Increased myocardial ischemia-reperfusion injury in renal failure involves cardiac adiponectin signal deficiency

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CHRONIC KIDNEY DISEASE (CKD) is a major public health problem worldwide that has been repeatedly documented to be associated with increased risk for cardiovascular morbidity and mortality. It has been increasingly apparent that accelerated cardiovascular disease is prevalent in individuals with CKD and has become the leading complication of renal insufficiency. In particular, the incidence of acute myocardial infarction among patients with CKD is more than twice that of patients without CKD (28). Therefore, the prevention and treatment of cardiac insult are critical considerations in the management of individuals with CKD.

Adiponectin (APN), a 30-kDa adipocyte-derived vasoactive peptide involved in the regulation of inflammation and energy metabolism, has shown beneficial effects on cardiovascular disorders (11). It is highly abundant in the circulation and exists as trimers, hexamers, or high-molecular-weight multimers (22). Hypoadiponemia has been observed in individuals with increased body fat mass and various obesity-related pathological disorders such as insulin resistance, type 2 diabetes mellitus, hypertension, and cardiovascular disease (7). Previous studies by us as well as others have reported that plasma levels of APN decline following myocardial ischemia-reperfusion (MI/R) injury and that exogenous administration of APN protects the heart via inhibiting oxidative/nitritive stress (36), suppressing cardiac hypertrophy and interstitial fibrosis, and protecting against myocyte and capillary loss (30). However, in patients with CKD, plasma levels of APN are significantly increased and are inversely related to the risk of cardiovascular morbidity and mortality. The mechanism underlying the paradoxical relationship between high adiponectin and poor cardiac outcome remains unclear. More importantly, there are no publications to date that evaluate the manipulation of APN level on cardiovascular outcome in the presence of CKD.

Therefore, the purposes of the present study were to 1) determine the changes in plasma and urinary APN in a mouse model of renal failure and the cardiac responses to I/R injury and 2) delineate the role of APN in I/R in the context of renal failure and the underlying mechanisms using APN-knockout (APN-KO) mice and administration of human recombinant globular domain of adiponectin (gAd).

MATERIALS AND METHODS

Experimental protocols. All experiments were performed in adherence to the National Institutes of Health Guidelines on the Use of Laboratory Animals and were approved by the Fourth Military Medical University Committee on Animal Care. Cardiac-specific APN-knockout (APN-KO) mice of both sexes were generated and back-crossed as described previously (6, 31). Age (8–10 wk) and sex-matched C57B16/J littermates [wild-type (WT) Experimental Animal Center, Fourth Military Medical University] were used as controls. A flow chart diagram was shown in Fig. 1. Both APN-KO and WT mice were randomized to receive either vehicle (PBS, pH 7.5) or human recombinant gAd (2 μg/g body wt) (36) via intraperitoneal injection once daily for 7 consecutive days.
SN. Animals were randomized to receive a two-stage SN or a sham procedure according to the previously published protocol, with slight modifications (18, 23, 25, 27). In brief, animals were anesthetized with 2% isoflurane inhalation with an isoflurane delivery system (Viking Medical, Medford, NJ). Via a left paramedian incision, the left kidney was decapsulated and approximately two-thirds resected, leaving adrenal gland intact. Hemostasis was achieved with direct compression, and the remaining kidney was returned to the retroperitoneal space before the incision was closed. The animals were allowed 14 days to recover before undergoing the second stage of the procedure, right total nephrectomy, which followed a similar procedure as described above via a right paramedian incision. Sham-operative animals (sham SN) received the same surgical protocol except for nephrectomy. Creation of SN animals was carried out by a single operator to reduce variability in renal function within groups.

Induction of MI/R. Mice were anesthetized with 2% isoflurane, and myocardial infarction (MI) was produced by temporarily exteriorizing the heart via a left thoracic incision and placing a 6-0 silk suture slipknot around the left anterior descending coronary artery. After 30 min of MI, the slipknot was released, and the myocardium was reperfused for 3 (for myocardial apoptosis evaluation) or 24 h (for cardiac function and infarct size determination) (36). Sham-operated control mice (sham MI/R) underwent the same surgical procedures, except that the suture placed under the left coronary artery was not tied. At the end of reperfusion, the suture around the coronary artery was retied, and 2% Evans Blue dye was injected into the left ventricular cavity. The heart was quickly excised, and the I/R cardiac tissue was isolated and processed per the protocols described below.

