Endothelin-A receptor blockade slows the progression of renal injury in experimental renovascular disease

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Kelsen S, Hall JE, Chade AR. Endothelin-A receptor blockade slows the progression of renal injury in experimental renovascular disease. Am J Physiol Renal Physiol 301: F218–F225, 2011. First published April 6, 2011; doi:10.1152/ajprenal.00089.2011.—Endothelin (ET)-1, a potent renal vasoconstrictor with mitogenic properties, is upregulated by ischemia and has been shown to induce renal injury via the ET-A receptor. The potential role of ET-A blockade in chronic renovascular disease (RVD) has not, to our knowledge, been previously reported. We hypothesized that chronic ET-A receptor blockade would preserve renal hemodynamics and slow the progression of injury of the stenotic kidney in experimental RVD. Renal artery stenosis, a major cause of chronic RVD, was induced in 14 pigs and observed for 6 wk. In half of the pigs, chronic ET-A blockade was initiated (RVD+ET-A, 0.75 mg·kg−1·day−1) at the onset of RVD. Single-kidney renal blood flow, glomerular filtration rate, and perfusion were quantified in vivo after 6 wk using multidetector computer tomography. Renal microvascular density was quantified ex vivo using three-dimensional microcomputer tomography, and growth factors, inflammation, apoptosis, and fibrosis were determined in renal tissue. The degree of stenosis and increase in blood pressure were similar in RVD and RVD+ET-A pigs. Renal hemodynamics, function, and microvascular density were decreased in the stenotic kidney but preserved by ET-A blockade, accompanied by increased renal expression of vascular endothelial growth factor, hepatocyte growth factor, and downstream mediators such as phosphorilated-Akt, angiopoietins, and endothelial nitric oxide synthase. ET-A blockade also reduced renal apoptosis, inflammation, and glomerulosclerosis. This study shows that ET-A blockade slows the progression of renal injury in experimental RVD and preserves renal hemodynamics, function, and microvascular density in the stenotic kidney. These results support a role for ET-1/ET-A as a potential therapeutic target in chronic RVD.

renal artery stenosis; imaging; apoptosis

Renal artery stenosis is an important cause of chronic renovascular disease (RVD), accounting for up to 16% of all cases of chronic kidney disease and end-stage renal disease in the US adult population (16). RVD increases with age affecting 18% of individuals between the ages 65 to 74 years and >40% of those older than 75 (11). As the US population continues to age, RVD will increasingly represent a burden for health care costs. Hence, identification of potential therapeutic targets to slow the progression of renal injury in RVD could have significant benefit.

Endothelin (ET)-1, one of the most potent renal vasoconstrictors, plays pivotal roles in the kidney by governing vascular tone, salt reabsorption, and extracellular matrix proliferation through its specific ET-A and ET-B receptors. Renal ischemia upregulates ET-1 and via the ET-A receptor can induce renal injury (10). Recent evidence suggests that ET also regulates microvascular (MV) function in different vascular beds such as the kidney (3) and the myocardium (22, 23), partly by close interactions of ET-A receptors with vascular endothelial growth factor (VEGF) and downstream angiogenic and prosurvival mediators. We also showed that ET-A blockade improved the intrarenal MV architecture and function, augmented VEGF expression, and preserved renal function in experimental early atherosclerosis (1, 3).

Hepatocyte growth factor (HGF) is a mesenchyme-derived pleiotropic growth factor and a powerful stimulator of angiogenesis. HGF also promotes renal regeneration after ischemia-induced injury by stimulating cell survival, vascular proliferation, and decreasing fibrosis. We showed that augmenting renal expression of HGF is associated with decreased renal injury in experimental atherosclerotic RVD, although the mechanisms are unknown (6). There is a close interaction between ET and HGF (17, 18) as well as stimulatory effects of HGF on VEGF (15), which is also decreased in the stenotic kidney (21, 41).

The role of the ET pathway in promoting renal injury in chronic RVD and the potential impact of ET-A blockade on the MV architecture and function, and the progression of injury in the stenotic kidney, have, to our knowledge, not been previously reported. Therefore, using a large animal model of chronic experimental RVD, we first tested the hypothesis that chronic ET-A receptor blockade would preserve the hemodynamics and function and slow the progression of injury in the stenotic kidney. Second, we tested the hypothesis that the underlying mechanisms of renoprotection of ET-A blockade are associated with stimulation of the VEGF and HGF pathway.

