EDITORIAL COMMENT

Deleterious Effect of Altered Myocardial Fatty Acid Metabolism in Kidney Disease*

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Metabolic adaptation likely represents one of the earliest responses to myocardial ischemia. The myocardium preferentially oxidizes free fatty acids for energy production. However, the dependency of fatty acid metabolism on oxygen makes this process particularly vulnerable to ischemia. Under hypoxemic or ischemic conditions, the energy requirements of the myocardium are met by glucose rather than free fatty acids. Furthermore, recovery of fatty acid metabolism after myocardial ischemia lags behind restoration of perfusion, resulting in the phenomenon of "metabolic stunning." This decrease in fatty acid utilization following ischemia can be imaged with fatty acid radiotracers, particularly β-methyl iodophenyl-pentadecanoic acid (BMIPP), which demonstrate markedly limited metabolism

via beta oxidation, resulting in prolonged retention in the cardiomyocyte (1,2). Thus, abnormal myocardial BMIPP uptake at rest reflects metabolic alteration caused by the preceding ischemia, also termed "ischemic memory." There is reason to believe that such a relationship between cardiac ischemia and metabolism is accentuated in patients with chronic kidney disease (CKD). In this issue of the *Journal*, Nishimura et al. (3) demonstrate the deleterious effect of altered metabolism in relationship to ischemia among patients with end-stage renal disease (ESRD) with a report of a significant association between abnormal BMIPP uptake (indicating myocardial ischemia) and subsequent cardiac death among asymptomatic dialysis patients without history of prior myocardial infarction (MI).

## Prevalence of Cardiovascular Disease in CKD

Cardiovascular disease accounts for most of the morbidity and mortality in both the predialysis stages of CKD and after the onset of ESRD. Chronic kidney disease is common in the U.S. with almost 17% of adults older than 20 years having impaired renal function or urinary protein excretion (4). This is largely due to the rising frequency of hypertension and type 2 diabetes, which are the most common causes of CKD among Americans. It has been reported that those who suffer from ESRD, and receive some form of dialysis, have as much as a 100-fold higher risk of death from cardiovascular disease than healthy people matched for age, race, and gender (5). Beyond ischemic heart disease, congestive heart failure accounts for a significant portion of the cardiovascular-related events observed in CKD.

Several sequelae of kidney failure that accrue with loss of renal function can contribute to the myocardial remodeling and heart failure seen with the uremic variant of cardiomyopathy (Fig. 1). Elevated blood pressure, for example, becomes increasingly volume dependent with a concomitant increase in arterial stiffening, activation of neurohormones, and endothelial dysfunction as renal function declines. Individuals with CKD, therefore, are faced with both pressure- and volume-overload states contributing to the development of left ventricular hypertrophy (6). Additionally, CKD is associated with excess parathyroid hormone (7,8), anemia (9), and high angiotensin II levels (10) that are also likely to contribute to myocardial injury.

Metabolic Alterations in CKD and Uremic Cardiomyopathy

With the diffusely ischemic and oxygen-poor milieu described with uremic cardiomyopathy, one might expect a decline in myocardial fatty acid utilization and a shift to anaerobic glucose metabolism. Disturbances of calcium and phosphorus metabolism and a secondary increase in circulating parathyroid hormone levels have been proposed as one possible mechanism in modulating myocardial growth and structure in uremic cardiomyopathy (8). In isolated myocardial mitochondria, parathyroid hormone was shown to inhibit myocardial energy production from long- and short-chain fatty acids and to uncouple oxidative phosphorylation (11). Because uptake of BMIPP in the myocardium reflects activation of fatty acids by coenzyme A, and indirectly of cellular adenosine triphosphate (ATP) production, reduction in ATP production secondary to diminished fatty acid metabolism is mirrored by decreased myocardial BMIPP uptake (12). Consequently, unless the myocytes compensate for the decreased fatty acid metabolism by switching to anaerobic glycolysis for ATP formation, myocellular cell death will ensue.

The relationship between myocardial glucose utilization and severity of renal dysfunction was recently reported in pre-dialysis CKD patients (13). Among nondiabetic CKD patients without overt coronary artery disease (CAD), there
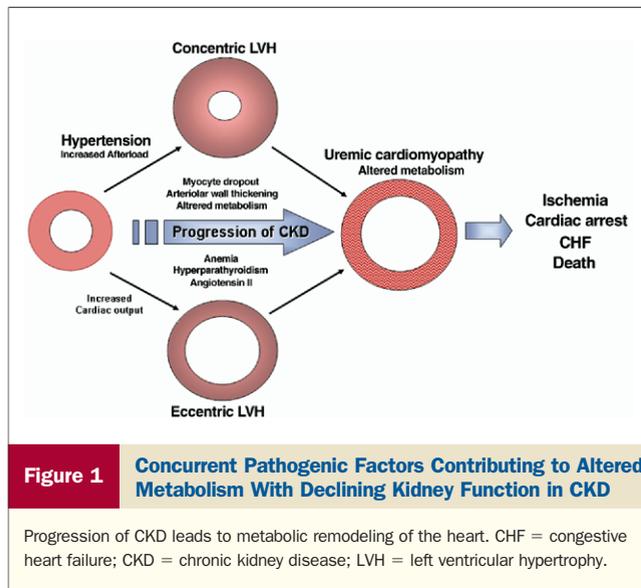
was a significant inverse correlation between myocardial glucose utilization (measured in μmol/min/100 g of myocardial tissue) and glomerular filtration rate (Spearman's rho = -0.67, p = 0.008). In the future, dynamic fluorodeoxyglucose positron emission tomography (PET) may provide a sensitive, noninvasive, quantitative tool for investigating subclinical myocardial abnormalities in patients with CKD.

