Mild DOCA-salt hypertension: sympathetic system and role of renal nerves

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Kandlikar SS, Fink GD. Mild DOCA-salt hypertension: sympathetic system and role of renal nerves. Am J Physiol Heart Circ Physiol 300: H1781–H1787, 2011. First published February 25, 2011; doi:10.1152/ajpheart.00972.2010.—Excess sympathetic nervous system activity (SNA) is linked to human essential and experimental hypertension. To test whether sympathetic activation is associated with a model of deoxycorticosterone acetate (DOCA)-salt hypertension featuring two kidneys and a moderate elevation of blood pressure, we measured whole body norepinephrine (NE) spillover as an index of global SNA. Studies were conducted in chronically catheterized male Sprague-Dawley rats drinking water containing 1% NaCl and 0.2% KCl. After a 7-day surgical recovery and a 3-day control period, a DOCA pellet (50 mg/kg) was implanted subcutaneously in one group of rats (DOCA), while the other group underwent sham implantation (Sham). NE spillover was measured on control day 2 and days 7 and 14 after DOCA administration or sham implantation. During the control period, mean arterial pressure (MAP) was similar in Sham and DOCA rats. MAP was significantly increased in the DOCA group compared with the Sham group after DOCA administration (day 14: Sham = 109 ± 5.3, DOCA = 128 ± 3.6 mmHg). However, plasma NE concentration, clearance, and spillover were not different in the two groups at any time. To determine whether selective sympathetic activation to the kidneys contributes to hypertension development, additional studies were performed in renal denervated (RDX) and sham-denervated (Sham-DX) rats. MAP, measured by radiotelemetry, was similar in both groups during the control and DOCA treatment periods. In conclusion, global SNA is not increased during the development of mild DOCA-salt hypertension, and fully intact renal nerves are not essential for hypertension development in this model.

whole body norepinephrine spillover; renal denervation

A LARGE BODY OF EVIDENCE SUGGESTS that increased sympathetic nervous system activity (SNA) is involved in the pathophysiology of hypertension, particularly in the developmental phase (22). There are many potential causes of sympathetic overactivity in hypertension, but recent studies have created renewed interest in the possibility that mineralocorticoids may be one such cause (33, 45, 57). Administration of deoxycorticosterone acetate (DOCA) plus high salt intake (DOCA-salt hypertension) in the rat has been extensively studied as an experimental animal model of mineralocorticoid-dependent hypertension. There is compelling evidence that increased SNA contributes to DOCA-salt hypertension (17, 42) but also some evidence against this idea. For example, neonatal sympathectomy was shown to actually accelerate, rather than impair, the development of DOCA-salt hypertension (45).

The majority of these studies have been conducted in the traditional mineralocorticoid/salt model, which consists of a uninephrectomized rat being treated with a high dose of DOCA (150–200 mg/kg) and drinking a solution containing 0.9–1.0% NaCl in water. This model has some deficiencies when used to probe specific causes of the development of human hypertension. Severe hypertension, with mean arterial pressures (MAPs) in the range of 180–200 mmHg, is seen within a few weeks. Both the rate and magnitude of hypertension development are significantly greater than the slower-developing and more modest increase in blood pressure observed in most human hypertensive patients. Very high blood pressure in the model contributes to the rapid onset of extensive end-organ damage (19, 54). For example, glomerular sclerosis, interstitial fibrosis, cell proliferation, and inflammation are seen in the kidney (13, 26). Hypertrophy and fibrosis in the heart leads to cardiac dysfunction (36). Vascular injury and inflammation occur, as revealed, for example, by vascular fibrosis, increased endothelin and superoxide production, and reduced nitric oxide bioavailability (2, 18, 46, 55). Typically, a significant loss of total body fat and lean body mass is seen (51). Some of these responses to high blood pressure also probably serve as mechanisms to help maintain or even amplify the hypertension. Moreover, the engagement of many primary causative mechanisms (renal, neural, hormonal) seems to be required to initially raise blood pressure to the very high levels seen in the model. Together these factors make it difficult to use the standard DOCA-salt model to dissect out the relative contribution of any one mechanism to hypertension development.

