Acute renal failure after whole body ischemia is characterized by inflammation and T cell-mediated injury

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Burne-Taney, Melissa J., Julia Kofler, Naoko Yokota, Myron Weisfeldt, Richard J. Traystman, and Hamid Rabb. Acute renal failure after whole body ischemia is characterized by inflammation and T cell-mediated injury. Am J Physiol Renal Physiol 285: F87–F94, 2003.—Acute renal failure (ARF) commonly occurs after whole body ischemia. Most experimental models of ARF have relied on the isolated renal artery clamping model; however, there is a pressing need to develop and understand the pathogenesis of new models with more “clinical relevance.” We evaluated a new murine model of ARF after whole body ischemia reperfusion injury (WBIRI). WBIRI was induced by an infusion of potassium chloride and a cardiac arrest period of 10 min. Resuscitation was achieved by cardiac compressions, ventilation, epinephrine, and fluids. WBIRI leads to a significant increase in serum creatinine (SCr) and renal tubular injury by 24 h. Renal myeloperoxidase (MPO) levels increased at 24 h after WBIRI. Increased expression of the proinflammatory genes, ICAM-1 and IL-6, was also observed in the kidney following WBIRI. On the basis of recent data that T cells are important mediators of isolated renal IRI, WBIRI was evaluated in T cell-deficient nu/nu mice. T cell-deficient mice had a significantly reduced rise in SCr and decreased tubular injury compared with wild-type mice. T cell-deficient mice had a decrease in ICAM-1 expression after WBIRI, but no decrease in renal MPO. This study describes a new, clinically relevant, model of ARF after WBIRI in mice and identifies the T cell as an important mediator of renal injury following WBIRI. Reduced ICAM-1 expression may provide a mechanism for this involvement.

lymphocytes; cardiac arrest; kidney dysfunction

ACUTE RENAL FAILURE (ARF) in the native kidney remains a disease of high prevalence and is associated with a mortality rate of ~50% (37). Despite significant advances in the pathophysiology of ARF and the development of novel therapeutics that have been protective in rodent models, no effective therapy has yet emerged in humans (3, 30, 34). The vast majority of in vivo experimental studies on ischemic ARF have relied on renal artery or pedicle clamping to simulate renal ischemia-reperfusion injury (IRI). Important underlying mechanisms of injury have been elucidated, including abnormalities in regional blood flow, inflammation, tubular obstruction, apoptosis, and endothelial/epithelial cell dysfunction. Although the isolated clamp approach continues to be extremely useful, it is clearly distinct from human ARF, in which most cases of IRI occur after whole body IRI (WBIRI) rather than isolated renal artery IRI. Furthermore, when biopsies are performed in human ARF, a patchy pattern of injury is seen, clearly distinct from the clamp model, where uniform injury is seen (22, 35). Thus there is an important need for development of new experimental models of ischemic ARF.

The mouse is a useful species in which to develop animal models of disease due to the availability of genetically modified animals and specific reagents. However, mouse models are limited by the constraints of experimenting in small animals, as well as other potential differences between mice and humans. Nevertheless, mouse models of human disease are proving invaluable in uncovering new pathogenetic pathways. To study ischemic ARF reflective of whole body ischemia, we studied a new model of ischemic ARF that was modified from a WBIRI model to examine successful resuscitation from cardiac arrest (20). This new model is relevant because renal insufficiency is an established distant organ injury that occurs with cardiac arrest (8). Approximately 30% of patients resuscitated from in-hospital cardiac arrests develop clinically overt ARF (25). Preexisting renal disease is also an important predictor of outcome after cardiac arrest (40). Not only is cardiac arrest a suitable model to study renal IRI, but evaluating kidney responses after WBIRI may also help in understanding how interorgan modulation alters outcome after severe hypotension.

We modified a mouse model of cardiac arrest (20) to focus on kidney outcomes following WBIRI. Renal function, structure, and inflammatory responses were measured and analyzed between mice undergoing WBIRI and sham-operated mice. To identify a possible mechanism of injury and in view of recent data implicating a pathophysiological role for T cells in the isolated clamp model of renal IRI (4, 7, 31, 38, 42), we evaluated the role of T cell deficiency on kidney outcomes follow-
ing WBIRI. Ribonuclease protection assays were used to focus on cytokine changes that occur in the kidney following WBIRI.

