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EDITORIAL

Kidney Failure: Cardiorenal and Venorenal

This issue of *Advances in Chronic Kidney Disease* is guest-edited by John P. Middleton and Uptal Patel. It is a timely one and is focused on the hope that CKD and cardiovascular disease (CVD) providers can collaborate with and learn from each other. CVD is rampant among patients with CKD. Patients with heart failure, valvular disorders, and arrhythmic disorders occupy significant space in the realm of CKD. The concomitance of cardiac and kidney disease has led to the nosology of cardiorenal syndrome that conveys the kidney as victim, types 1 and 3, and perpetrator of the syndrome, types 2 and 4.[1] Needless to say, coherent and cohesive collaboration between kidney and heart physicians is an absolute necessity to optimize treatment for patients with both CKD and CVD.

Systolic cardiac failure is marked by supranormal neurohormonal activation. Tremendous elevations of catecholamines were detected by Cohn and colleagues[2] in individuals with severely depressed left ventricular (LV) ejection fractions. These elevations of catecholamines are accompanied by a highly activated renin-angiotensin-aldosterone system, which led the kidney toward untoward effects, sodium retention and increased peripheral vascular resistance that increased blood pressure and aggravated left ventricular impedance, with resultant congestion. As well, this pathophysiology is synergized by the deleterious effects of hypercatecholaminemia on cardiomyocytes. Conversely, in CKD, there is enhanced sympathoadrenal activity, which may aggravate heart failure by the same mechanisms.

Classically, individuals with left ventricular failure and forward output failure, especially when acute and severe, develop acute kidney injury. This scenario occurs in approximately 27% to 42% of cases of acute cardiac insufficiency.[1] In fact, the greater the increment in serum creatinine, the more severe the heart failure. Valvular disorders on the left side of the heart are also associated with azotemia, an ominous sign. As left ventricular function declined, the nephrologist is often consulted for enhancement of a failing diuretic regimen coinciding with a rising serum creatinine, the strategy essentially one of left ventricular unloading with restoration of the ventricle's pressure-volume relationships to a more optimal circumstance. Yet diuretic therapy is often not optimized for fear of "overdiuresis" with consequent hypotension.[3]

Nearly every hospital, medical group, or health care system (including my own) employs some sort of protocol for their heart failure patients that includes sodium restriction, medication adherence, and daily bodyweight readings.[4] But how many protocols actually optimize diuretic therapy or defer decision-making to an "expert?" Likely few. Moreover, the Joint Commission on Accreditation of Healthcare Organizations quality of care indicators for heart failure do not explicitly mandate an assessment of kidney function, only LV function.[5] The employment of combination diuretic therapy is underused, and combination treatment can often break through diuretic resistance. For example, using a high dose of thiazide-type diuretic or a loop agent with a mineralocorticoid receptor antagonist (MRA) would augment diuresis and attenuate the anticipated hyperkalemia from the latter agent.[6] Although, using an MRA in patients with depressed LV function, as delineated by the Randomized Aldactone Evaluation Study (RALES)[7] and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[8] have clearly provided an improvement in CV end points, there is often avoidance of MRAs whenever there is concomitant CKD, in part because of an apprehension of inducing hyperkalemia.[9] The latter finding was less common in blacks compared with nonblacks who participated in RALES, but nonblacks comprised 93% of participants, and 87% of participants treated with spironolactone were white.[7,10]

Presumably, hyperkalemia may be sidestepped in heart failure altogether by avoiding angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin 2 receptor blockers (ARBs), in favor of isosorbide dinitrate and hydralazine compounds. The latter, compounded as a fixed dose combination, received a race-based recommendation in heart failure patients in the African American population, the population most vulnerable to CKD. This recommendation was based on a retrospective analysis of Vasodilator Heart Failure Trial (V-HeFT) II, which demonstrated a

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superior effect on 2-year mortality of nitrate-hydralazine over enalapril/placebo in African Americans.

The results of the V-HeFT I and II studies in which blacks constituted just 27% of the participants, plus an analysis of Studies of Left Ventricular Dysfunction (SOLVD) in which blacks only constituted 12% of the participants, demonstrated that black participants fared better with a nitrate-hydralazine regimen, whereas white participants fared better with ACE inhibition. Quite notably in SOLVD, enalapril therapy in whites was associated with only a modest blood pressure reduction after 1 year, 5.0/3.6 mm Hg.[11] The results of these trials fundamentally improved the care of heart failure, but they had the unintended consequence of denying important aspects of care to heart failure patients with CKD. Essentially, black CKD patients with heart failure can be treated with ACEIs or ARBs to attenuate CKD progression and white patients with heart failure and CKD may be treated with nitrates and hydralazine, if intolerant to ACEI or ARB treatment. In addition, the Beta-Blocker Evaluation of Survival Trial (BEST) determined that black patients did not benefit from bucindolol treatment, whereas whites did.[12] Nonetheless, beta-blocker therapy in white CKD patients with heart failure is underemphasized. Lastly, the induction of hyperkalemia using ACEI/ARB therapy can be offset in most instances by dietary restriction of potassium and diuretic therapy.