Methods

The Institutional Animal Care and Use Committee at the University of Mississippi Medical Center approved all the procedures. Twenty-one prejuvenile domestic pigs (50–55 kg) were studied after 6 wk of observation. In 14 pigs, unilateral renal artery stenosis was induced at baseline by placing a local-irritant coil inside the main renal artery, which induced gradual arterial stenosis, as previously shown (4, 21), and constitutes a surrogate of RVD. The pigs were then randomized into two groups: those that were not further treated (RVD, n = 7) and those chronically treated with a specific ET-A receptor blocker (ABT 627, 0.75 mg·kg−1·day−1 PO, RVD+ET-A) from the onset of the stenosis. We previously showed this dose to be effective in improving renal hemodynamics and function and preserving the MV architecture in early atherosclerosis, without decreasing blood pressure (3). Blood pressure in the current study was continuously monitored using a telemetry system and pressure transmitter probes implanted at baseline (PhysioTel, Data Sciences International). Mean arterial...
pressure was recorded at 5-min intervals and averaged for each 24-h period (4, 21, 26). Additional animals were used as normal controls (normal, n = 7).

At 6 wk after induction of RVD, all the pigs underwent renal angiography to quantify the degree of renal artery stenosis. The pigs were anesthetized with intramuscular telazol (5 mg/kg) and xylazine (2 mg/kg), intubated, and mechanically ventilated on room air. Anesthesia was maintained with a mixture of ketamine (0.2 mg kg⁻¹ min⁻¹) and xylazine (0.03 mg kg⁻¹ min⁻¹) in normal saline and administered via an ear vein cannula (0.05 ml kg⁻¹ min⁻¹). Under sterile conditions and fluoroscopic guidance, a 9F arterial catheter was advanced to the renal artery proximal to the stenosis and renal angiography was performed, as previously described (21). Extent of the stenosis was quantified by measuring the decrease in luminal diameter of the renal artery at the most stenotic point compared with a proximal stenosis-free segment. After angiography, the catheter was positioned in the superior vena cava, and in vivo helical multidetector computer tomography (MDCT) flow studies were performed. Briefly, sequential acquisition of 160 consecutive scans was obtained after a central venous injection of iopamidol (0.5 ml kg⁻¹ 2 s⁻¹), for assessment of single-kidney renal blood flow (RBFl min⁻¹ g tissue⁻¹), and glomerular filtration rate (GFR; ml/min), as previously detailed and validated (4, 7, 25). Renal vascular resistance was calculated by dividing the mean arterial pressure (measured during the in vivo studies) and MDCT-derived RBFl. Blood from the inferior vena cava and renal veins (from the stenotic kidney) was collected to measure ET-1 using ELISA and plasma renin activity (PRA) using radioimmunoassay. ET-1 concentration was also measured in urine using ELISA.

Upon completion of all the in vivo studies, the pigs were allowed 2 days to recover to ensure proper contrast media washout and then euthanized with a lethal intravenous injection of pentobarbital sodium (100 mg/kg). Kidneys were immediately removed using a retroperitoneal incision and immersed in heparinized saline (10 U/ml). A lobe of kidney tissue was used for micro-CT reconstruction, while another lobe was removed from one end of the kidney, snap-frozen in liquid nitrogen, and stored at −80°C to quantify the protein expression of the ET-A and ET-B receptors, angiogenic and survival factors VEGF, HGF, angiotensin (Ang)-1, the specific Ang receptor Tie-2, total and phosphorylated Akt, endothelial nitric oxide synthase (eNOS), and the apoptotic mediators Caspase-3, Bax, and Bcl-xL. Finally, another portion of the kidney was preserved in 10% formalin to quantify the fraction of apoptotic cells using TdT-mediated dUTP nick end labeling (TUNEL) and to investigate renal morphology in midhilar renal cross-sections stained with trichrome (4).