MATERIALS AND METHODS

Mice. Male 6- to 8-wk-old C57BL/6 mice were purchased from the Jackson Laboratory (Bar Harbor, ME) to establish the WBIRI model. In later experiments, T cell-deficient mice (nu/nu; B6.Cg-Foxn1<sup>nu/nu</sup>) and C57BL/6 wild-type littersmates were purchased from the same source. The two main defects of mice homozygous for the nu/nu spontaneous mutation (Foxn1<sup>nu/nu</sup>) are abnormal hair growth and defective development of the thymic epithelium.

Murine cardiac arrest model. Cardiac arrest was produced by stopping the heart and then using cardiopulmonary resuscitation to “survive” the animal. Animals across treatment groups were age matched to ensure uniformity of parameters. Anesthesia was induced with 2% halothane and maintained with 1–1.5% halothane in oxygen-enriched air via a face mask. A rectal probe was inserted and connected to an automatic temperature controller to maintain body temperature at ~37°C during surgery using a heating pad and lamp. For drug administration, a PE-10 catheter was inserted into the right jugular vein and flushed with heparinized saline solution. Another PE-10 catheter was inserted into the right femoral artery, flushed with saline, and connected to a pressure transducer system for monitoring or arterial blood pressure (Gould Instrument Systems, Valley View, OH). After completion of the surgery, the animal was endotracheally intubated using a 22G Baxter Quick Cath (length 2.5 cm; Baxter Healthcare, Deerfield, IL) as an endotracheal tube and then connected to a mouse ventilator (Harvard Apparatus, Holliston, MA) set to a respiratory rate of 190 breaths/min and 100% oxygen. An arterial blood pressure cuff was used to initiate spontaneous ventilation. For mechanical ventilation, a PE-10 catheter was inserted into the right femoral artery, flushed with saline, and connected to a pressure transducer system for monitoring or arterial blood pressure (Gould Instrument Systems, Valley View, OH). After completion of the surgery, the animal was endotracheally intubated using a 22G Baxter Quick Cath (length 2.5 cm; Baxter Healthcare, Deerfield, IL) as an endotracheal tube and then connected to a mouse ventilator (Harvard Apparatus, Holliston, MA) set to a respiratory rate of 190 breaths/min. The tidal volume was adjusted according to the animal’s size to maintain the arterial PCO2 within the physiological range, which was tested in pilot experiments. The animals were allowed to stabilize for 10 min before baseline temperature and blood pressure were recorded.

The method of cardiac arrest has recently been described (20). To induce cardiac arrest, 2.8 μl/g body wt of cold 0.5 M KCl was administered via the jugular venous catheter. Cardiac arrest was confirmed by a drop of arterial blood pressure (Fig. 1). The endotracheal tube was disconnected from the ventilator, and the ventilator and halothane administration were turned off. At 9 min and 30 s after the induction of cardiac arrest, the ventilator was turned on and set on a respiratory rate of 190 breaths/min and 100% oxygen. And at 9 min and 45 s, the endotracheal tube was reconnected. At 10 min, 20 μl/g body wt of prewarmed epinephrine (diluted in 0.9% saline with a final concentration of 16 μg/ml NaCl) were injected via the jugular venous catheter, and simultaneously chest compressions were initiated at a rate of 300 compressions/min. When restoration of spontaneous circulation (ROSC) was achieved, defined as a sustained systolic arterial blood pressure of 60 mmHg (15), cardiac massage was terminated. In the case of sustained cardiac arrest, additional doses of epinephrine (40% of first dose) were administered. If ROSC could not be achieved by 12 min, resuscitation efforts were stopped. Once spontaneous breathing was achieved, mechanical ventilation was stopped and the endotracheal tube was removed after gentle suctioning. Catheters were then removed and wounds were closed. Animals post-WBIRI were observed until complete recovery. Sham-operated animals underwent identical surgical procedures; however, cardiac arrest was not induced nor was the animal resuscitated. These procedures have been approved by the Institutional Animal Care and Use Committee Review Board.

Assessment of renal function. Blood samples were obtained from the tail vein at 0, 24, and 72 h post-WBIRI under halothane and serum creatinine (SCr) was used to measure renal function as previously described (4). SCr concentration was measured on a Roche Cobas Fara Mira Plus automated system (Roche, Nutley, NJ) using a creatinine 557 kit (Sigma, St. Louis, MO).