In heart failure patients, the optimal blood pressure floor has not been established: "How low should you go?" The dictum has generally been to lower blood pressure as much as possible because this reduces impedance to left ventricular output—the cardiocentric view. Contrariwise, the kidneys may now reside at a subthreshold level of ischemia where any further renal insult(s) can induce an episode of acute kidney injury (AKI)—the nephrocentric view. AKI often occurs in the face of normal blood pressure,[13] particularly when there is predisposing CKD with its right-shifted, sodium-pressure sigmoidal curve.[14] A mean arterial pressure of 60 mm Hg does not necessarily equate to adequate renal perfusion in man as it does in rats whose vascular trees have not been damaged by hypercholesterolemia, smoking, or aging. Lastly, the primary care physician may note that the patient is symptomatically hypotensive—the Internal Medicine view.

Guidance here is critical and will require collaborative trials between cardiologists and nephrologists. This is especially true since the 2013 publication of the American Heart Association's blood pressure guideline[15] that has redefined the blood pressure thresholds for hypertension in diabetes and CKD. A comprehensive evaluation of high-quality observational and retrospective analyses of heart failure patients with CKD (and vice versa) must be done, and these can inform the basis of randomized, controlled studies that should be designed and implemented by a team of kidney failure and heart failure collaborator-investigator groups.

The importance of right-sided heart failure in CKD has been emphasized recently. Not all patients with CKD and heart failure manifest impaired LV ejection fractions of less than 25% to 30%. These patients typically manifest LV diastolic dysfunction with preserved LV ejection fraction and cardiac output at the expense of elevated left ventricular end-diastolic pressure. This circumstance is seen in 40% to 50% of patients with congestive failure. Consequently, the pulmonary artery wedge pressure is elevated, which is transmitted in retrograde fashion to the renal veins. This augmented renal venous pressure is central to the pathogenesis of CKD.

Irving H. Page tightly enveloped the rat kidney in cellophane to produce an encasing fibrocollagenous hull, and the concept of kidney compression as causative of AKI was born.[16,17] Since his original description, kidney failure in man from a "Page" kidney has been recounted in numerous circumstances, often with the compression by a subcapsular or perinephric hematoma. However, the importance accorded to tissue compression may have masked the true underlying pathophysiological mechanism inherent to the Page kidney. Recently, investigators, in a carefully done, experimental, swine model, demonstrated that the decline in glomerular filtration was independent of organ compression but dependent on renal vein pressure. Higher renal venous pressure was negatively correlated with rat inulin clearance. Another group has forwarded the hypothesis that interstitial inflammation is the inciting mechanism or, at a minimum, contributory.[18]

The Page kidney's wrapping included the hilum and likely increased renal venous pressure although this was not reported in Page's original report. Expanding the concept of increased renal venous pressure as the cause of depressed glomerular filtration unifies the kidney failure associated with multiple other etiologies in which no parenchymal disorder had been previously established. Several of these include the abdominal compartment syndrome, bilateral renal vein thrombosis, inferior vena cava (IVC) thrombosis, and many cardiopulmonary disorders characterized by high central venous pressures or pulmonary artery pressures. In each of these problems, there is elevated renal venous pressure, the renal consequences of which are elevated plasma renin activity, increased aldosterone, hypertension, loss of autoregulation, and diminished glomerular filtration rate.[19,20]

Importantly, in the abdominal compartment syndrome, the pressure on the renal vein is not linearly related with volume of ascites. A more complicated pressure-volume relationship exists that does not follow Boyle's law—namely, that pressure is not inversely related to volume in linear fashion. However, akin to cardiac tamponade from pericardial effusion, removal of a relatively small volume of fluid can rapidly lead to an improvement of renal function. Ironically, large-volume paracentesis frequently is associated with delayed AKI, despite an improvement in the overall hemodynamic profile.[21] Notably, IVC thrombosis, bilateral renal vein thrombosis, and cardiopulmonary disorders are also characterized by elevated renal venous pressures.

Whether the CKD associated with obesity is aggravated by elevated renal vein pressure is unknown; however, adipose tissue-induced venous compression manifested by lower extremity edema reflects elevated IVC pressure. The notion that reduced glomerular filtration attributable

to high renal venous pressure in obesity complicates obesity-related glomerulopathy (ORG)[22] has substantial credence because the relatively rapid improvement in kidney function associated with weight loss would not be attributed to the repair of ORG-related lesions that had resulted from glomerular hyperfiltration. In addition, weight loss attenuates the marked elevations of plasma renin and aldosterone that are associated with this disorder.

In addition, does the obstructive sleep apnea that is prevalent among morbidly obese individuals perpetuate or initiate kidney failure? This hypothesis may be substantiated when secondary pulmonary hypertension is present and leads to elevated renal vein pressure. Acute elevations of pulmonary arterial hypertension in patients with exacerbations of chronic obstructive pulmonary disease explain in part the appearance of AKI. Hypoxia-induced increases in pulmonary artery pressures reduce left ventricular filling pressures dependent on an already impaired right ventricle. Right ventricular dysfunction consequently elevates central venous pressure that is reflected in the renal veins with consequent depression of glomerular filtration. Here, oxygen, not a loop diuretic, is reparative.

Taken collectively, heart failure, with or without congestive symptoms and left- or right-sided, produces a cardiorenal syndrome that demands an integrated and collaborative care model that involves cardiologists and nephrologists. The more recently exemplified venorenal syndromes will also require coordinated care between nephrologists and less familiar partners, including hepatologists, bariatric specialists, and pulmonary hypertension physicians. This should not prove difficult as CKD has become the new nexus of care of in Internal Medicine and Family Medicine. Certainly, we have surpassed the conventional and passive model of severe left ventricular depression as the sole cause of cardiorenal failure.

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