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Coronary Revascularization in Patients with Obstructive Sleep Apnea Syndrome

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ABSTRACT

Background. There is a paucity of clinical information regarding therapy for ischemic heart disease (IHD) in patients with obstructive sleep apnea syndrome (OSAS). We evaluated our experience with surgical revascularization in this subset of patients.

Methods. Between January 1998 and April 2001, 20 patients with OSAS underwent isolated coronary artery bypass grafting (CABG). Outcomes were compared to a matched control group consisting of 65 patients.

Results. Patients with OSAS and the controls were similar with regard to age (65.8 years versus 65.2 years), ejection fraction (44.5% versus 46.9%), and systolic blood pressure (141 mmHg versus 142 mmHg). However, they were comparatively heavier (212 lb versus 188 lbs, $P < .03$), had higher pulmonary artery pressures (42 mmHg versus 34 mmHg, $P < .001$), higher pulmonary capillary wedge pressures (17 mmHg versus 14 mmHg, $P < .01$), higher left ventricular end diastolic pressures (20 mmHg versus 18 mmHg, $P < .04$), and a greater incidence of diabetes (55% versus 30%, $P = .049$). Patients with OSAS were more likely to require prolonged ventilation (40% versus 0%, $P < .001$) and tracheostomy (10% versus 0%, $P = .01$) and have a protracted intensive care unit (ICU) course (9 days versus 3 days, $P = .002$) and hospitalization (24 versus 13, $P = .003$). There were no peri-operative deaths, and both groups had significant improvement in angina and functional class. At a mean follow-up of 59 months, angina recurrence was 10% and survival was 95% in patients with OSAS.

Conclusion. Patients with OSAS and IHD requiring coronary revascularization have substantial risk for pulmonary morbidity that impacts the duration of hospitalization but not mortality. Good symptom control and early to mid-term survival may be achieved in this subset of patients with aggressive peri-operative management of their OSAS.

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), also known as sleep-disordered breathing, affects approximately 6% to 20% of the population [Young 2002]. It has been causally associated with the development of various cardiovascular diseases, including hypertension [Peppard 2000], stroke [Dyken 1996], ischemic heart disease (IHD) [Shahar 2001], and congestive heart failure [Shahar 2001]. OSAS has been shown to be a poor prognostic indicator in patients with IHD and portends a four-fold increase in mortality compared to patients without OSAS [Peker 2000]. Those suffering from both OSAS and IHD make up a unique subset of OSAS patients, as they frequently require surgical management for IHD, often at significant risk for morbidity and mortality. The impact of OSAS on the surgical treatment of IHD remains largely uninvestigated, except for such epidemiological studies as mentioned above. As our population ages and the incidence of obesity rises, the coexistence of OSAS and IHD is anticipated to become a more prevalent problem, and this question will become increasingly relevant.

In order to further understand the impact of OSAS on the treatment of IHD, we evaluated our experience with surgical revascularization in patients with OSAS to determine its safety, efficacy, and durability as treatment in this subset of patients.

METHODS

Study Subjects

Between January 1998 and April 2001, 20 male patients with OSAS underwent isolated coronary artery bypass grafting (CABG) for IHD. A matched control group consisting of 65 male patients was identified based on availability of left and right heart catheterization data during the study period. Data were prospectively collected and analyzed retrospectively. OSAS was diagnosed with a documented sleep study or clinically based upon the presence of 2 of the following 3 criteria: snoring, persistent daytime sleepiness or drowsiness while driving, and obesity or hypertension.

Therapeutic Interventions

All patients underwent preoperative left and right ventric-

Table 1. Baseline Characteristics for the Control and Study Groups*

Variable	OSAS, n = 20	Control, n = 65	*P*
Age, y	65.8 ± 6.8	65.2 ± 10.4	.82
Weight, lb	212 ± 33	188 ± 33	.006
Creatinine, mg/dL	1.4 ± 0.6	1.5 ± 1.4	.70
Albumin, g/dL	3.8 ± 0.8	4.0 ± 0.4	.12
FEV_1, L	2.31	2.57	.19
COPD, %	45	28	.15
Diabetes, %	55	31	.049
Smoking, %	50	54	.763
Prior MI, %	70	55	.245
PVD, %	70	55	.245
CVD, %	30	28	.841