Histological assessment of renal injury. Kidneys were dissected and longitudinal sections were obtained from mice at either 24 h or 1 wk post-WBIRI. Tissue was fixed in 10% formalin and processed for histological examination (4). Five-micrometer sections were cut from paraffin blocks and stained with hematoxylin and eosin. Sections were analyzed in a blinded fashion to describe the extent of injury. Injury indexes include infiltration of mononuclear cells, dilation of tubular cells, flattening of tubular epithelial cells, and tubular necrosis.

Leukocyte detection using myeloperoxidase assay. Leukocyte (phagocyte) infiltration post-WBIRI was measured in mouse kidney 24 h after WBIRI. Briefly, kidney samples were homogenized (1:20 wt/vol) in ice-cold KPO<sub>4</sub> buffer. Samples were spun at 17,000 g for 30 min at 4°C, and pellets were washed and spun an additional two times. Then 0.5% hexadecyltrimethylammonium bromide-10 mM EDTA was added to the remaining pellet (6:1). Suspensions were sonicated and freeze-thawed three times and then incubated at 4°C for 20 min. After final centrifugation at 17,000 g at 4°C for 15 min and addition of assay buffer (4:1), supernatants were measured for myeloperoxidase (MPO). Change in absorbance over 3.5 min was recorded at 480 nm. One unit of MPO was defined as a change of absorbance of one per minute. Results were expressed as units of MPO per gram of protein that was detected using a bicinchoninic assay (Pierce Chemical, Rockport, IL).

Renal mRNA cytokine expression. Cellular RNA was isolated from snap-frozen native kidney and post-WBIRI kidneys using TRIzol Reagent (Invitrogen Life Technologies, Carlsbad, CA). The quantity of RNA was evaluated by the presence of GAPDH housekeeping RNA. A ribonuclease protection assay was used to characterize the cytokine/chemokine expression. We used the mouse-specific multiple cytokine assays RIBOQUANT from Pharmingen (San Diego, CA). We focused on the following cytokines: IL-6, ICAM-1, TNF-α, and IL-1β due to previous studies associating them with renal IRI (9, 13, 19, 21, 32).

Statistical analysis. Data are expressed as means ± SE. Comparisons of group means were performed using one-way ANOVA with the Student-Newman-Keuls multiple group comparison test. P < 0.05 was considered significant.

![Fig. 1. Mean arterial blood pressure before, during, and post-cardiac arrest. No differences in blood pressure were observed between T cell-deficient mice and wild-type mice.](http://ajprenal.org/)
RESULTS

**WBIRI in mice produces a decrease in renal function along with tubular injury.** The mean time to ROSC for all experiments was $11.08 \pm 0.07$ min from the time of infusion of KCl and the mean dose of epinephrine was $0.37 \pm 0.07 \mu g/g$ body wt. We compared SCr as a marker of renal function in mice undergoing WBIRI compared with sham-operated mice. We previously validated SCr as a marker of glomerular filtration rate postischemia in mice (27). WBIRI mice underwent cardiac arrest for 10 min followed by resuscitation. Sham-operated animals underwent identical surgical procedures; however, cardiac arrest was not induced nor was the animal resuscitated. Sham-operated mice do not show an increase in SCr. Mice undergoing WBIRI show an increase in SCr at 24 h post-WBIRI ($1.52 \pm 0.30$ vs. $0.63 \pm 0.05$ mg/dl, $P < 0.05$). SCr returns to baseline levels by 72 h post-WBIRI ($0.55 \pm 0.03$ vs. $0.35 \pm 0.05$ mg/dl) (Fig. 2).

Sham-operated animals showed normal histology (Fig. 3A). Twenty-four hours after WBIRI, kidneys are extensively damaged (Fig. 3B) with mononuclear cell infiltration, increase in tubular necrosis, and tubular dilation. Of note is that the injury is generalized rather than patchy. At 1 wk following WBIRI, there is still extensive damage to the kidney as seen by cast formation and tubular necrosis (Fig. 3D) compared with the sham-operated mouse (Fig. 3C).

