Implications of obesity in cardiac surgery: pattern of referral, physiopathology, complications, prognosis

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Abstract: A U-shaped relationship between body mass index (BMI) and outcomes emerged after cardiac surgery. This review analyses the physio pathologic basis of obesity related complications and evaluates prognostic implications. Both leaner and morbid obese should be considered pre-operatively rather than reactively and, when referred for elective surgery, should undergo a focused metabolic status management, and a thorough evaluation of health status. Adherence to sound surgical principles, and tailored patient blood management and perioperative care are mandatory.

Keywords: Body mass index (BMI); obesity; cardiac surgery; mortality; complications

Introduction

Although obesity is a major risk factor for cardiovascular disease and cancer, its prevalence is dramatically increasing in developed countries. Referrals for cardiac surgery of these patients have consistently increased underscoring the need to optimize strategies to provide quality and efficient care.

Pattern of referral

At first glance, the prevalence of obesity among the population presenting for cardiac surgery seem to mirror that reported in the general adult population; with a steep increase in the last decade in most of the industrialised countries. Nevertheless, to a closer examination, at least three biases are evident. There is a lead-time bias, since patients with high body mass index (BMI) tend to be treated sooner. A referral bias also emerged since most of the obese are younger in age, with very few coexisting co-morbidities. Finally, a treatment allocation bias has been described, since extremely obese are seldom considered surgical candidates,

and, when referred, the majority undergoes isolated surgical myocardial revascularization while combined or complex procedures are under prescribed (1-3).

Evidence, lack of evidence and source for confounders

Despite lots of studies have assessed the effect of BMI on clinical outcomes, several sources of cofounders long prevented definitive conclusions. Different BMI cut-offs to define obesity, grouping patients in classes with widely varying BMIs (obese versus non-obese), analysing BMI as a continuous variable are some of the most serious limitations of available data. More, retrospective study design, small sample sizes, case series including patients undergoing both myocardial revascularization and valvular procedures (in whom obesity may alternatively play as an aetiological factor or as a physiological adjunct), limited length of follow-up, lack of data on potentially confounding factors, further jeopardized the clarity of this issue. Nevertheless, several observational data have shown a clear,

counterintuitive, obesity survival advantage in the cardiac surgical population. Indeed, lower operative mortality and better early and mid-term survival have been consistently reported in the overweight and moderately obese. A reverse J- or U-shaped relationship between BMI and outcomes has been repeatedly described (1,2).

The obesity paradox: explanation and clinical implications

The explanation of this obesity paradox or reverse epidemiology, already described in many acute and chronic disease states, points well beyond statistical correlation and bear biological plausibility (1). Age, concomitant medical treatment, body composition, muscle mass and strength, cardiorespiratory fitness, nutritional status, altered systemic vascular resistance and plasma renin activity, different patterns of coronary anatomy and calcification, along with peculiar inflammatory and hormonal milieus, are known potential underlying mechanisms. The clinical bottom line is complex (4,5). Underweight is a surrogate of severe underlying illness. A feature that is poorly described or, even, underreported in surgical and administrative datasets. At the same time, low BMI is marker of a lower tolerance for surgical stress. Careful evaluation of these patients is mandatory for outcomes improvements. On the other side, the potential for better outcomes in those overweight or moderately obese should be soberly analysed. Apart from the peculiar patterns of surgical referral described above, the aetiological role of obesity in the illness that ultimately lead to the cardiac surgery procedure cannot be forgotten (6). Besides, the few available long-term survival analyses clearly demonstrate that, beyond early surgical course, the progression of cardiometabolic disease make this obesity paradox disappear. Indeed, Gurm and co-workers analysed 1,526 patients undergoing coronary artery bypass grafting (CABG) who were evaluated by taking their BMI at study entry from the randomized series and observational registry of the Bypass Angioplasty Revascularization Investigation (BARI). Despite no difference in the in-hospital outcome was observed according to BMI, each unit increase in BMI was associated with an 11% higher adjusted risk of 5-year cardiac mortality (7).

