Left Ventricular Systolic Dysfunction
A Sudden Killer in End-Stage Renal Disease Patients

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Patients who enter into the most advanced phase of chronic kidney disease, that is, end-stage renal disease (ESRD), show an exceptionally high risk. Although the proportion of patients dying because of cardiovascular disease in this population does not differ from the corresponding proportion in the general population, the absolute risk for all-cause and cardiovascular death is so high that the probability of these outcomes in ESRD patients is ∼10 to 20 times higher than that in age- and sex-matched individuals in the general population. A most concerning aspect of such a high risk condition is that a class of drugs that has demonstrated unquestionable beneficial effects in primary, secondary, and tertiary prevention in the general population, namely 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, is quite ineffective in ESRD. A likely explanation for this phenomenon is that the etiology of cardiovascular death in ESRD substantially differs from that in the general population.

Although the classical sequelae of atherosclerosis, myocardial infarction and stroke, rank as the most frequent causes of cardiovascular death in the general population, in ESRD the scene is dominated by heart failure and sudden death, that is, 2 conditions that are hardly modified by treatment with 3-hydroxy-3-methylglutaryl-coenzyme A inhibitors. The incident rate of sudden death in the dialysis population is 93‰ per year. An alarming figure makes identification of dialysis patients predisposed to sudden death an important goal both for clinical and public health reasons.

ESRD patients harbor several risk factors that have been linked to sudden death in experimental and clinical studies (see Figure). Left ventricular (LV) hypertrophy (LVH) in hypertensive subjects is associated with several pathophysiological features that promote myocardial electric instability and ventricular arrhythmias. Also, because it potently activates the sympathetic system, LV systolic dysfunction is an even stronger predictor of sudden death than LVH at the community level. Both, LVH (prevalence rate 78%) and systolic dysfunction (48%) are highly prevalent in asymptomatic patients with ESRD, which sets a high background risk in this population. Yet, specific evidence that LVH and/or LV dysfunction predict sudden death in ESRD still remains to be produced. In this regard, it is important to note that myocardial fibrosis and capillary rarefaction, 2 hallmarks of cardiomyopathy in uremia, are notorious triggers of electric instability of the myocardium. Inadequate vasodilatory reserve of thickened coronary microvessels and capillary rarefaction easily eventuate into ischemia, an established proarrhythmogenic factor. LVH in dialysis patients is frequently associated with an acquired form of long-QT syndrome characterized by a low number of K channels. Because of their reduced myocardial expression, these channels are supersensitive to a variety of commonly used drugs that inhibit the outward K channel I\textsubscript{o}, including antihistamines, antidepressants, erythromycin, and the β-blocker sotalol. These medications in individuals with long QT syndrome may trigger polymorphic ventricular tachycardia, a deadly arrhythmia. Potassium shifts during the dialysis session represent another major arrhythmogenic stimulus in the hemodialysis patients, standard hemodialysis being an established trigger of complex arrhythmias.

Several factors confound to increase sympathetic activity in ESRD patients, including low vagal tone, afferent signals originating in the end-stage kidneys, and sleep apnea, a condition that is ≥10 times more frequent in ESRD patients than in the background general population. Sympathetic overactivity poses a high arrhythmogenic risk in ESRD. Indeed, chronic uremia on one side enhances central sympathethic drive and on the other side damages autonomic nerves determining patchy denervation, an alteration in turn setting off noradrenergic receptor supersensitivity. Last but not least, the high prevalence of diabetes mellitus (∼30% in most Western countries) and of coronary heart disease in the dialysis population, per se, generates an exceedingly high risk of sudden death in these patients.

Although electrolyte shifts are far more pronounced during hemodialysis than during peritoneal dialysis, the frequency of sudden death is similar in hemodialysis and in peritoneal dialysis patients. This observation suggests that patient-related rather than treatment-related factors underlie the excess risk for sudden death in ESRD. To identify predictors of sudden death in ESRD, Wang et al\textsuperscript{8} now make a series of sound analyses in a reasonably large cohort of peritoneal dialysis patients. A feature that renders almost unique the database built on this cohort is that it includes accurate echocardiographic studies along with measurements of established biomarkers of LV mass and function (N-terminal pro-B–type natriuretic peptide) and of cardiac ischemia (Tropinin T), as well as information on risk factors peculiar to ESRD (phosphate, hemoglobin, and volume status), biomarkers of inflammation (high-sensitivity C-reactive protein and fetuin-A), and hopeful in identifying the ESRD patients at highest risk for sudden death and selecting appropriate preventive measures.
and oxidative stress. This is important because risk factors in ESRD do not coincide with those in the general population, with inflammation and vascular calcification/arterial stiffening having a much more relevant role in ESRD. Although the issue is well framed in studies at the community level, Wang et al for the first time produced specific documentation that LV systolic dysfunction is the main factor predisposing ESRD patients to sudden death. Furthermore, they show that the identification of patients at higher risk of sudden death may be pursued also by a biomarker of LV function (N-terminal pro-B-type natriuretic peptide). However, LV dysfunction entails a high risk also for other causes of death, from pump failure to thrombotic events. Given the high prevalence of LV dysfunction in the dialysis population and the very high risk of this alteration for all-cause death, measurements of LV systolic function and/or N-terminal pro-B-type natriuretic peptide are unlikely to be applied just for selective identification of individuals at high risk for sudden death, particularly because the discriminatory power of a low ejection fraction for this outcome is of a moderate degree.

In the study by Wang et al, multivariate modeling of the risk of sudden death based solely on biomarkers and on biomarkers in conjunction with echocardiography produced somewhat incoherent results, Troponin T being valueless in an N-terminal pro-B-type natriuretic peptide–based model but contributory in a model based on LV systolic function. These discrepancies, which may depend on the limited study power, demand further analyses in larger cohorts. Yet these nice observational data represent a strong call to action for renal physicians to effectively implement preventive measures for diagnosing and treating LV dysfunction. Observational studies suggest that β-blockers are associated with longer survival in dialysis patients, and a randomized trial in ESRD patients with LV dysfunction showed improved LV performance and better clinical outcomes, including longer survival and reduction in arrhythmia episodes by the addition of a β-blocker to a regimen including angiotensin-converting enzyme inhibitors. However, β-blockers remain scarcely prescribed to ESRD patients. Beyond drug treatment, the American College of Cardiology recommends that implantable cardioverters should be used in patients with an ejection fraction <30%, mild-to-moderate symptoms of heart failure, and a life expectancy >1 year. Although the issue still remains to be tested in a clinical trial, implantable cardioverter use appears to be beneficial in ESRD. However, here again, just a mere 8% of ESRD patients eligible for implantable cardioverter implantation actually receive this device.

ESRD patients are at exceptionally high risk of sudden death, and LV dysfunction is the major driver of this outcome. Timely identification and treatment of patients with this disturbance may improve the dismal prognosis of ESRD.

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References
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