In an attempt to avoid these complications, in the present experiments we investigated the role of the sympathetic nervous system in a modified model of DOCA-salt hypertension: no nephrectomy was performed and a lower dose of DOCA was used. The goal was to produce a hypertension that was more modest in magnitude and developed more slowly than in the standard DOCA-salt model. We theorized that this would allow a clearer identification of any mechanisms that serve as a primary cause of hypertension development. Sodium and water retention clearly contribute to DOCA-salt hypertension (51). Since regionally specific changes in SNA are capable of producing hypertension (43), we studied not just overall activity of the sympathetic nervous system but also the effects of sympathetic activity specifically to the kidney, using renal denervation (RDX). Previous studies on the importance of sympathetic activity to the kidney in the development of the standard model of DOCA-salt hypertension have yielded conflicting conclusions (9, 25, 28).

METHODS

Animals

Male Sprague Dawley rats (225–275 g) were used for all experiments. All protocols were approved by the Michigan State University Institutional Animal Care and Use Committee. Before any experiments, rats were acclimatized to the animal room for 7 days under controlled temperature and humidity conditions with an alternate 12:12-h light-dark cycle. At this time they were allowed free access to water and standard rat chow.
Mild DOCA-Salt Hypertension

Under isoflurane anesthesia, a DOCA pellet (50 mg/kg) was implanted subcutaneously in one group of rats, while the other group underwent sham implantation surgery with both kidneys left intact. Both groups received water containing 1% NaCl and 0.2% KCl. Several doses (5, 15, 25, 50, 100, 150 mg/kg) of DOCA were tested in initial experiments with the goal of inducing mild hypertension, i.e., an increase in blood pressure of −10–20 mmHg. On the basis of these preliminary studies we chose 50 mg/kg as the dose for all additional experiments, since this was the smallest dose required to induce a significant, sustained increase in blood pressure (data not shown).

Catheterization

Under 2% isoflurane anesthesia, catheters were implanted into the abdominal aorta and vena cava through the left femoral artery and vein, respectively. A Tecoflex polyurethane catheter (Strategic Applications) was placed into the abdominal aorta. A silicone catheter (Dow Corning) was placed into the abdominal vena cava through the left femoral vein. Both catheters were tunneled subcutaneously to the back and exteriorized at the neck between the scapulae. Catheters were then passed through a stainless steel spring attached to the rat by a loosely fitting nylon harness (Instech Solomon). The other end of the spring was attached to a swivel to allow the rat free movement in a plastic cage. Rats were allowed free access to water and food and were allowed to recover for 7 days. Catheters were flushed and refilled everyday with heparin-saline (100 U/ml). Postsurgical analgesia was achieved with carprofen (5 mg/kg sc). Meloxicam (1 mg/kg po) was administered daily for 3 additional days after surgery. Ticarcillin-clavulanate (60 mg/kg iv) and enrofloxacin (5 mg/kg iv) were administered daily for the entire duration of the experiment to achieve antimicrobial prophylaxis.

Whole Body Norepinephrine Spillover

Whole body norepinephrine (NE) clearance and spillover were measured by an established method described previously by King et al. (32). Briefly, tracer amounts of levo-[5,2,5,6-3H]NE ([3H]NE, PerkinElmer) were infused intravenously at 0.13 ml/min for 90 min to produce a steady-state plasma concentration of [3H]NE. One milliliter of blood was collected from the arterial catheter after the infusion and stored at −80°C until further analysis. Plasma NE concentration was determined by batch alumina extraction followed by separation using high-performance reverse-phase liquid chromatography with coulometric detection (ESA Biosciences). Quantification was accomplished with a modified method originally reported by Holmes et al. (23). After chromatographic analysis, the NE fraction was collected and [3H]NE was quantified by liquid scintillation counting. NE clearance and spillover were calculated with the following formulas (31):

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\text{NE clearance (ml/min)} = \frac{[3H]\text{NE infusion rate (dpm/min)}}{\text{steady-state } [3H]\text{NE (dpm/ml)}}
\]

\[
\text{NE spillover (ng/min)} = \text{NE clearance (ml/min)} \times \text{plasma NE concentration (ng/ml)}
\]

Renal Denervation and Radiotelemetry Implantation

To study the role of renal nerves in the development of hypertension, bilateral RDX was performed in a separate group of rats as described previously by Trostel and Osborn (52). Briefly, renal vessels were exposed via a ventral midline laparotomy. Renal vessels were stripped of fat, connective tissue, and nerves. The vessels were then painted with 10% phenol to ensure destruction of any remaining nerve fibers. Sham surgery was performed by visualizing the renal nerves after laparotomy (Sham-DX). A TA11-PA-C40 radiotelemetry transmitter (Data Sciences International), implanted during the same surgery for RDX or sham operation, was used for the measurement of arterial pressure (AP) and heart rate (HR). The tip of the transmitter catheter was placed in the abdominal aorta through the left femoral artery under isoflurane anesthesia. The body of the transmitter was placed in a subcutaneous pocket in the abdomen. Enrofloxacin (5 mg/kg sc) was administered once for antimicrobial prophylaxis, and postsurgical analgesia was achieved with carprofen (5 mg/kg sc).