Postoperative complications in the obese patient

Obesity significantly affects all aspects of healthcare including perioperative care. Indeed, obese individuals appear to be at a higher risk for perioperative complications concerning all organ systems. However, it can be difficult to determine whether this condition is a risk factor or a marker of risk. The peculiarities of the cardiac surgical setting further increase this uncertainty. Cardiopulmonary bypass (CPB) is associated with the activation of different coagulation, proinflammatory, survival cascades and altered redox state. Haemolysis, ischaemia/reperfusion injury and neutrophils activation during CPB play a pivotal role in oxidative stress and the associated activation of proinflammatory and proapoptotic signalling pathways which can affect end-organ function and recovery. Ore, well beyond tissue injury and extracorporeal circulation, profound perioperative metabolic changes are exerted by the systemic inflammatory response, perioperative hypothermia, cardiovascular and neuroendocrine responses, along with drugs and blood products used to maintain cardiovascular function and anaesthesia (8,9). The following paragraph summarises the available evidences linking the physio-pathological derangements of this surgical approach to those induce by obesity and their synergistic effect on perioperative adverse events.

Postoperative pulmonary dysfunction affects virtually every treated patient. Both anomalies in gas exchange and lung mechanics contributes to the expressiveness of postoperative respiratory dysfunction, which is clinically evidenced by increased work of breathing and respiratory rate, shallow respirations, ineffective cough, hypoxemia and changes in chest radiographs. Widening of the alveolar-arterial oxygen gradient, increased lung microvascular permeability along with increased pulmonary vascular resistance and shunt fraction are commonly observed after cardiac surgical procedures. Accordingly, reductions in vital capacity, functional residual capacity and static as well as dynamic lung compliance are usually evident. Pathogenesis of these derangements stems from a complex interplay between patient's baseline end organ function, type, extent and urgency of underlying cardiovascular pathology and the distinct features of this surgical setting. This operative approach, indeed, encompasses general anaesthesia, peculiar surgical trauma (median sternotomy, pleural dissection), CPB, topical cooling for myocardial protection (which may cause phrenic nerve dysfunction), transfusion of blood products and postoperative pain, which, individually, and synergistically affect respiratory performance. Acute respiratory distress syndrome, transfusion-related lung injury and ventilation associated pneumonia, though infrequent are the most dreaded of these complications because of inherent dismal outcomes (10). The link

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between obesity and postoperative respiratory dysfunction is multifactorial with a complex interplay between baseline pulmonary function and operative features. On one side, obesity implies several well-known physiological airway and respiratory changes, which have been thoroughly described. Lung volume, oxygen consumption and carbon dioxide production, gas exchange, lung compliance and resistance as well as respiratory efficiency and work of breathing are indeed all and synergistically affected by obesity with a clear exponential pattern with increasing BMI (11). The well-recognized harmful effects of anaesthesia add significantly to these derangements. Guidelines for perioperative care of the obese have been repeatedly updated to optimize respiratory management algorithms even though the ideal ventilation strategy, besides recruitment manoeuvres added to positive end expiratory pressure (PEEP), remains obscure (12). On mere clinical ground, the risk of postoperative hypoxia (as reflected by a low PaO_2/FIO_2) almost doubles for each increase in BMI class. Nevertheless, only the morbidly obese, a fairy small proportion of cardiac surgery recipients, experience an increased risk of prolonged ventilation, re-intubation, pulmonary infections, intensive care recidivism and prolonged process of care (13).

Issues concerning transfusional need and perioperative bleeding may play a protective effect in this subset of patients. Indeed, a growing body of evidence has disclosed that obesity is a predictor for protection against blood loss and transfusion in patients undergoing myocardial revascularization (14). Similar evidence derived from valvular and combined surgery (4). Obese patients require significantly lower rates of re-exploration for bleeding and allogenic blood products transfusions, which are, in turn, major determinants of lung impairment (13,15). Data from a multi-institutional perfusion database demonstrated, that a BMI in obese I category was associated with a 9.9% decrease in transfusion risk (P<0.05). Overweight and mild obesity have a protective role in reducing intraoperative blood transfusion during CPB surgery. Indeed, given the increased total blood volume and higher body surface area, these patients are less prone to the hemodilution caused by the priming volume of the CPB; this reduces the hemodilution-related extravascular lung water accumulation and blunts CPB-related coagulopathy (16). The abundant mediastinal fat and the compression of minor bleeding sites by the higher intrathoracic pressure secondary to mass loading further reduce bleeding risk (4).