MDCT analysis. Manually traced regions of interest were selected in MDCT images in the aorta, renal cortex, medulla, and papilla, and their densities were sampled. Time-density curves were generated by recording the number of sclerotic glomeruli out of 100 counted glomeruli as previously described (4, 21). To quantify apoptosis, the fraction of apoptotic cells was calculated in 10 randomly selected fields in each slide (one per animal), as previously described (5).

Statistical analysis. Results are expressed as means ± SE. Comparisons within groups were performed using paired Student’s t-test, and among groups using one-way ANOVA, with Bonferroni correction for multiple comparisons. Statistical significance was accepted for P ≤ 0.05.

RESULTS

ET in RVD. ET-1 in renal vein blood (collected from the stenotic kidney) was increased in RVD pigs, while ET-1 in systemic vein blood was not significantly different than in normal controls (Fig. 1). ET-1 in urine was also increased in RVD pigs, suggesting augmented renal ET-1 production (8). In addition, renal protein expression of the ET-A receptor was substantially increased in RVD kidneys, while the expression of the ET-B receptors was unchanged (Fig. 1), implying renal upregulation of the ET-1/ET-A pathway. On the other hand, PRA was similar among the groups (Table 1), as we previously showed (21) and has been observed in the chronic phase of renovascular hypertension (31, 33).

General characteristics. Blood pressure and the angiographic degree of stenosis were similarly and significantly greater in RVD- and RVD+ET-A-treated animals while the medullary volume of the stenotic kidney was reduced compared with normal untreated controls (Table 1; P < 0.01 vs. RVD and RVD+ET-A). On the other hand, the reductions in cortical volume were attenuated in RVD+ET-A compared with RVD (Table 1; P < 0.05 vs. RVD) albeit not normalized (P < 0.05 vs. normal).

MDCT-derived single-kidney hemodynamics and function. Basal RBFl and GFR were reduced in RVD, while regional perfusion remained unchanged. All of these parameters were substantially augmented in the stenotic kidney (except medullary perfusion which remained unchanged) by ET-A blockade.
that correlates with the preserved MV density in the stenotic kidney, and urine. Right: renal cortical protein expression of the ET-A and ET-B receptors in normal and experimental renovascular disease (RVD) animals. Renal vein and urine concentration of ET-1 as well as the renal expression of the ET-A receptor were significantly elevated in RVD pigs. *P < 0.05 vs. normal.

**MV 3-dimensional architecture.** The density and distribution of microvessels between 9 and 200 µm in the stenotic RVD kidney [which includes interlobar, arcuate, radial, and smaller branching orders microvessels (2)] were significantly decreased throughout the renal cortex (P < 0.05 vs. normal), but they did not change significantly in the medulla. Notably, the cortical MV density was significantly augmented in RVD+ET-A-treated kidneys (P = 0.05 vs. RVD; Fig. 2, top) and was not different than in normal kidneys (P = 0.19 vs. normal), which suggests a vascular protective effect of ET-A treatment in the stenotic kidney.

**Angiogenic and apoptotic factors.** VEGF expression was reduced in the stenotic kidney. Decreased renal VEGF was accompanied by decreased expression of downstream mediators of VEGF, such as p-Akt and Ang-1/Tie-2. On the other hand, eNOS remained unchanged while HGF and its c-Met receptor were slightly attenuated. Nevertheless, chronic ET-A blockade in RVD significantly augmented the expression of all these factors, indicating a proangiogenic and prosurvival effect that correlates with the preserved MV density in the RVD+ET-A kidney (Fig. 2, bottom). In addition, ET-A blockade attenuated the elevated renal expression of caspase 3 and the Bax/Bcl-xL ratio, suggesting decrease apoptotic activity in the stenotic kidney (Fig. 3, top).

**Renal apoptosis, inflammation, and fibrosis.** The decreased apoptotic activity was confirmed by quantifying the fraction of apoptotic cells. RVD kidneys showed a significant increase in the fraction of TUNEL+ cells compared with controls (11.4 ± 0.7 and 6.5 ± 0.6%; P < 0.001 vs. normal). There was a substantial reduction in TUNEL+ cells in the RVD+ET-A-treated kidneys (7.7 ± 0.3%; P < 0.001 vs. RVD, P = 0.06 vs. normal) that was more evident at the tubulointerstitial compartment (Fig. 3, bottom), indicating an overall decrease in apoptosis. In addition, ED-1+ cells (macrophages) were decreased in the glomerular and tubulointerstitial compartments of the RVD+ET-A kidneys compared with RVD, indicating attenuation of renal inflammation (Fig. 4, top). Finally, glomerulosclerosis and tubulointerstitial fibrosis in the RVD kidney were largely attenuated by ET-A blockade (Fig. 4, bottom).