Hemodynamic Measurements

Whole body NE spillover. Hemodynamic measurements were made with methods previously established in our laboratory (17, 32). Briefly, the arterial catheter was connected to a pressure transducer (TDX-300, Micro-Med) that senses changes in AP. The pressure transducer was connected to a digital pressure analyzer (BPA-400, Micro-Med) that provided MAP, systolic pressure, diastolic pressure, and HR at a sampling rate of 1,000 Hz. The pressure analyzer was linked to a computer in which the data were analyzed by data acquisition software (DMSI-400, Micro-Med). The pressure transducers were calibrated at the beginning of the experiment with a sphygmomanometer and balanced daily against a water column located at the level of the rat’s heart. AP and HR were measured daily for an hour in the morning.

Renal denervation. Rats instrumented with a radiotelemetry device were housed in individual plastic cages placed on top of a radiotelemetry receiver (RPC-1, Data Sciences International). The receiver relayed signals to a computerized data acquisition program (Dataquest ART 3.1, Data Sciences International). Hemodynamic measurements were sampled for 10 s every 10 min, 24 h/day, for the duration of the experiment. Data are reported as 24-h averages.

Confirmation of Denervation

At the end of the experiment, rats were euthanized with an intraperitoneal injection of pentobarbital (100 mg/kg). Both kidneys were harvested from each animal, frozen in liquid nitrogen, and stored at −80°C for later analysis. Tissue NE content of the samples was measured by high-performance liquid chromatography analysis with electrochemical detection. Data are reported as nanograms of NE per gram of tissue.

Experimental Protocols

Whole body NE spillover. After a 7-day recovery after catheterization and a 3-day control hemodynamic measurement period, DOCA pellets (50 mg/kg sc) were implanted in one group of rats while the other group underwent sham implantation surgery. Plasma NE, clearance, and spillover were measured on control day 2 and days 7 and 14 after DOCA implantation.

Renal denervation. Seven days after RDX or sham operation and 3 subsequent days of control hemodynamic measurements, a DOCA pellet (50 mg/kg sc) was implanted in both RDX and Sham rats. Rats received free access to water containing 1% NaCl and 0.2% KCl, and AP was measured throughout the period of the experiment. Acute hemodynamic responses to hexamethonium (30 mg/kg ip) were measured on days 14 and 21 after DOCA treatment. Saline intake was also monitored during the control period and on days 7, 14, and 21 after DOCA administration.

Statistical Analysis

Within-group hemodynamic differences were assessed by repeated-measures ANOVA with Bonferroni’s multiple-comparisons test. Between-groups hemodynamic differences were analyzed by two-way ANOVA followed by Bonferroni’s test. Plasma NE concentration, NE clearance, and NE spillover were analyzed by paired t-test. A P value of <0.05 was considered significant. Data are presented as means ± SE.
RESULTS

Whole Body NE Spillover

MAP and HR responses to chronic DOCA treatment are shown in Fig. 1. During the control period, MAP was similar in Sham (105 ± 3.3 mmHg) and DOCA (110 ± 4.3 mmHg) rats. HR was also not different between the two groups. MAP significantly increased in the DOCA group compared with the Sham group (day 14: Sham = 109 ± 5.3, DOCA = 128 ± 3.6 mmHg) during the treatment period (Fig. 1A). Changes in HR were not different between the two groups (Fig. 1B). Whole body NE spillover was measured after a 90-min infusion of [³H]NE. This infusion did not alter blood pressures in either group. Total plasma NE concentration, NE clearance, and NE spillover (Sham: 31 ± 3, DOCA: 39 ± 6 ng·min⁻¹·kg⁻¹) were not different between the two groups during the control period. Total plasma NE concentration, NE clearance, and NE spillover also were not different in the DOCA and Sham groups on days 7 and 14 of DOCA treatment (Fig. 2).