Biochemical assays. Mice were placed in metabolic cages to collect spontaneously voided 24-h urinary samples between 8 and 11 AM at 24 h, 72 h, 1 wk, 2 wk, and 4 wk after subtotal nephrectomy. Blood samples were obtained from the retroorbital sinus from these mice at 24 h, 72 h, 1 wk, 2 wk, and 4 wk after nephrectomy. Plasma creatinine, urinary creatinine, urea nitrogen, urinary albumin, and cystatin C levels were measured using commercial assay kits to evaluate the extent of renal injury after subtotal nephrectomy. To standardize urinary albumin excretion, albuminuria was expressed as milligrams of urinary albumin per gram of urinary creatinine. Plasma or urinary concentrations of total APN were determined using mouse total APN ELISA kit (R & D Systems and Biovendor Laboratories, respectively) per the manufacturer’s instructions. Urinary adiponectin levels (ng/ml) were adjusted for urinary creatinine excretion and expressed as micrograms per gram of creatinine for statistical analysis.

Determination of cardiac function, myocardial infarct size, and apoptosis. At the end of the 24-h reperfusion period, mice were reanesthetized, and cardiac function was determined by noninvasive echocardiography (VisualSonics VeVo 2100 imaging system). Upon completion of the functional determination, the ligature around the coronary artery was retied, and MI size was determined by the Evans blue/TTC double-staining method (35, 37). Myocardial apoptosis was determined within the entire I/R region via TUNEL staining and caspase-3 activity assays, as described previously (35).

Determination of total nitric oxide, nitrotyrosine content, and superoxide production. At 4 wk after SN, hearts were excised and homogenized. The tissue nitric oxide (NO) in the supernatant was measured with nitrate reductase kits (Jiancheng Bioengineering, Nanjing, China). Nitrotyrosine content, a footprint of in vivo peroxynitrite formation and an index for nitrosative stress, was determined by ELISA, and myocardial superoxide content was determined by lucigenin-enhanced luminescence, as described in our previous study (36). In situ superoxide detection was performed with dihydroethidium (DHE) staining (Molecular Probes, Carlsbad, CA), as described previously (36).

Western blot analysis. At 4 wk after SN, proteins from cardiac tissue homogenates were separated for immunoblotting analysis. Primary antibodies included antibodies against endothelial NO synthase (eNOS), phosphorylated eNOS (p-eNOS), inducible NOS (iNOS), AdipoR1 (Abcam, Cambridge, MA), AdipoR2 (LifeSpan Biosciences, Seattle, WA), p-AMPK, and total AMPK (Cell Signaling Technology, Danvers, MA). Nitrocellulose membranes were then incubated with HRP-conjugated anti-rabbit immunoglobulin G antibody (Santa Cruz Biotechnology) for 1 h. Blots were developed with an ECL-Plus chemiluminescence reagent kit and visualized with UVP Bio-Imaging Systems. Blot densities were analyzed with Vision Works LS Acquisition and Analysis Software.

Immunohistochemistry. Pараformaldehyde-fixed tissues were cut into semithin sections (about 4–5 μm thick) and stained with antibodies against nitrotyrosine and APN. Immunostaining was developed with a Vectastain ABC kit (Vector Laboratories, Burlingame, CA).

Statistical analysis. All values in the text and figures are presented as means ± SE of n independent experiments. All data (except for Western blot density) were subjected to ANOVA followed by Bonferroni correction for post hoc t-test. Western blot densities were analyzed with the Knusl-Wallis test followed by a Dunn post hoc test. P values <0.05 were considered statistically significant.

RESULTS

Renal failure is induced successfully by SN. SN mice exhibited significantly higher plasma urea nitrogen, creatinine, and cystatin C, as well as urinary albumin level, than normal mice after 24 h of SN, whereas creatinine clearance was significantly lower (Table 1), suggesting that severe renal impairment resulted from SN.