The incidence of cardiac surgery associated acute kidney injury (CSA-AKI) ranges from 7.7% to 28.1% according

to the different definition criteria, with 1.4% to 3% of the patients ultimately in need for renal replacement therapy. It is a major determinant of early and late postoperative morbidity and mortality and implies a steep increase in the length of hospitalization and overall cost. Exogenous and endogenous toxins, metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation and oxidative stress: though acting at different times and with different intensity synergistically induce renal perioperative damage (17). Several studies have disclosed a significant association between obesity and CSA-AKI following both CABG and valvular surgery (18). At least three different pathways may explain such an association. An underlying, specific, glomerulopathy which is known to affect the obese and induce chronic renal disease. The distinctive hypertrophy and adaptive focal segmental glomerulosclerosis, found at pathology in this disease, are strictly linked to the obesity-induced increases in glomerular filtration rate, renal plasma flow, filtration fraction and tubular sodium reabsorption. Altered fatty acid and cholesterol metabolism are the key mediators of renal lipid accumulation, inflammation, oxidative stress and fibrosis, which synergistically induce maladaptive responses to the mechanical stress of renal hyperfiltration (19). Another well-defined link between CSA-AKI and obesity is the higher prevalence of the metabolic syndrome and diabetes in these patients 'subset. Data on patients undergoing CABG, operated either on-pump and off-pump, strongly support this notion (20,21). Finally, obesity-related response to intraoperative oxidative stress are clearly emerging as a direct causative pathway. Recently, Billings and co-workers explored the relationship between BMI and AKI in 445 patients undergoing on-pump cardiac surgery (CABG, valvular and combined) and whether oxidative stress contribute to any identified relationship. These authors found that BMI was an independent risk factor for AKI and that the association between obesity and AKI is partially mediated by BMI's effect on oxidative stress (22).

Conventional wisdom suggests that obesity is associated with higher postoperative infectious complications prolonged ICU stay and exponential resource utilization (2,13). Superficial and deep sternal as well as harvest site wound infections are known to plague the postoperative course of this patients' subset (23). Several technical challenges, such as poor operative exposure of the heart, greater operating depth within the chest, poor artery and venous grafts exposure during harvesting imply longer operative times, extended surgical sites exposure and

enhanced potential for contamination. Poor healing of under perfused adipose chest wall tissue, reduced response to antibiotic prophylaxis and poor glycaemic control are other contributing factors. Enhanced surgical skill and meticulous operative conduct along with the development of preventative strategies have been consistently advocated (24). In the setting of myocardial revascularization, a long-standing debate concerned the clinical implication of bilateral internal mammary artery usage. It is well-known that a second arterial graft improves long term survival but it implies a significantly higher rate of deep sternal wound infections in the early post-operative setting (25). In the vulnerable obese population conflicting results have been forwarded but the consensus is that diabetic female patients might be best treated by more conventional grafting through a single mammary artery graft plus saphenous veins (26-28). Similarly, higher rates of ICU acquired urinary tract, pulmonary, catheter and blood-stream infections have been reported in the highest BMI classes with a net increase in the incidence of sepsis. Intriguingly despite this higher vulnerability, reported overall mortality rates as well as the death rates for septic shock are inferior (2,13,24). The preserved or increased lean body mass and better nutritional status related to higher BMI imply a sufficient nutritional reserve, a more efficient metabolic state and a better inflammatory and immune response to surgery, which account for this protective effect once obesity-induced infectious complication may develop.