**Contralateral kidney.** To determine whether the effects of ET-A blockade occurred only in the stenotic kidney, we also quantified RBF, GFR, and fibrosis in the contralateral kidney (CLK) of RVD and RVD+ET-A pigs. We observed that after Table 1. Mean arterial pressure, degree of stenosis, plasma renin activity, and basal single-kidney hemodynamics and function in normal, RVD, and RVD pigs treated with ET-A receptor blocker (RVD+ET-A)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n = 7)</th>
<th>RVD (n = 7)</th>
<th>RVD+ET-A (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>90.1 ± 2.1</td>
<td>132.4 ± 4.1*</td>
<td>124.7 ± 4.0*</td>
</tr>
<tr>
<td>Degree of stenosis, %</td>
<td>0.0 ± 0.0</td>
<td>75.4 ± 6.7*</td>
<td>73.6 ± 5.2*</td>
</tr>
<tr>
<td>Plasma renin activity, ng·ml⁻¹·h⁻¹</td>
<td>0.22 ± 0.04</td>
<td>0.20 ± 0.04</td>
<td>0.20 ± 0.03</td>
</tr>
<tr>
<td>Renal vascular resistance, mmHg·ml⁻¹·min⁻¹</td>
<td>0.16 ± 0.03</td>
<td>0.55 ± 0.12*</td>
<td>0.24 ± 0.04†</td>
</tr>
<tr>
<td>Renal volume (ml) Cortex</td>
<td>131.5 ± 7.4</td>
<td>65.9 ± 6.7*</td>
<td>80.7 ± 2.7*†</td>
</tr>
<tr>
<td>Medulla</td>
<td>39.5 ± 2.3</td>
<td>22.2 ± 2.2*</td>
<td>25.9 ± 2.3*</td>
</tr>
<tr>
<td>Renal blood flow, ml/min</td>
<td>551.8 ± 58.5</td>
<td>242.1 ± 36.2*</td>
<td>516.2 ± 59.6†</td>
</tr>
<tr>
<td>Perfusion, ml·min⁻¹·g cortex⁻¹</td>
<td>3.4 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>4.9 ± 0.4†</td>
</tr>
<tr>
<td>Medulla</td>
<td>2.6 ± 0.4</td>
<td>2.4 ± 0.5</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min</td>
<td>51.1 ± 3.1</td>
<td>30.9 ± 2.7*</td>
<td>50.3 ± 4.1†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Mean arterial pressure, degree of stenosis, plasma renin activity, and basal single-kidney hemodynamics and function in normal, renovascular disease (RVD), and RVD pigs treated with endothelin-A (ET-A) receptor blocker (RVD+ET-A). *P < 0.05 vs. normal. †P < 0.05 vs. RVD.
6 wk of sustained hypertension, the CLK of RVD and RVD+ET-A showed similar changes. RBF was similar between the control (551.8 ± 58.4 ml/min) and experimental groups (584.9 ± 79.9 and 665.2 ± 104.8 ml/min in RVD and RVD+ET-A, respectively, \( P \) not significant). On the other hand, GFR was similarly increased in RVD and RVD+ET-A CLK compared with normal (85.5 ± 7.8 and 68.7 ± 8.0 ml/min, respectively, \( P < 0.05 \) vs. normal controls). Histological analysis of the CLK showed only a mild perivascular and tubulointerstitial fibrosis, which was not modified by chronic ET-A blockade (data not shown).

