Original Paper

Obesity-Related Cardiorenal Syndrome

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The term obesity cardiomyopathy *has previously been used to describe a clinical syndrome in obese patients typically consisting of eccentric left ventricular hypertrophy with preserved ejection fraction and diastolic dysfunction and is often associated with right ventricular dysfunction independent of the presence of the obstructive sleep apnea syndrome. Although several publications have described the early stages of this syndrome, little is known about the end stages of the disease. The authors conducted a retrospective study of a subset of edematous obese patients with multiple common medical comorbidities who present with a clinical syndrome in the setting of physiologic stress or infection. Under severe physiologic stress these patients developed pulmonary hypertension, right-sided volume overload, decreased effective arterial blood volume, and renal failure. Often, these findings were in the setting of obstructive sleep apnea. This retrospective study focuses on an obesity-related cardiorenal syndrome but also serves to provide a foreground for acknowledging the broad spectrum of cardiovascular pathology, including pulmonary hypertension, diastolic dysfunction, and sleep apnea, seen in the obese.*
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A recent publication discussed the issue of "decreased effective arterial blood volume" in patients with edematous disorders.[1] In clinical states, including septic shock and arterial vasodilation due to other physiologic stressors, Schrier proposed that the arterial circulation undergoes an acute on-chronic underfilling. Obesity is a common factor in many such patients. Further literature supports obesity-related cardiac dysfunction with normal ejection fraction (EF) in otherwise healthy patients.[2–4] Several large retrospective trials of obese but otherwise healthy young women, including a study by Peterson and colleagues,[2] demonstrated that body mass index (BMI) was the only independent predictor of early diastolic dysfunction with eccentric left ventricular (LV) remodeling.

We have observed a subset of hospitalized patients with morbid obesity, pulmonary hypertension, and right-sided volume overload with edema that go on to develop renal failure in the absence of LV systolic dysfunction. We observed high rates of in-hospital mortality, as they lacked the reserve to respond to stressors such as sepsis, hypovolemia, and surgery. In retrospect, these patients likely had obesity-related cardiorenal dysfunction with pulmonary hypertension, right-sided volume overload, and reduction in effective arterial volume with resulting renal hypoperfusion. In the setting of such stressors, acute on-chronic arterial hypoperfusion, oliguric renal insufficiency, and massive right-sided volume overload occur.

Increased right-sided overload with arterial hypoperfusion in this population presents a difficult clinical management issue when it arises. There are

Table I. Patient Characteristic by Chart Review

Medical History	No. (N=10)
Diabetes mellitus	7
Obesity	9
Coronary artery disease	5
Congestive heart failure	2
Obstructive sleep apnea	4
Hypertension	8
Atrial fibrillation	4
History of valvular heart disease/valve replacement	1
Documented chronic kidney disease	7
Patients deceased at time of data collection	5

many yet-to-be-described issues for this clinical scenario. What are the implications of the renin-angiotensin-aldosterone system in regards to renal sodium and water retention? What is the role of diastolic dysfunction? What diagnostic and therapeutic measures can be undertaken to prevent and treat this problem? What role does undiagnosed obstructive sleep apnea (OSA) play?

Unfortunately, the therapeutic options for these patients are quite limited. Based on our clinical experience, in difficult clinical scenarios such as sepsis or physiologic stress, these patients are often symptomatic as a result of their right-sided volume overload, whether due to lower extremity edema, bowel wall edema, ascites, or complications such as lower extremity cellulitis, venous insufficiency, or skin breakdown. Initial diuretic therapy may or may not be effective in decreasing right-sided fluid volume, but often leads to a further decrease in effective arterial volume and subsequent worsening of renal function. Angiotensin-converting enzyme inhibitors (ACEs) or angiotensin II receptor blockers (ARBs) can be used for more effective blood pressure control and left-sided afterload reduction, but may worsen renal function, as glomerular afterload and filtration pressure are further reduced by ACE inhibitors and ARBs. Dialysis is often required for azotemia and volume overload, typically after diuretic therapy fails.