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Table 1. SN induces renal dysfunction

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<th>Sham-Operated WT Mice</th>
<th>WT Mice With SN</th>
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<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>30.11 ± 9.8</td>
<td>71.7 ± 14.7**</td>
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<tr>
<td>Plasma creatinine, mg/dl</td>
<td>0.11 ± 0.05</td>
<td>0.24 ± 0.05**</td>
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<td>Creatinine clearance, µl/min</td>
<td>213.3 ± 30.8</td>
<td>108.5 ± 30.0**</td>
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<tr>
<td>Cystatin C, mg/l</td>
<td>0.04 ± 0.009</td>
<td>0.06 ± 0.016**</td>
</tr>
<tr>
<td>Urinary albumin, mg/g creatinine</td>
<td>33.9 ± 9.1</td>
<td>54.2 ± 11.5*</td>
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Data are means ± SE; n = 6–8/group. SN, subtotal nephrectomy; WT, wild type. Blood urea nitrogen, plasma creatinine, plasma cystatin C, urinary albumin levels, and creatinine clearance at 24 h in sham-operated WT mice and WT mice with SN. *P < 0.05 and **P < 0.01 vs. sham-operated WT mice.

APN concentration increased in plasma and urine but decreased in kidney following SN. Plasma total APN levels declined slightly at 24 h after SN and achieved significant reduction at 72 h. This trend was reversed at 1 wk and increased gradually through the remainder of the study (4 wk) (Fig. 1). Urinary total APN concentration presented a continuous increase after SN (4 wk) (Fig. 2B). In addition, a strong staining for APN was detected on the endothelial surface of both intrarenal arteries/arterioles and glomerular and peritubular capillaries in sham mice (Fig. 2C), whereas the SN mice shows markedly decreased APN staining (Fig. 2C). These results indicated that SN resulted in elevated levels of APN in both plasma and urine but reduced concentration of APN in glomeruli and interstitium.

MI/R injury is increased in SN mice. We next investigated whether SN may influence MI/R injury, and thus we induced 30 min of ischemia followed by 24 h of reperfusion in SN mice and determined infarct size and cardiac function. MI/R resulted in significant cardiomyocyte death (>45% of area at risk) and impaired cardiac function. Compared with sham SN mice, SN mice displayed significantly depressed cardiac function (Fig. 3, A–D) and enlarged infarct size (Fig. 3E). Moreover, TUNEL staining and caspase-3 activity assay in I/R cardiac tissue demonstrated markedly increased cardiomyocyte apoptosis in SN mice following MI/R mice (Fig. 3, F–H). These data, in line with previous clinical findings, demonstrated increased susceptibility to MI/R injury in the context of renal dysfunction.

MI/R injury is increased markedly in APN-KO mice with SN and is rescued by administration of gAd but not fAd. Data from our previous study as well as others have demonstrated that APN protects hearts from MI/R injury, and intraperitoneal administration of both human recombinant gAd and fAd is capable of improving cardiac function and inhibiting myocyte apoptosis (32, 36). However, it has been suggested that in the context of renal dysfunction, the supplement of gAd is likely superior to fAd, as gAd lacks NH2-terminal domains and thus is free of cystatin C binding and inhibition (7). To investigate whether APN plays a role in the detrimental effects of SN on the cardiac response to I/R injury, we first included APN-KO mice with SN and assessed their response to MI/R. Compared

Fig. 2. APN levels in plasma, urine, and renal tissue after subtotal nephrectomy (SN). A and B: plasma total APN (A) and urinary total APN levels (B) were determined by ELISA at indicated time points after SN. C: APN expression in the renal tissue was determined by immunohistochemical analyses in sham-operated and SN mice at 4 wk after surgery; n = 6–8/group. *P < 0.05 and **P < 0.01 vs. sham-operated mouse.
Fig. 3. Myocardial ischemia-reperfusion (MI/R) injury is increased in SN mice. A–D: left ventricular ejection fraction (LVEF; A), left ventricular fraction shortening (LVFS; B), left ventricular internal diameters of diastole (LVIDd; C), and left ventricular internal diameters of diastole (LVIDds; D) were determined by echocardiograph as indexes for cardiac function at the end of the 24-h reperfusion. E: myocardial infarct size was assessed by Evans blue/TTC double staining. F–H: cardiomyocyte apoptosis was determined by TUNEL assay and caspase-3 assay. Sham, sham SN/H11001 sham MI/R; SN, SN/H11001 sham MI/R; MI/R, sham SN/H11001 MI/R (n = 6–8/group). *P < 0.05 and **P < 0.01 vs. sham. #P < 0.05 and ##P < 0.01 vs. MI/R mice.
Fig. 4. Myocardial reperfusion injury is increased markedly in APN-knockout (KO) mice with SN and is rescued by administration of gAd but not fAd. A–D: LVEF (A), LVFS (B), LVIDd (C), and LVIDds (D) were determined by echocardiograph as indexes for cardiac function at the end of the 24-h reperfusion. E: myocardial infarct size was assessed by Evans blue/TTC double staining. F–H: cardiomyocyte apoptosis was determined by TUNEL assay and caspase-3 assay.