**DISCUSSION**

The current study shows an important role for the ET-1/ET-A pathway in mediating renal injury in chronic RVD. Our studies indicate that chronic ET-A blockade exerts important vascular- and renoprotective effects in the stenotic kidney, resulting in a slower progression of renal injury. ET-A blockade augmented the renal expression of VEGF, HGF, and shared downstream mediators such as Ang, Akt, and eNOS in the stenotic kidney, which are important promoters of vascular proliferation and cell survival. In parallel, this study shows that ET-A blockade in RVD also reduces apoptosis in the stenotic kidney, an important mechanism of tissue injury after an ischemic insult. These effects induced by ET-A blockade were functionally important since they preserved the renal MV density, RBF, GFR, and cortical perfusion of the stenotic kidney.

Renal artery stenosis is an independent predictor of cardiovascular mortality and is remarkably frequent in patients with vascular disease elsewhere, being present in 40−60% of those with overt coronary artery disease, aorto-iliac disease, or peripheral vascular disease (20). The chronic sustained obstruction of blood flow to the stenotic kidney triggers a cascade of events that leads to progressive renal dysfunction and structural injury, decreasing the chances for full recovery of renal function as RVD evolves. It is possible that the combination of multiple concurrent insults such as hypertension, ischemia, vascular damage, and remodeling represents a burden for the stenotic kidney that often is not possible to overcome. Thus, the goal of this study was to elucidate the potential underlying mechanisms to identify potential therapeutic targets and interventions that might be used to protect the RVD kidney.

ET-1 is the major isoform expressed in the kidney and is produced throughout the vascular, glomerular, and tubular compartments. ET-1 exerts its effects through two specific G protein-coupled receptors, ET-A and ET-B. The ET-A receptors mediate the vasoconstrictor and mitogenic effects of ET-1 in the kidney, while ET-B activation increases eNOS, reduces salt reabsorption, and promotes ET-1 clearance (35). These beneficial effects of ET-B receptor activation supported the rationale for selective blockade of ET-A receptor-mediated effects in pathological settings such as acute renal ischemia (13). We previously showed that chronic ET-A blockade improves the renal MV hemodynamics, function, and architecture in experimental hypercholesterolemia (3). However, the role of the ET-1/ET-A pathway in inducing renal injury and the potential effects of ET-A blockade in chronic RVD has not been previously reported.
Our current study shows that chronic ET-A blockade preserved the hemodynamics and function of the stenotic kidney despite the similar degree of renal artery stenosis and hypertension in RVD and RVD+ET-A pigs. This reflects beneficial effects of ET-A blockade on slowing the progression of renal injury, distal to the stenosis and independent of blood pressure. The targeted effects of chronic ET-A blockade on the stenotic kidney are underscored by the similar changes in RBF, GFR, and mild fibrosis that were observed in the CLK of RVD and RVD+ET-A pigs after 6 wk. Furthermore, our results imply that functional impairment associated with RVD in our model is a function of micro- rather than macrovascular dysfunction since ET-A antagonism had no effect on the degree of stenosis but corrected the MV disorders in the stenotic kidney.

Part of the beneficial effects on the stenotic kidney was likely the result of a distinct protective effect on the renal microcirculation by ET-A blockade. Indeed, the density of cortical microvessels between 9 and 200 μm of diameter in the stenotic kidney was diminished in untreated RVD pigs but preserved after ET-A blockade, accompanied by augmented expression of VEGF, a key proangiogenic and survival factor involved in vascular proliferation and repair.

ET-A blockade also augmented renal expression of HGF, a pleiotropic growth factor with robust direct and VEGF-mediated angiogenic effects (15). Recent evidence supports a strong cross-talk between these angiogenic cytokines, with shared downstream mediators and additive/synergistic effects on angiogenesis (28, 37). We observed that the expression of pivotal angiogenic and prosurvival factors such as Ang-1 and its Tie-2 receptor, p-Akt, and eNOS was substantially augmented in the stenotic kidney of the RVD+ET-A pigs. These are shared downstream mediators of VEGF and HGF, indicating a possible stimulation of both pathways after ET-A blockade in RVD. In turn, it is possible that blockade of the ET-A receptor may have led to further stimulation of eNOS via ET-1/ET-B as well (19). Furthermore, chronic ET-A blockade resulted in a distinct protective effect on the renal microcirculation reflected not only by preserved cortical MV density, but also by augmented cortical perfusion in the stenotic kidney, compared with normal controls facing a similar MV density. The latter suggest that

