Biomarkers of endothelial stress to estimate volume status and cardiovascular risk in dialysis patients

1. Background

Adequate dialysis is more than just small molecule clearance as measured by urea kinetic (kt/V), it also encompasses adequate volume control. While the former is not difficult to achieve in times of high-efficiency dialyzers, the latter is more challenging. Yet, volume control is a critical element in dialysis care and increasing evidence indicates that congestion is the main factor contributing to high morbidity and mortality of patients on dialysis[1]. Congestion has been shown to be associated with arterial hypertension, left ventricular hypertrophy, cardiovascular events and organ dysfunction. On the other hand, excessive fluid removal induces hypovolemia which may cause cardiac stunning and organ hypoperfusion. As a result, hypervolemic and hypovolemic states are linked to increased mortality [1,2]. Therefore, *volume first approach* has been proposed to better take into account the reno-cardial axis and therefore improve outcome in hemodialysis patients[3].

Assessment of fluid balance in dialysis patients remains a challenge as there is no widely available gold-standard tool, for accurately determining dry weight. Bedside assessment of fluid status has been shown to be often inprecise. The most commonly used tool for assessing volume status in dialysis patients is bioelectrical impedance measurement (BCM), which estimates body composition including total body water (i.e. extracellular and intracellular water), lean tissue mass and fat mass[4-7]. Of note, with bioelectrical impedance measurement, no differentiation is possible between intravascular and interstitial water content. This however, might be of substantial relevance for a correct interpretation of hemodynamics in dialysis patients. Accumulation of fluids in the extracellular and intracellular spaces ("organ congestion"), is the final step of the congestive cascade, which begins with an increase in the intravascular volume and pressure ("hemodynamic congestion"). Notably, tissue edema may be the consequence of pathological conditions (such as hypoproteinemia impaired venous or lymphatic drainage, capillary leak, dysfunctional glycosaminoglycan network), and not be directly related to hemodynamically relevant congestion related to intravascular volume overload. Therefore, the assessment of fluid balance by global body composition measurement using bioelectrical impedance measurement might not accurately reflect the cardiovascular risk associated with inadequate volume control in dialysis patients.

Biomarkers are emerging as useful clinical tools to evaluate hemodynamic congestion. The group of Prof. Mebazaa in Paris, recently characterized endothelial biomarkers released upon endothelial stress as a novel class of biomarkers in hemodynamic monitoring. Particularly, soluble CD146 (sCD146) performed better than natriuretic peptides for diagnosis of acute decompensated heart failure[8,9]. They showed a predominant extracardiac, vascular source of sCD146 with increased release in presence of experimental and clinical venous congestion[8]. sCD146 is a junctional adhesion molecule, expressed on human vascular endothelial cells and involved in the control of vessel integrity and released upon endothelial stress. Since sCD146 is released by endothelial cells in presence of "hemodynamic congestion", this biomarker may better reflect volume control in dialysis patients than currently used natriuretic peptides (BNP/NT-proBNP). Natriuretic peptides are released by the cardiac myocytes in response to increased wall stretch, primarily reflecting severity of myocardial dysfunction (a parameter not necessarily appropriate to quantify volume status in dialysis patients)[10,11].Moreover, sCD146 might indicate hypervolemia at an earlier stage as compared to BCM.

Thus, biomarkers of endothelial stress, such as sCD146, might be particularly appropriate to precisely assess volume control in dialysis patients and – in consideration of the pivotal role of water balance - correlate with cardiovascular morbidity and mortality.