WT, wild type (n = 6–8/group). *P < 0.05 and **P < 0.01 vs. MI/R WT mice with SN. #P < 0.05 and ##P < 0.01 vs. MI/R KO mice with SN.
with WT mice with SN, cardiac function was further depressed and infarction further enlarged in KO mice with SN. To further assess the potential protection by exogenous APN, we administered gAd or fAd for 7 days immediately after SN. gAd treatment significantly improved cardiac function (Fig. 4, A–D), reduced infarct size (Fig. 4E), and cardiomyocyte apoptosis, as evidenced by reduced TUNEL staining and caspase-3 activity (Fig. 4, F–H) in both WT and KO mice with SN. In contrast, fAd supplement resulted in no significant change in post-I/R injury. These interesting findings suggested that, although renal failure is accompanied by plasma accumulation of APN, endogenous APN is an essential component of stress adaption, and exogenous gAd supplement but not fAd is cardioprotective for MI/R injury.

SN increases myocardial NO production via upregulation of iNOS expression. Previous studies have demonstrated that adiponectin stimulates NO production via Akt-mediated eNOS phosphorylation (2, 4, 8, 21). However, data from the present study showed that total NO production was increased markedly in cardiac tissue obtained from both WT and KO mice with SN and reduced by treatment with gAd (Fig. 5A). Because it is known that low concentration of NO released from eNOS or NO donors is antiapoptotic and cardioprotective, whereas excess production of NO is responsible for ONOO⁻ synthesis, a major source of cellular nitrative stress (6), we proceeded to identify the molecular sources responsible for this increased NO production, and eNOS/iNOS protein expression and eNOS phosphorylation were determined. There was no change in myocardial eNOS expression in all animals. However, eNOS phosphorylation was reduced following SN and increased by gAd treatment (Fig. 5B). In contrast to eNOS phosphorylation, the iNOS expression was elevated following SN, and more importantly, the SN-induced increase in iNOS expression was blocked by gAd treatment (Fig. 5C). Together, these results delineated that SN reduced eNOS phosphorylation and upregulated iNOS expression, with both contributing to increased NO production in cardiac tissue, and gAd treatment produced the opposite effects.

SN increases myocardial O₂⁻ and peroxynitrite production, which can be reversed by gAd administration. Adiponectin has been implicated to alleviate oxidative stress in hemodialysis patients (16). Our previous study has reported that APN exhibits cardioprotective effects after I/R through the reduction of oxidative/nitrative stress (36). Therefore, we hypothesized that increases in O₂⁻ and peroxynitrite production played a key role in mediating SN-induced myocardial injury. To test this hypothesis, myocardial O₂⁻ and peroxynitrite production in SN mice were determined. As illustrated in Fig. 6, superoxide and peroxynitrite induced by SN were further intensified in cardiac tissue obtained from WT and KO animals, and gAd treatment attenuated both superoxide and peroxynitrite production.

Change in cardiac AdipoR/AMPK signaling following SN. Our present study has addressed increased MI/R injury despite increased plasma and urinary APN levels in SN mice. Because AMPK is a downstream signaling molecule known to be partially responsible for APN cardioprotection, and I/R injury has been indicated to associate with decreased AdipoR1 expression (26), we next sought to explore the mechanism un-
derlying the increased MI/R injury induced by renal dysfunction, with particular focuses on the APN/AdipoR/AMPK signaling. As illustrated in Fig. 7, AdipoR1 expression was reduced 4 wk after SN, whereas AdipoR2 expression showed no significant change. More importantly, AMPK activation was also inhibited after SN and exogenous gAd supplementation reversed this change.