Despite differences in patient population, pre-existing comorbidities, surgical procedures and strategy prevent an exact definition of incidence rates; atrial fibrillation (AF) is, by far, the most common arrhythmia after cardiac surgery. Postoperative AF is associated with a significant lengthening of the process of care and an excess in resource utilization, it also enhances the rates of rehospitalisation and, ultimately, jeopardises outcomes. Indeed, through a reduction in atrial pooling and ventricular filling, it predisposes to hypotension, intracardiac thrombus formation, pulmonary oedema and pacemaker placement (27). A recent authoritative systematic review and meta-analysis found that obesity was associated with a nominally statistically significant, slightly higher risk of postoperative AF, which, in turn was associated with substantially higher risk of the major postoperative complications (stroke, respiratory failure) and operative mortality after all types of cardiac surgical procedures (28). A growing body of knowledge has disclosed obstructive sleep apnea (OSA) as the link between postoperative AF and obesity (29).

OSA is a prevalent condition in this subset of patients, which exerts well-known acute and chronic effects on the cardiovascular system, among which there are arrhythmias. Both epidemiological and clinical cohorts disclosed a strong association between OSA and AF, which, well beyond mere correlation, seems to point toward direct causation. The physiopathologic link between AF and OSA is still under investigation, never the less both structural and functional effects are implied. Repetitive pharyngeal collapse during sleep, leading to hypoxemia, hypercapnia, and persistent inspiratory efforts against an occluded airway until arousal characterise OSA clinical manifestation (28,29). The large negative swings in intrathoracic pressure, which affect left atrial remodelling, and the increases in both cardiac sympathetic and parasympathetic activity, which provoke large surges in blood pressure and alteration of atrial electrical properties, together with inflammation appear the major pathways in AF genesis (28,29).

Table 1 summarises the above reported effects of BMI on outcomes in cardiac surgery setting. In particular the interaction between obesity induced physiologic derangements, cardiac surgical procedure and early complications are detailed.

Resource utilization

Cardiac surgery procedures are major contributors to medical resource utilization. Several studies have tried to identify risk factors for increased early complications and extended length of stay to enhance quality and provide more cost-efficient pattern of care. The impact of BMI has been consistently analysed (2,9). These studies have disclosed that morbid obese patients are usually denied cardiac surgery candidacy and managed medically or by percutaneous approaches. When referred for surgery, they experience longer surgical time, as well as increased length of intensive care unit and overall hospital stay mainly due to infectious complications. Intriguingly, management of underweight patients implied similar resource utilization. These studies showed also that surgical risk scoring systems such as the EuroSCORE have no statistical correlation with BMI and are poor predictors of the length of the process of care (2,4). Such evidences prompted the concept that both underweight and morbid obese should be considered pre-operatively rather than reactively and, when referred for elective surgery, should undergo a focused metabolic status management, and a thorough evaluation of health status (13,23).

Table 1 Interaction between obesity physiologic derangements and cardiac surgical procedure on early complications (for each target organ are reported the alterations induced by obesity, the burden of the surgical procedure, and the clinical outcome)

Target organ/system	Obesity induced physiologic changes	Cardiac surgery induced physiologic changes	Interaction and net clinical effect	References
Lung	< Lung volume > Oxygen consumption and > carbon dioxide Production < Gas exchange < Lung compliance and > resistance < Respiratory efficiency and > work of breathing	Atelectasis Increase in parenchymal lung water Damage to the lung architecture and function by inflammatory molecules and micro emboli	Interstitial pulmonary oedema and abnormal gas exchange Increased risk of prolonged ventilation, re-intubation, pulmonary infections in high BMI classes	(9-12)
Kidney	> Diabetes and metabolic syndrome Specific glomerulopathy	Impaired kidney function by: exogenous and endogenous toxins, metabolic factors, ischemia and reperfusion, neurohormonal activation, inflammation and oxidative stress	> Rates of acute kidney injury	(17-22)
Coagulation cascade	> BSA > Circulating blood volume > Mediastinal fat > Intrathoracic pressure secondary to mass loading	Hemodilution due to CPB priming CPB coagulopathy Hemolysis	Reduced blood transfusion Reduced need for surgical revision Reduced extravascular lung water accumulation	(14-16)
Heart	Indirect damage by metabolic derangements Obstructive sleep apnea induced cardiac chambers damage	Ischemia/reperfusion injury Myocardial oedema	Higher rates of atrial fibrillation	(27-29)
Nutritional status	> Lean mass > Muscle mass and strength > Fat mass >/< Cardiovascular fitness Hostile surgical setting Under perfused adipose chest wall tissue, reduced response to antibiotic prophylaxis poor glycaemic control > Nutritional reserve; ≥ immune response	Systemic inflammatory response > Metabolic stress due to tissue injury, cardiopulmonary bypass, perioperative hypothermia, cardiovascular and neuroendocrine responses, along with drugs and blood products	> ICU acquired urinary tract, pulmonary, catheter and blood-stream infections > Incidence of sepsis < Death by septic shock	(23-26)