METHODS

We conducted a retrospective chart review of hospitalized patients with acute oliguric kidney failure characterized by underperfusion as indicated by urinary indices (sodium, creatinine), preserved LV systolic function, and evidence of right-sided volume excess identified on the nephrology consulting service. The patients were required to be admitted to the hospital with an acute illness and to have acute kidney failure, defined per RIFLE criteria (risk, injury, and failure, sustained loss, and end-stage kidney disease), as tripled serum creatinine, glomerular filtration rate decrease by 75%, or serum creatinine $\geq$4.0 mg/dL with urinary output $<$0.3 mL/kg/h for 24 hours or anuria for 12 hours.[5] Targeted data include serum urea nitrogen and creatinine, urine sodium and creatinine, systolic pulmonary artery pressure (SPAP) derived from echocardiographic data, LVEF, body weight or BMI, and pertinent medical history. All patients had to have an echocardiogram performed during hospitalization. Inclusion criteria were age 18 years or older with documented pulmonary hypertension and documented acute decline in renal function in the setting of normal LV systolic function. No restrictions were placed on sex or racial or ethnic background. Patients with LVEF $<$40% were excluded. Patients with primary/idiopathic pulmonary hypertension, connective tissue disease, or sarcoidosis known to cause pulmonary hypertension were excluded.

RESULTS

Sixteen patient charts were referred for review; 6 patients were excluded due to not having all the required target data or not meeting inclusion criteria. The remaining 10 met all inclusion criteria and had the required target data. The characteristics of the patients' medical history as specified in medical records (physician documentation or coding lists) are listed in Table I. None of the patients had previously diagnosed primary idiopathic pulmonary hypertension, sarcoidosis, or connective tissue disease known to cause pulmonary hypertension. All patients originally presented with or developed acute renal failure as an inpatient between the time frame of 2004 and 2007. Table II lists the data points of age, LVEF, SPAP, urine sodium, BMI/weight, and fractional excretion of sodium. Patients had elevated pulmonary artery pressures as estimated by echocardiography. Table III presents a summary of patient data. Eight of 10 patients were obese based on BMI $>$30 kg/m^2; one patient was known to be obese, but a measurement of height was unavailable to calculate BMI. One patient did not meet BMI obesity criteria, although the BMI was calculated to be 29.2 kg/m^2, within the overweight range. Nine of 10 patients had a calculated fractional excretion of sodium $<$1% in the setting of acute renal failure. Seven of 10 patients had urine sodium measured to be $<$20. Of those patients with urine sodium $>$20, 2 of 3 had a fractional excretion of sodium $<$1%. The patient

Table II. Patient Data

Patient No.: Admitting Diagnosis	Age, y	LVEF, %	SPAP, mm Hg	BUN/ Creatinine, mg/dL	Baseline Renal Function	U-Na, mg/dL	BMI or Weight	FENa, % (Diuretics, Yes/No)
1: Endocarditis	64	60	50–75	80/4.2	48/2.0	16	30.4	0.68 (Yes)
2: Syncope	75	60	50–55	126/3.1	51/1.8	11	40.3	0.39 (Yes)
3: Back pain	51	50–55	55	145/7.2	38/1.6	22	49.1	0.59 (No)
4: Sepsis	62	65	52	86/4.8	14/1.7	<5	44.6	0.04 (No)
5: LE edema	32	50	64	90/6.5	41/1.8	15	>50	0.12 (Yes)
6: LE edema	75	50	80	83/4.4	18/1.1	38	47.9	1.22 (Yes)
7: AKD	60	55	50–55	74/4.9	72/1.9	15	136 kg	0.39 (No)
8: PNA, congestive heart failure	62	55	60	34/1.8	30/0.8	54	37.9	0.55 (Yes)
9: AKD	66	50	46	108/5.1	NA	15	29.2	0.57 (Yes)
10: Postoperative hysterectomy	79	65	>55	67/3.1	31/1.5	17	45.3	0.34 (Yes)

Abbreviations: AKD, acute kidney disease; BMI, body mass index; BUN, serum urea nitrogen; FENa, fractional excretion of sodium; LE, lower extremity; PNA, pneumonia; LVEF, left ventricular ejection fraction; NA, not applicable; SPAP, systolic pulmonary artery pressure; U-Na, urine sodium.

with a fractional excretion of >1% who was not previously known to have kidney disease was included because the clinical scenario was consistent and exclusion criteria were not met. This patient and 7 of 10 of the patients in the study were treated with diuretics, either prior to admission or during their acute illness. All patients had LVEF >50% as measured by transthoracic echocardiography. The precipitating presenting illnesses were dyspnea, symptomatic edema, heart failure, acute renal failure, or suspected infection. At the time the data was collected, 5 of the patients were deceased. The immediate causes of death were not clearly documented in all cases but included congestive heart failure and infection/sepsis.