**DISCUSSION**

We have made several important observations in the present study. First, MI/R injury is amplified in the presence of chronic renal failure, as evidenced by impaired cardiac contractile function, enlarged infarct size, and increased cardiomyocyte apoptosis in a mouse model of subtotal nephrectomy. This phenotype is paradoxically in parallel with significantly increased plasma and urinary levels of APN, an adipocyte-derived hormone known to be cardioprotective. Second, the MI/R injury in mice with renal failure is further intensified in the absence of cardiac APN and is ameliorated markedly by exogenous supplement of the human recombinant globular domain of APN but not full-length APN, which thus provides the first evidence for the benefits of gAd administration after renal failure on cardiovascular outcomes. Finally, we have demonstrated increased myocardial oxidative and nitrative stress with downregulated APN/AdipoR1/AMPK signaling following renal dysfunction, which may explain in part the adverse effects of renal failure on MI/R injury and, more importantly, the rescued phenotype afforded by gAd treatment.

By successfully establishing a mouse model of subtotal nephrectomy, we confirmed with the previously published observation the increased accumulation of APN in the blood circulation in the context of renal failure. Indeed, several clinical studies have demonstrated an inverse association between circulating APN and renal function (17, 24, 34, 38, 42). Because the gradual increase in plasma APN concentration parallels the progression of CKD, the highest levels are usually found in end-stage renal disease patients (17, 24). Recent evidence indicates that APN may also serve as an important mediator of the progressive renal vascular sclerosis, a key feature of CKD, and is thus viewed as an independent predictor of CKD progression (14). However, the reasons for the observed hyperadiponectinemia are not fully understood. Potential explanations include reduced kidney clearance, leading to impaired biodegradation and abolition of APN (9, 15), and metabolic derangements in CKD (42). Volume overload with higher levels of natriuretic peptides (39) and salt retention (12) was also suggested to be contributive to high circulating APN levels in the complex uremic milieu.

In addition to increased plasma APN, we also observed elevated urinary APN levels despite a remarkable decline in local expression of APN in glomerular endothelium. We propose that the increase in urinary APN levels probably results from enhanced filtration of circulating APN through the changes of glomerular permselectivity and intraglomerular hydraulic pressure. It should be noted that given the decreased plasma APN level during the initial 72 h after SN, the elevated renal clearance of APN may represent a robust compensatory mechanism for acute renal dysfunction. However, as renal injury persists, the disposal ability of kidney may fail to proportionate with increased accumulation of plasma APN. It
has been suggested that binding of APN to the glomerular endothelium in nondiabetic kidneys could be essential for kidney homeostasis and that the appearance of urinary APN was associated with loss of glomerular APN in diabetic nephropathy (40). A recent study by Ohashi et al. (19) reported that APN prevented glomerular and tubulointerstitial injury by inhibiting inflammation and oxidative stress.

Accumulating clinical data have demonstrated reduced tolerance to myocardial ischemia in the context of renal failure, as evidenced by high mortality from myocardial infarction in patients with impaired renal function (5). The present study also revealed aggravated MI/R injury in mice with subtotal nephrectomy, as evidenced by impaired cardiac function, enlarged infarct size, and increased cardiomyocyte apoptosis. Therefore, hyperadiponectinemia as the result of renal insufficiency is accompanied by apparently unfavorable cardiovascular outcome. Paradoxically, APN has been widely implicated to exert protective effects on various cardiovascular disorders (13, 20). In particular, low plasma APN levels in both healthy individuals and CKD patients are strongly associated with ischemic heart disease (3, 17, 38, 40). Thus an important question arises regarding the exact role of APN in renal failure and the underlying mechanisms. Intriguingly, data from APN-KO mice in this study indicated further increased susceptibility to MI/R injury in the absence of cardiac APN, and more importantly, exogenous administration of APN using gAd significantly improved cardiac response to MI/R in both WT and APN-KO mice with subtotal nephrectomy. The cardiac benefits of exogenous gAd are unexpected given the widely acknowledged unfavorable role of hyperadiponectinemia in renal failure. More intriguingly, the failure of fAd supplement to reverse MI/R injury is in contrast to previous evidence that both human recombinant gAd and fAd treatment protect hearts from MI/R injury (32, 36). Previous reports have suggested that cystatin C, at high concentrations corresponding to renal failure, is able to bind APN and abolish the protective effects of APN (10, 15, 33). Therefore, exogenous supplement of gAd is likely superior to full-length APN in the context of renal dysfunction, as gAd lacks NH2-terminal domains and is thus free of cystatin C binding and inactivation. Our finding that gAd (instead of fAd) supplement could significantly reverse MI/R injury points to another possibility that endogenous APN is largely inactive in renal failure due to cystatin C blockage but achieved a high level in blood circulation.