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Fig. 3. Representative quantification of renal expression of proapoptotic mediators caspase-3 and Bax/Bcl-xL (top) and pictures showing immunoreactivity against caspase-3 (top; ×20) and apoptotic cells in the stenotic kidney (bottom; white arrows, ×40) and quantification. Chronic ET-A blockade significantly attenuated renal apoptosis in the stenotic kidney. *P < 0.001 vs. normal. †P < 0.001 vs. RVD. TUNEL, TdT-mediated dUTP nick end labeling.
part of the effects of ET-A blockade on renal hemodynamics may have also been induced by augmented recruitment of preexisting vessels, possibly via ET-1/ET-B receptor-mediated actions (35).

MV obsolescence with subsequent glomerulosclerosis is a prominent feature in most progressive renal diseases. Previous studies demonstrated that ET can promote apoptosis through the ET-A receptor, and this process could be prevented or reversed by ET antagonism (30). Apoptosis precedes renal fibrosis (24) and we previously showed a marked increase in apoptotic cells in the stenotic kidney (5), mainly evident at the peritubular compartment, and accompanied by a significant cortical MV loss, inflammation, and tubulointerstitial, glomerular, and perivascular fibrosis (4, 5, 21). The current study extends our previous observations and shows that the marked increase in apoptotic activity in the chronic RVD kidney was reduced by ET-A blockade, which correlated with the decreased fraction of TUNEL-positive cells. Since previous studies showed anti-apoptotic effects of VEGF (14) and HGF (40), it is possible that the dual increase in VEGF and HGF in RVD+ET-A may have had an additive protective effect on renal endothelial cells by augmenting the expression of pro-survival factors such as Akt (9) and Ang-1/Tie-2, hence diminishing renal apoptosis and consequently MV damage. In parallel, upregulation of renal HGF in RVD+ET-A may have also diminished apoptosis by decreasing caspase-3 (38), the “executioner pathway” of apoptosis, or by upregulating anti-apoptotic Bcl-xL (39). Furthermore, we previously showed that ET-A blockade induced a significant decrease in the expression and activity of the proinflammatory and proapoptotic NF-κB (1), which may have also contributed for the decreased inflammatory infiltrates and apoptotic cells in the stenotic kidney. Alternatively, blockade of the ET-A receptors may have also decreased apoptosis in the stenotic kidney by increasing ET-1 availability and thereby favoring its binding to the renal ET-B receptors (36). Although the role of ET in mediating apoptosis seems to be organ, tissue, or disease specific (12, 29, 32), our study suggests a novel vasculoprotective effect of ET-A blockade in the chronically stenotic kidney. However, further studies are needed to determine whether renal vasodilation with other pharmacological tools, such as renin-angiotensin blockers, may also have beneficial effects in preserving the microvasculature of the chronically stenotic kidney.

The micro-CT technique allows quantification of microvessels above 9 μm in diameter, hence excluding the capillaries from the renal MV quantification. Additional studies using histology, as we previously showed (21), or higher resolution imaging would be needed to include those smaller vessels in future studies. We are aware that our approach was largely preventive. ET-A blockade was administered from the onset of the effects of ET-A blockade on renal hemodynamics.
RVD to first elucidate the underlying mechanisms regulated by the ET-1/ET-A pathway in the stenotic kidney. The effects of ET-A blockade observed in our study may also slow-down the progression of renal injury in established disease, as supported by experimental evidence (27, 34). However, by showing that this intervention slowed the progression of renal injury, we open new avenues for future studies to elucidate the potential of ET-A blockade in reversing established renal injury and/or at more advanced stages of RVD. Furthermore, since the ET-B receptors play a key role in increasing NO and have been shown to have anti-apoptotic effects, studies will be needed to explore the role of the ET-B receptor in renal injury in chronic RVD.

The current study contributes to our knowledge by revealing a novel renoprotective mechanism of ET-A receptor blockade in a clinically relevant model of chronic RVD. These beneficial effects were achieved independently of changes in blood pressure. Our study indeed represents a solid first step that supports the roles of ET-1/ET-A in promoting renal injury, potentially opening new research avenues for the use of these agents to protect the kidney in a manner potentially applicable to patients with chronic RVD in the near future.

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REFERENCES


