Kidney–Heart Interactions in Acute Kidney Injury

Kent Doi
Department of Emergency and Critical Care Medicine, The University of Tokyo Hospital, Tokyo, Japan

Key Words
Acute kidney injury · Organ interaction · Mitochondria · Dynamin-related protein 1 · Apoptosis

Abstract
Acute kidney injury (AKI) is a common complication in critically ill patients treated in intensive care units. Renal replacement therapy (RRT)-requiring AKI occurs in approximately 5–10% patients in intensive care unit and their mortality rate is unacceptably high (50–60%), despite sufficient control of uremia using remarkably advanced modern RRT techniques. This suggests that there are unrecognized organ interactions following AKI that could worsen the outcomes. Cardiorenal syndrome has been defined based on clinical observations that acute and chronic heart failure causes kidney injury and AKI and that chronic kidney disease worsens heart diseases. Possible pathways that connect these 2 organs have been suggested; however, the precise mechanisms are yet to be clarified, particularly in AKI-induced cardiac dysfunction. This review focuses on acute cardiac dysfunction in the setting of AKI. A recent animal study demonstrated the dysregulation of mitochondrial dynamics caused by an increased dynamin-related protein 1 expression and cellular apoptosis of the heart in a renal ischemia reperfusion model. Although the precise mechanisms that induce cardiac mitochondrial injury in AKI remain unclear, cardiac mitochondria injury could be a novel candidate of drug targets against high mortality in severe AKI.

Introduction

The interaction between the kidneys and heart has been recognized as a clinical entity called cardiorenal syndrome (CRS) [1]. CRS includes both renal failure secondary to cardiac dysfunction and heart failure secondary to renal dysfunction. CRS can be categorized into 4 subtypes based on the time course and type of abnormality that first develops in the kidneys and heart (fig. 1). Type 1 CRS was previously recognized as a worsening in renal function (WRF). Reportedly, WRF complications predict considerably higher rates of mortality and hospitalization because of acute heart failure [2]. Type 1 CRS also includes acute kidney injury (AKI) that occurs in low car-
diac output syndrome caused by acute coronary syndrome. Type 2 CRS is frequently observed in a clinical setting as progressive renal dysfunction associated with chronic heart failure. Type 4 CRS is well described as chronic heart disease occurring with chronic kidney diseases (CKDs). For example, type 3 CRS is characterized by an acute reduction of renal function that leads to acute cardiac injury and/or dysfunction. Retention of uremic solutes and/or volume overload may contribute to heart injury in type 3 CRS. Few pre-clinical studies have reported on possible mechanisms that include the activation of sympathetic nervous and renin-angiotensin-aldosterone systems, increased oxidative stress and inflammation. Type 4 CRS is found in approximately 70–80% patients with end-stage renal disease who frequently go through cardiac dysfunction complications [3].

**Fig. 1. Four subtypes of CRS.**

Cardiac Injury Observed in AKI

Several animal experiments have reported cardiac changes induced by AKI. Cellular apoptosis and capillary vascular congestion were observed in the heart after renal ischemia reperfusion (IR) [4, 5]. In a rat renal IR model, tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and intercellular adhesion molecule-1 expressions were increased in the heart [4]. The number of TUNEL-positive nuclei was reduced by treatment with an anti-TNF-α antibody at the time of renal ischemia [4]. Renal IR induced in transgenic mouse expressing human sickle hemoglobin showed congestion in the capillary beds in the heart [5]. In a glycerol injection-induced rhabdomyolysis AKI model, an increase in mitochondrial calcium uptake and subsequent ventricular depression of inotropic response were observed [6]. Unilateral renal artery ligation increased cardiac infiltrating macrophages along with osteopontin gene expression [7]. Interestingly, these cardiac changes were attenuated by treatment with the angiotensin receptor 1 antagonist losartan, suggesting a possible contribution of the renin-angiotensin-aldosterone system.