Table III. Summary of Patient Data

Characteristic	Value
Mean age, y	62.6
Mean (median) BMI (excludes 1 patient)[a]	41.6 (44.6)
Patients treated with diuretics during and/or preceding acute illness, %	70
Number with BMI >40	6

[a]Patient excluded for not having recorded height for body mass index (BMI) calculation.

DISCUSSION

Our study describes a cohort of obese patients with preserved EF who developed acute renal insufficiency with right-sided volume overload and pulmonary hypertension in the setting of sepsis or infection. This obesity-related cardiorenal syndrome carried a significant mortality rate of 50%. The scenario of acute kidney injury and venous overload reflects acute on-chronic decreased effective arterial volume, which is typically seen in edematous disorders such as obesity when challenged by hemodynamic stressors such as infection and sepsis.[1] Obesity alone is correlated with an array of abnormal cardiac findings, even in the setting of the preserved EF similar to our cohort. Various studies support obesity correlating with diastolic dysfunction, pulmonary hypertension, and the OSA syndrome.[2,3,6,7] Our cohort showed a high incidence of pulmonary hypertension as well as sleep apnea and, although diastolic dysfunction was not specifically studied in our composite due to transthoracic echocardiogram limitations, our cohort was at risk for this due to their obesity. Although significant research remains to be done in determining all the effects of obesity on cardiac function, findings have been made that support underlying diastolic dysfunction, pulmonary hypertension, and sleep apnea as additional comorbidities.

Obesity leads to increased tissue metabolic demands and an increase in blood volume and epicardial fat, which can infiltrate the myocardium. Over time, this likely has deleterious effects on the heart. A high-output cardiac state, with increased LV stroke work, develops and eventually leads to LV enlargement and increased ventricular wall stress. Compensatory eccentric LV hypertrophy

results, leading to diastolic dysfunction.[8] This is seen in all levels of obesity, and the severity has been directly correlated with BMI.[9] Several studies detail abnormal diastolic filling, augmented atrial contributions, prolonged diastolic relaxation times, and lower systolic and early diastolic mitral annular velocities (Sm and Em, respectively) all consistent with the diagnosis of diastolic dysfunction.[2,10,11] These same parameters of diastolic dysfunction are also found in the overweight and not-yet clinically obese.[3] A retrospective study found a striking correlation between elevated LV end-diastolic pressures in a cohort of 4000 obese patients who had previous cardiac catheterization, even when controlled for volume, indicative of diastolic dysfunction. Although not specifically included in our cohort due to limited echocardiographic data, diastolic dysfunction likely contributed to their symptomatic pulmonary edema. Further research in such a population, including detailed transthoracic echocardiography, would be needed to clarify the presence of this risk factor.

A modest number of patients in our cohort (4 of 10) were previously diagnosed with OSA, likely explaining their elevated pulmonary pressures. Given the finding of lower extremity edema and pulmonary hypertension, it was clinically suspicious that more patients had undiagnosed sleep apnea given the lack of other causes of pulmonary hypertension including idiopathic primary pulmonary hypertension, sarcoidosis, or connective tissue diseases. Studies by Blankfield and colleagues[12] demonstrated in an outpatient cohort that the clinical finding of isolated lower extremity edema coupled with elevated pulmonary artery pressures on echocardiography was associated with having OSA on polysomnography. Given our similar findings of increased edema coupled with pulmonary hypertension on echocardiography, the high number of our patients diagnosed with OSA is supportive of the findings in Blankfield's study.