CPB, cardiopulmonary bypass; BMI, body mass index.

Obesity in the heart transplant recipient: from candidacy to long-term survival

Heart failure patients are an increasingly common demographic in cardiac surgical theatres. Despite enormous advancement in mechanical circulatory support, heart transplant is still the golden standard in the management of the end-stage disease. Recent studies have pointed out the role of nutritional issues in patients evaluated for heart transplant listing (30). Extremes in body habitus, cachexia and obesity, have been characterized and identified as independent prognostic factors and clinically relevant target for therapeutic interventions. Once on the elective waiting list, overweight and obese patients usually wait twice as long and are up to 46% less likely to receive a donor graft than patients of normal weight are (31). A similar pattern is also evident in those listed for urgent transplantation even independently of mechanical circulatory bridging status. As to mortality on the waiting list, highest rates were found in patients with normal or lower than normal weight as compared to overweight, obese or extremely obese (32). However, the effects of extremes of BMI exert prognostic implications well beyond waiting time up to early and late post-transplant survival. Studies examining the effects of BMI on posttransplant morbidity and mortality in solid organ transplantations disclosed a clear U-shaped relationship with recipients at the extremes experiencing the worst outcomes. This diminished survival in the leaner group resulted from excess morbidity in the first-year post-transplantation. Such recipients had an increased risk of infection during the transplant hospitalisation. However, with correction of their heart failure and subsequent reversal of their cachectic state, their risk of death, along with the mean BMI, normalized after the initial posttransplant period and such sample did not experience and elevated risk of any long-term complication of transplantation or posttransplant cardiovascular comorbidity (33). Diminished survival in moderate to severe obesity resulted instead from long-term events due to the cardiometabolic effects of the comorbidities associated with obesity, the development of new onset diabetes mellitus and worsening of metabolic syndrome under life-long immunosuppressive regimen (34). Implications for tailoring of immunosuppressive therapy and dietary prescription emerged as main stem of long-term recipient management (30,35).

Conclusions and key major recommendations

(I)   A U-shaped relationship between BMI and outcomes has been consistently described in overall cardiac surgery population including patients undergoing CABG, valve procedures and heart transplantation. The so-called obesity paradox should be carefully interpreted in the light of long-term outcomes and possible confounders.

(II)   A careful heart team evaluation of the individual patient, especially in the extreme BMI classes, is strongly advocated. Both leaner and morbid obese should be considered pre-operatively rather than reactively and, when referred for elective surgery, should undergo a focused metabolic status management, and a thorough evaluation of health status. This evaluation is maximally advocated in heart transplant candidates given the current paucity of donor organs.

(III)   Obesity presents technical challenges to the cardiac surgeon and adherence to sound surgical principles is mandatory. In the setting of myocardial revascularization tailored choice of conduits and harvesting technique is crucial to avoid in hospital morbidity and mortality.

(IV)   Patient blood management of underweight cardiac surgery recipients is a key perioperative step due to their enhanced vulnerability to CPB induced coagulopathy and hemodilution (9).

(V)   Pathophysiology of altered tolerance to perioperative stress remain largely undetermined and should be the aim of future research. Well-validated comorbidity and frailty indexes along with nutritional status scoring systems should be incorporated in surgical database (8,36).

(VI)   Interventions to modify the risks of adverse outcomes should be evaluated by randomized, controlled trials.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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