these covariates showed that depression, anxiety and stress were significant independent predictors of incident delirium (Table 2). Incident delirium was signifi-
Table 2. Incident delirium risk according to preoperative distress.

| Model structure | adjOR  | 95% CI   | \(P\) |
|-----------------|--------|----------|--------|
| Entered separately |        |          |        |
| Depression      | 1.08   | 1.03–1.13| 0.003  |
| Anxiety         | 1.07   | 1.02–1.13| 0.01   |
| Stress          | 1.05   | 1.00–1.09| 0.03   |
| Entered simultaneously | | | |
| Depression      | 1.08   | 0.98–1.18| 0.12   |
| Anxiety         | 1.03   | 0.93–1.14| 0.55   |
| Stress          | 0.98   | 0.91–1.05| 0.53   |

1Sub-scales of the DASS were entered separately into three logistic models and adjusted for male gender, hypercholesterolemia, diabetes and urgent surgery; 2Sub-scales of the DASS were entered simultaneously into one logistic model and adjusted for male gender, hypercholesterolemia, diabetes and urgent surgery. \(\text{adjOR: adjusted odds ratio; DASS: Depression, Anxiety and Stress Scales.}\)

significantly associated with a 1 point increase in depression (OR: 1.08; 95% CI: 1.03–1.13, \(P = 0.003\)), anxiety (OR: 1.07; 95% CI: 1.02–1.13, \(P = 0.01\)) and stress (OR: 1.05; 95% CI: 1.00–1.09, \(P = 0.03\)). However, when the distress measures were entered into models simultaneously, the previous significant association with depression was attenuated (OR: 1.08; 95% CI: 0.98–1.18, \(P = 0.12\)) and other individual distress scores were non-significant.

3.3 Quality of life

Among the preoperative distress symptoms only depression was associated with QOL. Preoperative depression scores were associated with poorer QOL in 5 of the SF-36 domains. Depression was significantly associated with lower and therefore worse scores on bodily pain (\(\beta = -0.39, P = 0.013\)), vitality (\(\beta = -0.32, P = 0.020\)), social functioning (\(\beta = -0.51, P \leq 0.001\)), emotional role function (\(\beta = 0.44, P = 0.003\)) and general health (\(\beta = -0.33, P = 0.038\)). Delirium was significantly associated with general health (\(\beta = -0.22, P = 0.004\)) but otherwise the delirium, anxiety and stress variables were not related to QOL. Among the covariates, alcohol use was consistently associated with poorer QOL.

A similar pattern of results was evident when postoperative DASS measures were analyzed, with depression and alcohol use consistently associated with QOL (data available from author on request). Delirium was associated with general health (\(\beta = -0.18, P = 0.031\)) explaining 5.1% of the variance, but otherwise delirium, anxiety and stress were not related to QOL.

4 Discussion

The results of this study demonstrated that preoperative depression, anxiety and stress were independently associated with incident delirium after CABG surgery even once the effect of medical and demographic variables were accounted for. However when depression, anxiety and stress were ex-

Table 3. Linear regression analysis for quality of life domains after CABG surgery with preoperative distress and delirium.

| QOL domain | \(^*\)Demographic and medical covariates | Depression (\(\beta\)) | Anxiety (\(\beta\)) | Stress (\(\beta\)) | Delirium (\(\beta\)) | \(F(df), P\) value |
|------------|----------------------------------------|------------------------|--------------------|-------------------|---------------------|-------------------|
| Bodily pain| Alcohol use*                           | –0.39*                 | 0.10               | 0.07              | –0.10               | \(F(9,115) = 5.04, P < 0.001\) |
| General health | Alcohol use** CHF*                   | –0.33*                 | 0.09               | –0.03             | –0.22*              | \(F(12,109) = 7.84, P < 0.001\) |
| Vitality   | Alcohol use**                         | –0.32*                 | 0.03               | 0.08              | –0.12               | \(F(12,112) = 7.85, P < 0.001\) |
| Social functioning | Alcohol use* HB*               | –0.51*                 | –0.10              | –0.09             | 0.13                | \(F(10,113) = 8.8, P < 0.001\) |
| Role emotional | Alcohol use** CVD*                | –0.44*                 | 0.04               | 0.01              | –0.14               | \(F(11,114) = 6.3, P < 0.001\) |
| Mental health | Alcohol use*                         | –0.17                  | 0.00               | –0.15             | –0.06               | \(F(8,115) = 10.38, P < 0.001\) |
| Physical functioning | Alcohol use** CHF**               | –0.14                  | –0.10              | 0.04              | –0.09               | \(F(15,106) = 7.34, P < 0.001\) |
| Role physical | Alcohol use* Age**                | –0.17                  | –0.05              | –0.14             | –0.04               | \(F(13,111) = 4.9, P < 0.001\) |

\(^*\) Only significant covariates are reported, pre-operative QOL domain was significant in all models. CABG: coronary artery bypass graft; CHF: congestive heart failure; HB: health behaviors; CVD: cardiovascular disorder; QOL: quality of life.
aminsed simultaneously, all distress symptoms were no longer significant predictors of incident delirium. The QOL findings indicated that depression measured during the perioperative period was significantly associated with QOL. Moreover, among the covariates alcohol use was a strong correlate of worse QOL.