*OSAS indicates obstructive sleep apnea syndrome; FEV_1, forced expiratory volume in 1 second; COPD, chronic obstructive pulmonary disease; MI, myocardial ischemia; PVD, pulmonary vascular disease; CVD, cardiovascular disease.

ular cardiac catheterization for evaluation of coronary anatomy, left ventricular function, and right heart pressures. Peri-operative medical management included beta-blocker, aspirin, and nitrate therapy. Patients with severe heart failure and significantly reduced ejection fraction or hemodynamic instability during cardiac catheterization underwent preoperative intra-aortic balloon pump (IABP) therapy. CABG was performed utilizing either standard CBP or on the beating heart utilizing the Octopus stabilizer system (Medtronic, Minneapolis, MN, USA). The left internal mammary artery (LIMA) was utilized for bypass to the left anterior descending coronary artery routinely, regardless of the surgical approach. Reversed saphenous vein was utilized for bypass in multivessel revascularization and when the LIMA was inadequate for use as a conduit.

Patients undergoing off-pump CABG (OPCABG) were treated with anti-platelet therapy consisting of an aspirin suppository (650 mg) within 2 postoperative hours and plavix (75 mg) starting on the first postoperative day (or within 12 postoperative hours). Amiodarone was utilized immediately postoperatively in all patients for the prevention and treatment of atrial fibrillation.

Table 2. Preoperative Cardiac Parameters for the Control and Study Groups*

Variable	OSAS, n = 20	Control, n = 65	*P*
CCA class III, IV, %	85	83	.417
NYHA class III, IV, %	75	34	.012
SBP, mmHg	149 ± 23	143 ± 30	.456
PAP, mmHg	42 ± 9	34 ± 9	.001
PCWP, mmHg	19 ± 8	14 ± 5	.004
LVEDP, mmHg	21 ± 7	17 ± 6	.18
EF, %	45 ± 11	47 ± 10	.357

*OSAS indicates obstructive sleep apnea syndrome; CCA, Canadian Class angina; NYHA, New York Heart Association; SBP, systolic blood pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; EF, ejection fraction.

Table 3. Operative Intervention Data for the Control and Study Groups*

Variable	OSAS, n = 20	Control, n = 65	*P*
Pre-operative IABP, %	15	17	.839
Number of Vessels Grafted			
1, %	10	17	.804
2, %	40	38	.804
3, %	35	35	.804
4, %	15	9	.804
IMA utilized, %	100	100	.574
OPCABG, %	13	13	.804
ACC time, min	60 ± 29	51 ± 18	.132
CPB time, min	101 ± 38	86 ± 28	.089

*OSAS indicates obstructive sleep apnea syndrome; IABP, intra-aortic balloon pump; IMA, ; OPCABG, off-pump coronary artery bypass grafting; ACC, aortic cross-clamping; CPB, cardiopulmonary bypass.

During the study period, evolution in the peri-operative management of patients with OSAS included aggressive peri-operative diuresis, hemofiltration during cardiopulmonary bypass, peri-operative continuous positive airway pressure (CPAP) therapy, and the utilization of OPCABG. All patients received postoperative cardiac rehabilitation and aggressive pulmonary toilet consisting of nebulized bronchodilators, percussive chest physical therapy, aggressive naso-tracheal suctioning, early ambulation, and incentive spirometry.

Statistical Analysis

Clinical data were compared allowing analysis of outcome data and identification of significant risk factors. Statistical analysis was performed utilizing Student *t* and chi-square tests. Survival was determined utilizing the Kaplan-Meier method.

RESULTS

Patient demographics for the study and control groups are compared in Table 1. The groups were similar except that patients in the study group were heavier (212 lb versus 188 lb, $P = .006$) and had a higher rate of diabetes (55% versus 31%, $P = .049$).