**WBIRI leads to an increase in renal leukocyte infiltration.** Leukocytes are important mediators of experimental renal injury; however, their specific roles are still being defined. Tissue MPO levels have been used extensively as a marker of neutrophil infiltration into tissue (2). A recent study demonstrated that the MPO assay, which was previously used to specifically measure neutrophil infiltration, also detects macrophages (43). We used the MPO assay in this study as a measure of both neutrophil and macrophage infiltration. MPO analysis of kidney sections revealed that neutrophil and macrophage infiltration increases at 24 h post-WBIRI (Fig. 4) compared with sham-operated animals ($58.1 \pm 18.6$ vs. $24.9 \pm 5.0$ units MPO/g protein, $P < 0.05$). A small rise in neutrophil and macrophage infiltration was evident at 24 h in sham-operated mice. This is most likely due to the surgical procedure itself causing a small inflammatory response. At 1 wk post-WBIRI, MPO levels decreased and were comparable between the WBIRI and sham-operated group ($11.3 \pm 0.4$ vs. $11.9 \pm 5.0$ units MPO/g protein).

**T cell-deficient mice are protected from post-WBIRI renal dysfunction and structural injury.** T cells have recently been found to be important mediators of renal injury following isolated kidney IRI (4, 31, 42). We therefore hypothesized that the T cell would modulate

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**Fig. 2.** Mice undergoing whole body ischemia-reperfusion injury (WBIRI) have worse renal injury than sham-operated mice. Serum creatinine (SCr) was significantly higher at 24 h ($*P < 0.05$) after WBIRI (●) compared with SCr in sham-operated mice (○). In all experiments, SCr (mg/dl) was measured from tail blood samples obtained from mice at 0 (pre-WBIRI), 24, and 72 h post-WBIRI; n = 6/group.

**Fig. 3.** Histological assessment ($\times 400$) of tubular injury at 24 h and 1 wk after WBIRI. A: at 24 h, sham-operated mice show no tubular injury. B: in contrast, 24-h post-WBIRI mice show extensive tubular damage. C: at 1 wk, sham-operated mice again show no tubular injury. D: in post-WBIRI mice at 1 wk, there is still major tubular damage present.

**Fig. 4.** Leukocyte infiltration into kidney at 24 h and 1 wk post-WBIRI. At 24 h post-WBIRI, there is a significant increase in leukocyte infiltration, as measured by myeloperoxidase (MPO) level, in mice undergoing WBIRI (filled bars) compared with sham-operated mice (open bars) ($*P < 0.05$). By 1 wk post-WBIRI, these levels are comparable between the WBIRI and sham groups; n = 6 (24 h) and 4 (1 wk) per group.
The injury response following WBIRI. T cell-deficient mice showed a significant decrease in SCr following WBIRI compared with wild-type littermates (Fig. 5). Within 24 h of WBIRI, T cell-deficient mice exhibited a significant functional protection (0.92 ± 0.17 vs. 1.90 ± 0.21 mg/dl, *P* < 0.05). All sham-operated mice showed an increase above baseline levels in SCr. Post-WBIRI kidney histology for T cell-deficient mice and wild-type mice is shown in Fig. 6. At 24 h after WBIRI, there is severe damage in the wild-type kidney (Fig. 6A). However, the T cell-deficient mouse kidney shows a reduction in tubular injury (Fig. 6B) compared with the wild type.

**MPO levels in T cell-deficient mice post-WBIRI.** To begin to explore the mechanism of how T cells mediate renal injury following WBIRI, we evaluated tissue MPO levels. MPO analysis of kidney sections at 24 h post-WBIRI revealed that neutrophil and macrophage infiltration is present in both T cell-deficient and wild-type mice post-WBIRI (Fig. 7). Sham-operated animals show baseline levels of MPO (Fig. 7). These results were similar to previously found results in the isolated kidney ischemia model where following bilateral renal ischemia there was no difference in neutrophil and macrophage infiltration between T cell-deficient mice and wild-type mice (4).

**Role of inflammatory cytokines post-WBIRI.** Cytokines and adhesion molecules can mediate the course of renal IRI, and hence the protection seen in T cell-deficient mice may, in part, have been mediated by these proinflammatory factors. We therefore studied the cytokine expression profiles of T cell-deficient mice vs. wild-type mice at 24 h post-WBIRI. We chose four important inflammatory cytokines: IL-6, ICAM-1, TNF-α, and IL-1β. These cytokines have previously been shown to be upregulated following renal IRI (21). Figure 8 is a representative gel that shows cytokine expression of T cell-deficient and wild-type mice before WBIRI (0 h) and at 24 h post-WBIRI. T cell-deficient mice show reduced levels of cytokines at 24 h compared with wild-type mice. Further quantitative analysis was performed, and ICAM-1 expression was significantly reduced in T cell-deficient mice post-WBIRI compared with wild-type mice (Fig. 9).