The findings with respect to depression support previous research indicating that depression is associated with delirium after cardiac surgery independent of medical risk factors.[7,10,34] However, our findings extend beyond prior reports as we showed that depression does not confer unique risk for delirium once anxiety and stress symptoms are contemporaneously accounted for in adjusted models. A possible explanation is regression dilution due to the common underlying component of general distress or negative affectivity that is measured by the DASS,[21] and shared between depression, anxiety and stress.[35] It has been suggested that depression and anxiety may not have separate, unique effects, but rather are risk factors due to their shared characteristics of experiencing negative emotions, i.e., negative affectivity.[35] Some plausible mechanisms through which depression and negative emotions might increase delirium risk include up-regulated stress response systems involving the limbic-hypothalamic-pituitary-adrenal axis, and an inflammatory response whereby fatigue, reduced appetite, anhedonia, and declines in cognition, motivation and mood are experienced.[15,36,37]

In contrast to the delirium results, depression was significantly associated with poorer QOL after CABG surgery even when entered simultaneously with anxiety and stress. This pattern of results supports prior research,[12,28] and bolsters the claim that depression is associated with poorer QOL independent of the effects of anxiety and stress.[14] It is possible that depression is more enduring throughout recovery from CABG surgery, whereas anxiety and stress may reflect a more transient state in the perioperative period dominated by somatic symptoms and concerns.[39] We also found that other than general health perception, longer term effects on QOL were generally unrelated to delirium. Considering that delirium is often a manifestation of serious underlying illness,[36] it was surprising that delirium was not associated with other QOL domains, contrasting to prior work.[5,40] One plausible explanation is that we contemporaneously assessed distress symptoms and delirium, which may have lessened the degree which delirium is associated with QOL in the longer term.

Among the covariates, alcohol was consistently associated with QOL even after the effects of distress were accounted for. Prolonged and harmful levels of alcohol consumption are associated with myocardial hypertrophy and increased risk of heart failure,[41] and are a notable behavioral risk factor among depressed individuals.[42] Though the association between alcohol withdrawal and in-hospital delirium is well established, to our knowledge no study has specifically examined alcohol’s association with post-CABG QOL alongside depression and general distress. Given that alcohol consumption is one of few modifiable risk factors that can be addressed in secondary prevention,[43] further research should elucidate the impact of alcohol risk reduction strategies on CHD and CABG patient outcomes. Even though the guidelines for alcohol adopted by this study were not specifically developed for cardiac populations, they were successful in predicting outcomes within the sample attesting to the robustness of these guidelines. One limitation that tempers these conclusions however is that the accuracy of self-reported alcohol use is unknown and we did not assess sporadic alcohol use or binge drinking.[29]

Findings from our study underscore the importance of identifying depression and risky alcohol consumption prior to surgery. Depression symptoms are associated with lower adherence to secondary prevention recommendations.[44] Several learned cardiology societies recommend routine depression screening,[42,45,46] possibly additional screening for high alcohol use might enable detection of a subgroup at an even higher risk for delirium and poor QOL. Prevention and early intervention are strongly indicated, yet outcome research presents conflicting messages with regard to the efficacy and acceptability of such interventions. Recent studies provided some direction for practice, concluding that intervention timing and patient and clinician characteristics require careful consideration.[47,48] For example, responses to depression intervention may vary by the type of intervention, with results favoring cognitive-behavioral therapy and problem-solving therapy.[49] This supports the need for careful clinical assessment and tailored interventions delivered by mental health trained professionals.[50] Etema, et al.[51,52] advised that preventive psychosocial interventions are more acceptable to patients and staff if presented as a core component within the medical admission process (not optional) and if staff have the requisite training to deliver them effectively.

The main strengths of this study were its prospective design and the evaluation of discrete patterns of associations between distress and delirium. Moreover, delirium was assessed using structured interviews and an assessment of consciousness was performed every day. The limitations include the use of self-report questionnaires rather than a structured depression interview. Also the study was observational, and delirium was probably actively managed following a delirium diagnosis, potentially explaining why post-operative delirium was not associated with poor QOL. Explicating direct causal links between depression and delirium after CABG necessitates a randomized trial to provide more definitive answers. Additional limitations include that we did not assess numerous other variables that could be associated.
with delirium including medication use and intra-operative factors.\textsuperscript{[5,34,36,33]} The study population came from a single hospital site, therefore the generalizability of the findings to a wider population are unknown. Unfortunately, the study’s high attrition rate may have introduced biases into the results. Finally, although multicollinearity was assessed and deemed acceptable, it cannot be ruled out that simultaneous entry of depression, anxiety and stress led to a reduction in unique predictive variance for delirium and QOL.

In conclusion, this study has shown that preoperative depression, anxiety and stress symptoms may be independent predictors of incident delirium after CABG surgery but only when analyzed separately. Depression was the only psychological risk factor for poor QOL. Importantly, our data revealed that harmful levels of alcohol use may be associated with worse QOL. These findings underscore the need to identify and address depression and high alcohol use in the CABG population.

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