**Mitochondrial Dysfunction in Acute Heart Disease**

Mitochondria continually fuse and divide under normal conditions (mitochondrial dynamics). Fusion and fission are mediated by several guanosine triphosphatases. Fusion of the inner membrane involves optic atrophy 1 (OPA1), whereas the outer membranes of mitochondria are regulated by mitofusin (Mfn) 1 and Mfn2. Fission is mainly regulated by dynamin (Drp1). Drp1 is a cytosolic protein that moves to the outer mitochondrial membrane. Mitochondrial fission is an early event during apoptosis, occurring before caspase activation and membrane blebbing. Cytochrome c release from mitochondria is considered to be the primary trigger of the caspase cascade. Cytochrome c is released through the outer mitochondrial membrane during apoptosis simultaneously with mitochondria fragmentation [8].

In the heart, mitochondrial function is assumed to be an important determinant of myocardial contractility. Mitochondrial structural changes have been evaluated in cardiac IR injury models. Cardiac IR with isolated neonatal murine cardiomyocytes and isolated perfused adult rat hearts (Langendorff preparation) showed that Drp1 inhibition preserved the mitochondrial structure after IR [9]. Moreover, a calcineurin inhibitor FK506 and therapeutic hypothermia inhibited Drp1 S637 dephosphorylation and attenuated mitochondrial morphological changes and myocardial dysfunction [9]. A dominant-negative mutant of Drp1 or a Drp1 inhibitor mdivi-1 treatment reduced mitochondrial permeability transition pore sensitivity and subsequent cell death [10]. In vivo treatment by mdivi-1 reduced infarct size in a murine coronary artery occlusion model [10]. Based on these observations, Drp1 inhibition seems to have the potential for reducing myocardial injury caused by IR.

**Mitochondrial Injury in the Heart Induced by AKI**

Although several preclinical studies showed cardiac injury induced by AKI, as described above, it is unclear whether mitochondrial injury in the heart could be caused by AKI. Recently, we reported on changes in the mitochondrial dynamics and subsequent cardiac apoptosis in a mouse renal IR model [11]. Fragmented mitochondria in
Kidney–Heart Interactions in Acute Kidney Injury

Cardiomyocytes was observed after 30 min of bilateral renal IR (fig. 2). Reduction of fractional shortening was observed 72 h later. Among the mitochondrial dynamics regulating molecules of Drp1, Mfn1, Mfn2, and OPA1, only Drp1 was increased in the mitochondrial fraction of the heart. The Drp1 protein was not increased in the cytosolic but in the mitochondrial fraction of the heart tissue, and mdivi-1 (Drp1 inhibitor) attenuated mitochondrial fragmentation. The mechanisms by which AKI enhances mitochondrial fragmentation in the heart are still unclear. TNF-α expression in the heart was increased after renal IR, in accordance with a previous report [4], although an mdivi-1 treatment did not suppress TNF-α expression in the heart. Several possible pathways can be considered. Unrecognized humoral mediators may be accumulated in the blood following AKI. The chemokine (C-X-C motif) ligand 1, IL-1β, and TNF-α were increased not only in the kidneys, but also in the spleen and liver following renal IR injury [12]. Increased blood levels of the high-mobility group box 1 protein and IL-6 were reported in mouse AKI models [13, 14]. Further investigations must be conducted to clarify the responsible pathways in cardiac injury caused by AKI.

**Perspectives**

It has been widely realized that AKI significantly worsens the outcomes of critically ill patients in intensive care units and improvement of AKI can reduce the mortality rate. However, dialysis-requiring AKI shows the highest mortality rate, despite reduction of uremia by sophisticated renal replacement therapy technologies. These patients are mostly complicated with sepsis and multiple organ failure, including the heart, lung, and liver and hematological disorders. Focusing only on kidney damage may not be sufficient to improve outcomes of patients with AKI. Recent studies have elucidated complex organ interactions in AKI between the kidneys and distant organs [15]. We further need to identify unrecognized organ interactions in AKI, such as mitochondria injury in the heart, to develop novel therapeutics against AKI and decrease the high mortality rate during AKI-related multiple organ failure.

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**Disclosure Statement**

The author has no conflicts of interest to declare.

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Fig. 2. Mitochondrial fragmentation in the heart after renal ischemic reperfusion. Mitochondrial fragmentation was observed in cardiomyocytes 24 h after renal IR injury.

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References