Preoperative cardiac parameters for the study and control groups are compared in Table 2. Patients in the study group had significantly higher pulmonary artery pressure (42 mmHg versus 34 mmHg, $P < .001$), pulmonary capillary wedge pressure (19 mmHg versus 14 mmHg, $P = .004$), and left ventricular end diastolic volume (21 mmHg versus 17 mmHg, $P = .018$). A significantly greater number of patients in the study group suffered from NYHA class III and IV heart failure (75% versus 34%, $P = .012$).

Table 3 compares the therapeutic intervention data for the study and control groups. The groups were similar with regard to completeness of revascularization, utilization of the LIMA, cardiopulmonary bypass parameters, preoperative use of IABP, and utilization of OPCABG.

Postoperative outcome data, including operative mortality,

Table 4. Postoperative Outcome Data for the Control and Study Groups*

Variable	OSAS, n = 20	Control, n = 65	*P*
Length of stay			
ICU, d	9 ± 14	3 ± 2	.002
Hospital, d	24 ± 25	13 ± 9	.003
MI, %	0	3.1	.427
Mediastinitis, %	5	3.1	.684
Bleeding, %	0	6.2	.256
Ventilation > 48 h, %	40	0	< .001
Tracheostomy, %	10	0	.010
CVA, %	0	3.1	.577
Early death, %	0	0	1.0

*OSAS indicates obstructive sleep apnea syndrome; ICU, intensive care unit; MI, myocardial ischemia; CVA, cardiovascular accident.

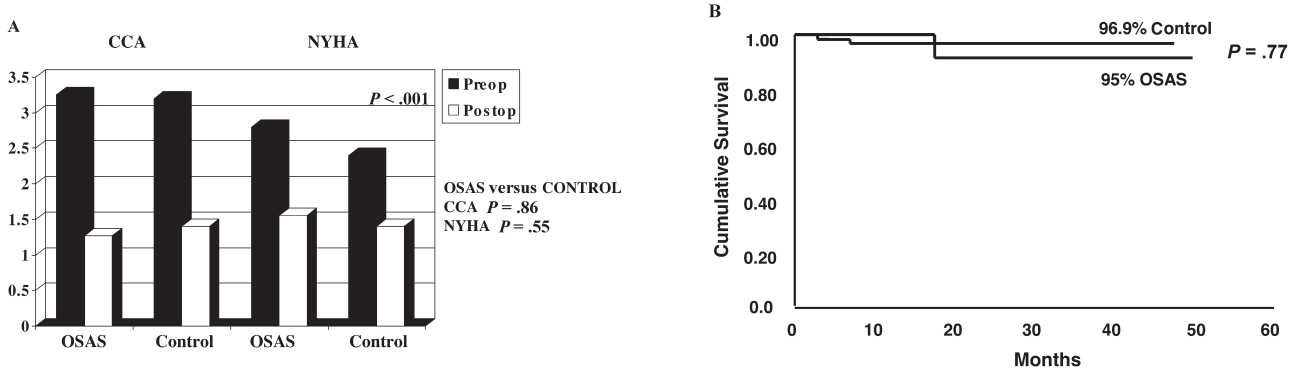
for the groups are compared in Table 4. Patients in the study group had a significantly longer intensive care unit (ICU) course (9 days versus 3 days, $P = .002$) and hospital length of stay (24 days versus 12 days, $P = .003$). Postoperative morbidity was similar in the groups with the exception of significantly greater pulmonary morbidity in the study group. Both prolonged ventilator dependence (8 patients versus 0 patients, $P < .001$) and need for tracheostomy (2 patients versus 0 patients, $P = .01$) was more likely among patients in the study group. There was no operative mortality in either group.

Angina (Canadian Class angina [CCA]) and heart failure (New York Heart Association [NYHA]) functional class improvement for the study and control groups are shown in Figure 1A. Both groups experienced significant postoperative improvement in CCA and NYHA classification with no significant difference between the study and control groups. Kaplan-Meier survival data for these patients are shown in Figure 1B. Survival at a mean follow-up of 59 months was 95% and 97% for the study and control groups, respectively ($P = .77$).