OSA is an underdiagnosed entity given the epidemic of obesity and is associated with pulmonary hypertension and cor pulmonale, presumably due to increased vascular tone from hypoxic vasoconstriction, endothelial dysfunction, and vascular remodeling. Treatment with nocturnal continuous positive airway pressure (CPAP) has been shown to improve hemodynamic structural parameters and decrease pulmonary arterial pressures.[13] Arias and colleagues[14] showed that patients with OSA and diastolic dysfunction undergoing 12 weeks of nasal CPAP also resulted in improvements in diastolic function, with increased E/A ratio, decreased mitral deceleration time, and decreased isovolumetric relaxation time. Correlation exists with severe OSA, typically defined as having an apnea/hypopnea index of >40/h and worsened diastolic dysfunction evidenced by prolonged isovolumetric relaxation times.[6,7] These findings were also reversible with appropriate CPAP therapy.[15] CPAP therapy has also been associated with significant decreases in pulmonary hypertension.[13,15] Other studies suggest a correlation between right ventricular dysfunction and obesity alone, with significant changes in Em, Sm, and other strain indices of the right ventricle regardless of whether OSA is present or not.[4]

Our retrospective review reveals a subset of obese patients with right-sided edema and pulmonary hypertension and normal EF who developed renal failure in the setting of infection or sepsis. About half of the patients had OSA and, clinically, it was likely that other patients in the group had undiagnosed OSA given their morbid obesity and isolated pulmonary hypertension. As we have detailed, there is evidence for diastolic dysfunction in the otherwise healthy obese as well as a high prevalence of OSA, which results in additional cardiac dysfunction. Our cohort represents a difficult clinical scenario due to its high mortality.

Initial treatment options for obesity seem to be intuitive, although some questions remain. Weight loss is easier said than done. For the morbidly obese it is appropriate to consider evaluation for bariatric surgery as an outpatient when usual weight loss techniques fail. Sex differences have been described in regards to the pathophysiology of obesity, the metabolic syndrome, and cardiovascular disease, and further description of these differences may eventually lead to sex-specific treatments.[16] Control of hypertension is paramount to prevent the compensatory responses in the heart of LV hypertrophy and diastolic dysfunction. It may be reasonable to consider lower blood pressure goals for obese patients, similar to blood pressure goals for diabetics, of $<130/80$ mm Hg.

In this syndrome, the role of diuretics remains an important issue because they can exacerbate the prerenal state described in these patients. Diuretics are often the first choice for volume overload and symptomatic edema. However, perhaps calculation of a fractional excretion of sodium prior to administration of diuretics in azotemic patients may have a role in guiding the decision regarding their usage. The role of ACE inhibitors and ARBs remains unclear given their prominent effects on arteriolar tone. The role of pulmonary vasodilators in this syndrome is unclear, although it is possible that

decreasing the pulmonary vascular resistance in patients who are predisposed to diastolic dysfunction could lead to LV overload, worsened heart failure, and pulmonary edema.

The pulmonary hypertension in these patients may be primarily related to the pathologic changes related to the chronic hypoxia in OSA or related to diastolic dysfunction. Right-sided heart catheterization in these patients would provide 3 important data points to confirm more accurately: (1) the level of pulmonary artery pressure noted on echocardiography, (2) the measurement of pulmonary capillary wedge pressure, and (3) the measurement of pulmonary vascular resistance. Certainly an elevated wedge pressure would support the presence of diastolic heart failure; an elevated pulmonary vascular resistance would suggest the effect of chronic hypoxia associated with OSA.

Early identification of such patients during hospitalization would allow dedicated echocardiography to focus on specific measures of diastolic dysfunction (E/A ratio, mitral deceleration time, isovolumetric relaxation) and pulmonary pressures during acute illness. It would also be helpful to see whether there are any changes in these parameters after the acute illness resolves. Early identification and inpatient treatment of undiagnosed OSA with CPAP could be initiated as well.

CONCLUSIONS

In a subset of obese patients with preserved EF and acute illness, there was a trend of developing acute renal failure, right-sided volume overload, and pulmonary hypertension. Evidence supports obesity contributing to diastolic dysfunction, pulmonary hypertension, and sleep apnea. This suggests an acute exacerbation of a chronic obesity-related cardiorenal syndrome in the patients described in our study. Further research is needed to identify these patients for early intervention and goal-directed therapy of the acute syndrome, as well as primary preventive measures.

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