**DISCUSSION**

This study demonstrates that ARF develops in a reproducible cardiac arrest-induced WBIRI model in mice. This is characterized by a rise in SCr, tubular injury, an influx of leukocytes, and upregulation of proinflammatory mediators following WBIRI, which was not found in sham-operated mice. Interestingly, the time of ischemia required to develop these findings is a surprising one-third of the ischemic time required to develop the same findings in an isolated model of renal IRI (5, 19, 26, 33). Furthermore, T cell-deficient *nu/nu* mice are markedly protected from renal injury after WBIRI. This protection is characterized by a decrease in SCr post-WBIRI and reduced tubular structural damage. A possible mechanism of protection involves a reduced ICAM-1 upregulation post-WBIRI in T cell-deficient mice.
Native kidney ARF in humans is frequently multifactorial, with ischemia, sepsis, and medications all overlapping. However, it is important to dissect the mechanisms of each one separately. In addition, a major aspect of ischemia in humans is that it occurs throughout the whole body. Due to the lack of effective therapy for ARF, there is an urgent need to develop in vivo experimental models of ARF that can be used as a platform to develop new therapies in humans (22, 35). The models should be relevant and reproducible and should improve with the present models of simple renal artery clamping. In addition, establishing such a model in the mouse would give a significant flexibility to test both interventions and genetic modifications. On the basis of these principles and our previous experience in rodent models of isolated renal IRI, we characterized renal responses in a WBIRI model that is based on a clinically common and important occurrence, cardiac arrest and resuscitation. ARF occurs in ~30% of patients who initially survive an in-hospital cardiac arrest (25).

During WBIRI, injury occurs in multiple organs simultaneously. The release of injury products into the circulation as well as the defective clearance function after shock can serve as additive stimuli for ischemic injury. WBIRI has been previously shown to also induce platelet, neutrophil, and endothelial activation (11). During development of the present model, we observed that 10 min of WBIRI was sufficient to cause a reproducible rise in SCr and renal tubular injury in the mouse. In the isolated renal artery clamping model, at least 30 min of total cessation of blood flow are needed to create similar rises in SCr (5, 19, 33). In addition, histological changes produced after 10 min of WBIRI are as pronounced as those after 30 min of renal artery clamping. The pattern of injury in the WBIRI model was similar to that found in isolated renal artery clamping with generalized changes occurring in the corticomedullary junction, whereas human ARF is characterized by a more patchy pattern. Given that a generalized pattern of tubular injury is seen in different rodent models, it is possible that the rodent models favor a generalized tubular injury after similar stimuli that would produce patchy changes in human kidney. Nevertheless, the significant decrease in time required to produce ischemic ARF is likely due to the combined effects of injury to distant organs and the

![Kidney cytokine expression profiles of T cell-deficient and wild-type mice at 0 (pre-WBIRI) and 24 h post-WBIRI as analyzed by RNase protection assay. Pre-WBIRI levels of all cytokines analyzed show comparable levels. At 24 h post-WBIRI, wild-type mice show an increase in all cytokines measured. T cell-deficient mice at 24 h also show an increase in cytokine expression, however, expression appears less than in wild-type mice; n = 3 (0 h) and 4 (24 h WBIRI) per group.]

![Semiquantitative analysis of ICAM-1, IL-6, IL-1β, and TNF-α expression in the kidney 24 h post-WBIRI. At 0 h, T cell-deficient and wild-type mice show equal levels of cytokine expression. At 24 h post-WBIRI, there is a significant decrease in ICAM-1 expression in T cell-deficient mice (*P < 0.05) compared with the wild type; n = 3 (0 h) and 4 (24 h WBIRI) per group. All other cytokines show no significant difference between T cell-deficient and wild-type mice at 24 h post-WBIRI.]

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inflammatory mediators they are activating. This important distinction from the isolated renal artery clamp model may be important in the translation of experimental studies to human trials. In addition, development of ARF frequently occurs in hospital situations when there is no documented drop in blood pressure or any other inciting agent. This observation can explain why even a very short period of severe hypotension can be missed when blood pressures are taken hours apart. The mechanism by which WBIRI leads to a marked susceptibility to ARF compared with isolated renal artery clamping is unknown, but it could be due to inflammatory mediators such as release of bowel proteins into the circulation (1).