DISCUSSION

Coincident with the epidemic of obesity in this nation, there is a growing awareness of OSAS as a significant, and potentially treatable, risk factor for cardiovascular disease [Littner 2002]. It is estimated that 1 in 5 adults has at least mild OSAS and 1 in 15 suffer from moderate OSAS [Young 2002]. There is a clear association with OSAS and obesity [Kopelman 1992], both of which often co-exist with established cardiac and vascular diseases such as hypertension, heart failure, arrhythmia, and stroke [Shamsuzzaman 2003]. OSAS is found in 25% to 50% of patients with IHD. Although a causal relationship between OSAS and the development of IHD has been suggested, this remains unproven and continues to be the focus of further investigation. Several studies, however, have shown a higher incidence of OSAS in patients with IHD than those without known heart disease and identified clinically important associations between disordered breathing, myocardial ischemia, and cardiac events in patients with known coronary disease [Hung 1990; Mooe 1996a; Mooe 1996b]. Several mechanisms have been cited as contributing to this heightened risk including sympathetic activation, endothelial dysfunction, vascular oxidative stress, and prothrombotic and athrogenic effects [Shamsuzzaman 2003]. Despite the growing evidence to suggest that OSAS negatively impacts cardiac function especially in patients with IHD, there have been no studies to date evaluating the impact of OSAS on outcomes after coronary revascularization in these patients. The present study was undertaken to evaluate how the presence of OSAS in patients with IHD affects the efficacy, safety, and durability of coronary artery revascularization.

To evaluate the cardiovascular physiologic baseline for these patients we compared data obtained from right and left heart catheterization between the control and study groups. Patients with OSAS had significantly higher indices of both right and left heart dysfunction (pulmonary artery pressure, pulmonary capillary wedge pressure, and left ventricular end-diastolic pressure) compared to patients in the control group. Several studies have documented a higher incidence of pulmonary hypertension in patients with OSAS, but this was often attributed to a high incidence of co-existing chronic lung disease [Bradley 1985; Weitzenblum 1988]. Independent studies by Bady and Sanner have also documented pulmonary



A, Angina and functional class for patients having surgical revascularization. B, Kaplan-Meier survival for patients after surgical revascularization. OSAS indicates obstructive sleep apnea syndrome; CCA, Canadian Class angina; NYHA, New York Heart Association.

hypertension in patients with OSAS without co-existing chronic lung disease, which they attribute to chronic hypoxic vasoconstriction, heightened sympathetic tone, and obesity [Sanner 1997; Bady 2000]. Although the patients with OSAS in the present study did have a higher incidence of chronic obstructive pulmonary disease (COPD) (45% versus 28%), which may contribute to the elevated pulmonary pressures, this difference was not statistically significant. Interestingly, patients with OSAS were significantly heavier than those in the control group by an average of 24 pounds. While the etiology of elevated pulmonary artery pressure in patients with OSAS is the subject of further investigation, it is becoming more evident that the cumulative effects of heightened sympathetic tone, hypoxic pulmonary vasoconstriction, obesity, and chronic lung disease contribute to its pathogenesis and the subsequent development of chronic right ventricular failure.

OSAS has been increasingly implicated in the progression and exacerbation of cardiovascular disease, and therefore its impact on the efficacy and durability of revascularization is of significant concern. Several potential mechanisms have been postulated to explain the link between OSAS and chronic cardiovascular disease. Elevated sympathetic tone in patients with OSAS has been linked to tachycardia, increased heart rate variability, and hypertension, all of which contribute to elevations in myocardial oxygen consumption [Narkiewicz 1998; Peled 1999]. The hypoxia, hypercapnia, and pressor surges associated with OSAS are thought to serve as stimuli for endothelin release and subsequent vascular endothelial dysfunction [Phillips 1999]. A similar mechanism is seen in patients with hypertension, hyperlipidemia, or diabetes, and in patients who smoke [Shamsuzzaman 2003]. Hypoxic stimulation of cytokine (interleukin 6, tumor necrosis factor-α) and c-reactive protein production contributes to vascular disease and dysfunction by inhibiting nitric oxide synthase and increasing expression of cell adhesion molecules [Venugopal 2002; Woolard 2002; Shamsuzzaman 2003]. These same factors would be expected to impact the long-term efficacy of revascularization in this group of patients. Interestingly, in the present study, OSAS did not negatively impact the improvement in angina and heart failure symptoms after revascularization, as measured by CCA and NYHA classification. Furthermore, long-term survival was not impacted by the presence of OSAS (Figure 1B). There have been no previous studies investigating surgical outcome from revascularization in patients with OSAS to which these findings may be compared.