Previous studies have demonstrated that APN increases NO production by activating the AMPK/Akt/eNOS signaling pathway (2, 4, 8, 21). Data from our present study showed that gAd significantly improved cardiac response to MI/R in both WT and APN-KO mice with subtotal nephrectomy. The cardiac benefits of exogenous gAd are unexpected given the widely acknowledged unfavorable role of hyperadiponectinemia in renal failure. More intriguingly, the failure of fAd supplement to reverse MI/R injury is in contrast to previous evidence that both human recombinant gAd and fAd treatment protect hearts from MI/R injury (32, 36). Previous reports have suggested that cystatin C, at high concentrations corresponding to renal failure, is able to bind APN and abolish the protective effects of APN (10, 15, 33). Therefore, exogenous supplement of gAd is likely superior to full-length APN in the context of renal dysfunction, as gAd lacks NH2-terminal domains and is thus free of cystatin C binding and inactivation. Our finding that gAd (instead of fAd) supplement could significantly reverse MI/R injury points to another possibility that endogenous APN is largely inactive in renal failure due to cystatin C blockage but achieved a high level in blood circulation.

Previous studies have demonstrated that APN increases NO production by activating the AMPK/Akt/eNOS signaling pathway (2, 4, 8, 21). Data from our present study showed that APN reduced myocardial NO production via downregulation of iNOS expression and upregulation of eNOS phosphorylation. These results are supported by our previous studies that

Fig. 7. Change in cardiac APN receptor (AdipoR) expression after SN. Cardiac expression of AdipoR1 (A), AdipoR2 (B), and p-AMPK/AMPK (C) expression determined by Western blot analysis; n = 4 –5/group. *P < 0.05 and **P < 0.01 vs. sham mice. #P < 0.05 and ##P < 0.01 vs. WT mice with SN. §P < 0.05 vs. KO mice with SN.
APN, under physiological conditions, increases NO production from eNOS and exerts vasodilatory/cardioprotective effects. On the contrary, under pathological conditions where iNOS expression is stimulated, APN inhibits NO overproduction by inhibiting iNOS expression and thus protects the heart from nitrative stress (36). Furthermore, the benefits of reducing excessive NO production lie in the fact that the NO/O$_2^-$ reaction with subsequent production of peroxynitrite results in oxidative/nitrative tissue injury (1). In the present study, we found that myocardial O$_2^-$ production, as well as peroxynitrite formation, was increased markedly in the APN-KO animals and reduced by administration of gAd, suggesting that the cardioprotective effect of gAd may derived, at least in part, from its inhibition of oxidative/nitrative stress via inhibiting O$_2^-$ and peroxynitrite production.

APN is known to exert its effects primarily via two membrane receptors, AdipoR1 and AdipoR2, the former initiating downstream signaling largely through the activation of AMPK (11). In the present study, both myocardial AdipoR1 expression and AMPK activation decreased after SN, although circulating APN levels increased. The downregulation of AdipoR1/AMPK signaling in the presence of hyperadiponemia suggested reduced APN ligand/receptor reactivity and compromised downstream signaling in local myocardium, namely “myocardial adiponectin resistance” (29). Thus we speculated that the increased circulating APN level following renal failure may also represent a compensatory mechanism for the impaired intracellular APN signaling, which, however, is apparently insufficient to improve cardiac outcomes due to the oxidative/nitrative stress induced by renal dysfunction, and the cardiac benefits of exogenous gAd supplement may result largely from the upregulation of myocardial AdipoR1/AMPK signaling. These findings may provide novel insights into the paradoxical connection between hyperadiponemia and poor cardiac outcome in renal dysfunction from previous clinical observations.

To the best of our knowledge, this is the first study that has investigated the dynamic changes of plasma, urine, and kidney APN level as well as impaired cardiac APN/AdipoR1/AMPK signaling in the presence of hyperadiponemia during the development of renal failure. The present study demonstrates that renal dysfunction increases cardiac susceptibility to I/R injury, which is associated with downregulated APN/AdipoR1/AMPK signaling and increased oxidative/nitrative stress in local myocardium, and provides the first evidence for the protective role of exogenous supplement of gAd on MI/R outcomes in renal failure.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

REFERENCES