Inflammation has recently emerged as one of the major pathophysiological pathways mediating ischemic ARF. Both cellular and soluble mediators have been implicated (29). We therefore evaluated the effects of WBIRI on renal inflammation that occur in conjunction with renal dysfunction. A significant increase in renal MPO levels was found at 24 h in mice undergoing WBIRI compared with the sham group. This reflects an active phagocyte infiltration and is a phenomenon also found following renal artery clamping for 30 min. Interestingly, at 7 days after WBIRI when MPO levels returned close to baseline, there was a marked mononuclear leukocyte infiltration into the interstitium, consistent with the delayed T cell infiltration observed in isolated renal artery clamping-induced ARF. We also found an increase in gene expression for ICAM-1, TNF, IL-1β, and IL-6, all proinflammatory pathways that have been directly implicated in the pathogenesis of ischemic ARF and contribute to the pronounced inflammatory response we found in this model. Thus WBIRI-induced ARF is characterized by significant inflammation in the kidney.

A number of studies have recently identified the T cell, particularly the CD4+ T cell, as an important modulator of experimental ischemic ARF after isolated kidney clamping (4, 7, 31, 38, 42). The mechanisms are only starting to be elucidated, but they may involve initial microvascular activation followed by upregulation of distal inflammatory events (29). We therefore tested the hypothesis that T cells could be important modulators of ischemic ARF after WBIRI. We found that T cell-deficient mice had a marked attenuation of renal dysfunction and structural injury. In an effort to understand the underlying mechanisms for this protection, we measured MPO levels in nu/nu mice. However, MPO levels were unchanged, much like the effects of T cell absence on the isolated renal clamp-induced ARF (4). Thus neutrophil and macrophage infiltration in this model is unlikely to be the mechanism involved in the protection seen in T cell-deficient mice. We found that nu/nu mice had an attenuation of ICAM-1 expression, which is consistent with the adhesion molecule upregulation modulation by T cells previously described in gut ischemia (14). ICAM-1 is found on leukocytes, epithelial cells, endothelial cells, and many other cell types (23). Interruption of the ICAM-1 pathway has led to substantial protection in models on cardiac (23, 41) muscle (36) and kidney IRI (12, 18, 19, 32). The presumed mechanism of protection has been the blockade of neutrophil recruitment to the site of injury; however, ICAM-1 has been shown to mediate other functions including signal transduction (17) and antigen presentation (16). It has also been recently demonstrated that ICAM-1 expressed on a T cell can deliver a costimulatory signal into that T cell (6).

A potential variable in our study that deserves highlighting was the use of epinephrine in the resuscitation procedure, which is clinically routine after cardiac arrest. High serum levels of epinephrine have been reported to induce ARF (10). This is due to the vasoconstriction mediated by epinephrine. However, both wild-type mice and T cell-deficient mice received similar doses of epinephrine (T cell-deficient mice: 0.36 ± 0.02 μg/g body wt; wild-type mice: 0.37 ± 0.02 μg/g body wt). To further investigate the role of epinephrine in our model, we intravenously injected epinephrine at similar concentrations into normal mice and followed their SCr for 3 days. After the injection of epinephrine, there was no rise in SCr, indicating that the epinephrine was not contributing to the ARF observed in our model. Another potential variable is the kidney effects of using potassium chloride to produce cardiac arrest. Previous animal work showed that potassium is released from cells during both ischemia and hypoxic insults (24). We found that potassium concentrations increase from 4.2 to 8.0 mM after 5 min of ROSC. Within 20 min, potassium levels decrease to 5.4. Although we feel that the transient rise in serum potassium was unlikely to alter the renal response to injury, this cannot be excluded. It is interesting to note that a previous canine study found a rise in serum potassium immediately after cardiac arrest even when a nonpotassium method of inducing arrest was used (24).

Even though we focused on WBIRI, human allograft ARF is likely also affected by the changes occurring during brain death. Brain death, a central catastrophe unique to the cadaver organ donor, produces profound physiological and structural derangements in the peripheral tissues of experimental animals both before and after placement in the recipient (28, 39). These include massive upregulation of major histocompatibility antigens, adhesion molecules, cytokines, and other acute-phase proteins.

WBIRI induced by cardiac arrest is a model where entire body integrative events are taken into consideration during ARF, much like occurs in humans. WBIRI-induced ARF is characterized by cellular and soluble inflammation, and the threshold for kidney dysfunction is greatly reduced compared with isolated renal artery clamping. In addition, T cells are an important modulator of this process. These findings have important ramifications for both an understanding of ischemic ARF as well as the pathogenesis of distant organ injury after cardiac arrest.

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REFERENCES