The presence of OSAS did have a marked impact on pulmonary morbidity as well as ICU and hospital lengths of stay after surgical revascularization. With a higher incidence of prolonged mechanical ventilation (40% versus 0%) and need for tracheostomy (20% versus 0%), patients with OSAS suffered greater pulmonary morbidity compared to their counterparts without OSAS. Several factors may have contributed to this difference in addition to the presence of OSAS. Patients with OSAS were heavier by an average of 24 pounds and had a higher incidence of co-existing COPD. Although the latter difference did not reach statistical significance, both factors are known to contribute to pulmonary morbidity after surgical revascularization for IHD. Although patients with OSAS did experience significantly higher pulmonary morbidity compared to controls, this did not negatively impact either functional outcome or survival. Additionally, the rates of pulmonary complications seen in this group of patients is similar to that found in other groups of patients with significant comorbidities such as advanced age, severely compromised pulmonary function, and heart failure.

Patients with OSAS and IHD pose a unique challenge to physicians involved in their management from both the surgical and the medical standpoint. Additional comorbidities such as advanced age, diabetes, obesity, COPD, renal insufficiency, and heart failure may co-exist with IHD in the patient with OSAS. Special emphasis must be placed on the medical management of these comorbidities with a multidisciplinary approach designed to optimize organ function. Patients with OSAS require special attention to optimize preoperative pulmonary function and to the treatment of their OSAS. Management of the right ventricular dysfunction often seen in patients with OSAS is paramount to successful peri-operative care. Our approach to the medical management of these patients has included aggressive preoperative diuresis, medical optimization of ventricular function, and administration of CPAP to improve right ventricular hemodynamics and prevent right ventricular failure in the peri-operative setting. Use of CPAP has been shown to reduce systolic and possibly pulmonary artery pressure, reduce frequency of nocturnal myocardial ischemia and angina, improve left ventricular function, and improve neurobehavioral outcomes (sleepiness, alertness, cognitive function, and quality of life) [Leung 2001; Kaneko 2003; Wolk 2003]. Additional routine measures such as nebulized bronchodilator therapy, incentive spirometry, nasotracheal suctioning, early ambulation, and chest physical therapy are paramount to achieving optimal outcomes.

Our surgical approach to the management of patients with OSAS has focused on providing durable conduits of revascularization while minimizing systemic inflammatory responses and volume overload to minimize right ventricular dysfunction. Routine use of hemofiltration during cardiopulmonary bypass minimizes volume overload and need for aggressive diuresis in the postoperative period, protecting the right ventricle from its deleterious effects. Hemofiltration also removes potentially harmful circulating cytokines released during cardiopulmonary bypass that may augment the systemic inflammatory response and capillary leak syndrome seen after moderate to long periods of extracorporeal support. Selective utilization of OPCABG techniques further allows for revascularization with minimal derangement of systemic inflammatory responses and endothelial dysfunction associated with the use of cardiopulmonary bypass. OPCABG has been increasingly applied and has become our procedure of choice for revascularization in this patient population.

Our results in this group of patients suggest that despite a heightened risk for peri-operative pulmonary morbidity, patients may achieve excellent early to mid-term control of angina and improvement in functional status without significantly higher mortality. Strategies to control known risk factors such as pulmonary hypertension coupled with aggressive treatment of OSAS during the peri-operative period may help

limit pulmonary morbidity and contribute to improved myocardial performance and subsequently long term survival. A flexible surgical approach utilizing OPCABG techniques may further help to limit morbidity during the peri-operative period by blunting the inflammatory responses associated with cardiopulmonary bypass. Further studies will be required both to elucidate the pathophysiological mechanisms underlying the role of OSAS in myocardial dysfunction and to further characterize risk factors impacting clinical outcomes following coronary revascularization in this group of patients.

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