Myocyte–Capillary Mismatch and High Angiotensin II Levels in CKD

The cardiomyopathy typical of CKD and the associated uremia is thought to lead to a myocyte-capillary mismatch, with a diminished vascular supply relative to the number and volume of functioning myocytes (14). Autopsy examinations of hearts from patients with CKD as well as endomyocardial biopsies of dialysis patients with cardiomyopathy have shown a substantial degree of myocyte disarray and interstitial fibrosis (15,16). It is now well established that the renin-angiotensin system (RAS) and its primary effector peptide, angiotensin II, are locally produced in the heart and are implicated in the pathophysiology of interstitial fibrosis, left ventricular remodeling, and heart failure. The discovery of tissue RAS has promoted the development of PET tracers targeting angiotensin-converting enzyme (ACE). Recently in explanted cardiac tissues from patients with ischemic cardiomyopathy, a specific binding of [^{18}F]fluorobenzoyl-lisinopril to tissue ACE was shown (17). ACE binding in peri-infarct segments was greater than binding in remote, noninfarct segments. If reproduced in vivo, this imaging technique sets the stage for future probes that target the ACE system in the heart and kidney, with the potential of monitoring both the progression of left ventricular remodeling in CKD and the effect of medical and interventional therapies in such patients. Delayed enhancement with cardiac magnetic resonance and myocardial

tissue characterization with echocardiography have also shown changes consistent with myocardial injury and fibrosis unique to kidney patients (18,19).

Clinical Studies With BMIPP in ESRD

In a recent prospective study of 130 asymptomatic ESRD patients undergoing hemodialysis, Nishimura et al. (20) investigated the prevalence of CAD by performing dual isotope thallium and BMIPP single-photon emission computed tomography (SPECT) at rest followed by coronary angiography. Significant coronary artery luminal narrowing ($\geq$75%) was present in 71% of ESRD patients. When a reduced myocardial metabolism with BMIPP summed score of >6 was used to define an abnormal scan, the sensitivity, specificity, and accuracy for detecting CAD with rest BMIPP SPECT was 98%, 66%, and 90%, respectively (20).

In this issue of the *Journal* (3), the same investigators have examined the prognostic significance of reduced myocardial metabolism with BMIPP in conjunction with perfusion abnormalities assessed with thallium in ESRD patients without prior MIs. Among the 318 prospectively enrolled asymptomatic hemodialysis patients, 50 (16%) died of cardiac events during a mean follow-up period of 3.6 ± 1.0 years. Stepwise Cox hazard analysis showed that cardiac death was significantly associated with highly abnormal BMIPP uptake (summed score of $\geq$12; hazard ratio = 21.9) and age ($\geq$70 years; hazard ratio = 2.4). Among patients with summed BMIPP scores of $\geq$12, event-free survival at 3 years was 61%, whereas event-free survival was 98% in those with summed BMIPP scores of $<$12. When BMIPP uptake (metabolism) was assessed in relation to regional thallium uptake (perfusion), indicating myocardial ischemia, the sensitivity and specificity of the metabolism–perfusion mismatch for predicting cardiac death was 86% and 88%, respectively. Among patients with BMIPP–thallium mismatch scores of $\geq$7, event-free survival at 3 years was 53%, whereas event-free survival was 96% in those with BMIPP:thallium mismatch scores of $<$7. These findings support the assertion that altered cardiac metabolism (indicating silent myocardial ischemia) is highly prevalent in ESRD patients and can identify subgroups of patients who are at high risk for cardiac death. The shift from a predominance of aerobic (fatty acid) to anaerobic (glucose) metabolism appears to account for a significant portion of the excessive cardiovascular morbidity and mortality observed across all stages of kidney disease. Potential limitations of the study include the relatively high mean age of the patients and the possibility that some of the deaths may have been caused by hyperkalemia or other metabolic disorders rather than myocardial ischemia or coronary artery event.

Because patients with histories of MI were excluded from the study, myocardial ischemia was implicated as the most likely explanation for the highly abnormal BMIPP SPECT

findings. Support for the latter comes from a recent publication that showed that patients without prior MIs who underwent clinically indicated exercise thallium SPECT followed by rest BMIPP SPECT (2). The location and extent of myocardial ischemia as determined by reversible thallium defects were correctly identified with BMIPP imaging during the subacute phase, at rest, and up to 30 h after the ischemic event. There was excellent patient-level agreement (>90%) between BMIPP and thallium data for the presence or absence of a scintigraphic abnormality. Furthermore, there was also good correlation between the extent and severity of the stress thallium defect and rest BMIPP defect when summed segmental scores were applied (2).

Summary

In asymptomatic hemodialysis patients with ESRD, impaired myocardial fatty acid metabolism assessed by BMIPP SPECT was used to identify the subgroup of patients who were at high risk for cardiac death. In the future, large clinical trials could provide further insight into the potential strengths of this metabolic agent as a target for ischemic memory and as a predictor of cardiac death. Targeting intracellular metabolic processes for imaging may expand our ability to diagnose and treat subclinical myocardial ischemia or progressive cardiomyopathy that often remains elusive with traditional imaging approaches.

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