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The Role of Protein-bounded Uremic Toxins in Cardiac Arrhythmias and Sudden Cardiac Death in End Stage Renal Disease

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Short Communication

The importance of cardiovascular diseases (CVD) and cardiac arrhythmias in chronic kidney disease (CKD) is currently well established [1-3]. Nearly half of deaths in end-stage renal disease (ESRD) patients are secondary to myocardial infarction, sudden cardiac death (SCD), malignant arrhythmias and other heart disease [4]. The high prevalence of diabetes, anemia, hyperparathyroidism, and hypertension among this population cause vascular calcifications and left ventricular hypertrophy which further results in CVD, cardiac arrrhythmias and SCDs. Moreover, fluid overload¸ transiet hemodynamic change during hemodialysis and metabolic abnormalities such as metabolic acidosis, potassium imbalance and dysmagnesemia also increase the risk of malignant arrhythmias and SCD. In addition, the sympathetic hyperactivity and activation of the renin-angiotensin-aldosterone system (RAAS) which will induce cardiac arrhythmias also noted in ESRD patients. However existing literatures revealed there are differences between SCD among this population and general individuals, traditional CVD risk factors seem to have a more muted effect in ESRD patients [5].

The hampering removal uremic toxins, such as indoxyl sulfate, p-cresyl sufate, huppuric acid, etc. mostly are protein-bounded, could not totally removed by hemodialysis, able to past through the cell membrane and accumulated in human body. They were recently determined as a potential additional cause for the excess of CVD and sudden cardiac dealth observed in CKD patients [6,7] .In past decade, series of studies has been published regarding these protein-bounded uremic toxins associated the severity of CVD and adverse major cardiac events [8,9], cardiomyopathy [10,11], QT prolongation [12,14] and vascular pathophysiology [15]. All these underlying pathogeneses could induce cardiac arrhythmias and the lethal SCD. In vitro, these protein-bound uremic toxins were found to have prohypertropic effects on cardiomyocyte [16], proinflammatory cytokines and free radical production [17], induction of endothelial microparticle release and endothelial damage [18], vascular smooth muscle cell proliferation [19], vascular endothelial cells adherens junctions disruption [20,21] and inhibit of leukocyte function [22]. The proinflammatory cytokines have been associated with arrhythmias through the modulation of ion channel function [23-25] and the aggravation of sympathetic tone [23]. In addition, myocardial fibrosis, which demonstrated in previous indoxul sulfate studies [16,26], has also been associated with the inflammatory process, and further affect ventricular conduction causing a delay in repolarization that could lead to ventricular arrhythmias [23,27,28]. As a result, it is therefore reasonable to propose these protein-bounded uriemic toxins may act as a pro-inflammatory cytokine and that it plays a role in chronic inflammation, thus contributing to the pathogenesis of CVD and cardiac arrhythmias [29,30]. In addition, indoxyl sulfate and p-cresyl sulfate also showed down-regulated of potassium current (I_K) channel protein phosphorylation and the I_K current activity that in turn increases the action potential duration and QTc interval in both experimental and theoretical electrophysiological studies [12,14].

Upto now, the mainstay of cardiovascular events prevention in ESRD patients still focus on the control of tranditional CVD risk factors, sympathetic outflow, blockade of the RAAS and prevention of electrolyte disorders. Numerous studies have been performed to develop more appropriate risk stratification tools, investigate the preventive antiarrhythmic medication or dialysis-specific cardiac arrhythmias prevention strategies. Although the oral charcoal adsorbent such as AST-120 could decreases serum protein-bounded uremic toxins level and reduces the oxidative stress by absorbing these uremic toxins precursor in intestine and decrease their absorption [31], there is still no standard guideline to prevent or decrease these protein-bounded uremic toxins

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clinically. In conclusion, we are here to emphasize the important role of these protein-bounded uremic toxins in the adverse cardiac events pathogenesis. An emergent need to investigate the solution how to lower and prevent the protein-bounded uremic toxins level and cardiotoxicity is suggested.

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