Renal Denervation

MAP in RDX and Sham-DX rats is shown in Fig. 3. During the control period, MAP was slightly lower in RDX (100 ± 1.4 mmHg) compared with Sham-DX (103 ± 1.6 mmHg) rats. After DOCA administration MAP increased significantly in

Fig. 1. Mean arterial pressure (MAP; A) and heart rate (HR; B) during the control (C) and deoxycorticosterone acetate (DOCA) treatment periods in Sham and DOCA groups. *Significant difference from day 3 (control period) values. bpm, Beats per minute.

Fig. 2. Plasma norepinephrine (NE) (A), NE clearance (B), and NE spillover (C) in Sham and DOCA-salt hypertensive rats on control day 2 and days 7 and 14 after DOCA treatment.
both groups to a similar degree. At no time point was the difference in MAP between the two groups significant. During DOCA treatment, HR fell progressively and similarly in RDX and Sham-DX rats. This fall in HR is different from what was observed in our earlier study of whole body NE spillover, likely because the earlier data were obtained daily in chronically catheterized rats during a 1-h period in the morning. Thus those values may not accurately represent 24-h average HR values as we obtained with telemetric measurements in this protocol. MAP responses to acute ganglion blockade on days 14 and 21 after DOCA treatment are shown in Fig. 4. On day 14, there was no significant difference between the groups in the peak fall in MAP after hexamethonium injection. On day 21 after DOCA administration, however, the fall in blood pressure was significantly attenuated in RDX rats compared with Sham-DX rats. Both the RDX and Sham-DX groups consumed similar quantities of saline during the control period and days 7, 14, and 21 after DOCA treatment (data not shown). Total renal NE content was significantly lower in both kidneys of rats with RDX (left kidney: 39.8 ± 6.1 ng/g, right kidney: 37.2 ± 5.9 ng/g) compared with kidneys from Sham-DX rats (left kidney: 129.5 ± 10.5 ng/g, right kidney: 129.8 ± 6.6 ng/g). Since this reduction in NE content was <90%, it is properly characterized as partial RDX.

**DISCUSSION**

Our study does not support the hypothesis that global sympathetic activation occurs in this model of mild DOCA-salt hypertension. Whole body NE spillover was not different between the hypertensive and normotensive groups on any experimental days. Another important observation is that renal nerves are not the only factor contributing to hypertension development in this model, as partial RDX did not attenuate the increase in blood pressure. It is important to note that this model was chosen specifically to minimize the development of end-organ complications generally associated with more severe models of hypertension. Since it is possible that these complications (e.g., renal injury) may be a cause of increases in renal or other regional sympathetic activity, interpretation of our results only applies to this mild model of DOCA-salt hypertension.

A recent clinical study showed that sympathetic nerve activity was elevated in patients with primary aldosteronism when compared with normal control subjects and that the increase in activity was comparable to that observed in patients with essential hypertension (33). This elevation of sympathetic nerve activity was normalized by adrenalectomy, which demonstrates that aldosterone can be sympathoexcitatory in humans. Additional support for increased sympathetic activity in human hypertensive subjects comes from a study showing an increase in whole body NE spillover compared with normotensive control subjects (47). Although previous studies in experimental DOCA-salt hypertension suggest that sympathetic activity is increased, most of the studies were done with indirect measures of sympathetic nerve activity (7, 24, 50). For example, plasma NE was reported to be higher in DOCA-salt hypertensive rats compared with normotensive control rats (7). We used the radioisotope dilution technique to measure NE
spillover, which is more accurate in assessing neurotransmitter release than measuring plasma NE alone (11). Plasma NE and NE spillover were found to be elevated in anesthetized DOCA-salt hypertensive rats, and this increase was proportional to the increase in blood pressure (3). We could not confirm this finding in conscious, unrestrained animals. One of the important things to note is that the model we used is quite different from many of the DOCA-salt hypertension models previously studied to demonstrate sympathoexcitation. Various factors could be responsible for our failure to find sympathoexcitation in our model, for example, the lower dose of DOCA, the presence of two kidneys, or the failure to engage mechanisms of sympathoexcitation linked to tissue injury caused by severe hypertension. One of the limitations of the spillover technique is that it measures sympathetic activity at a single point in time during the day; continuous measurement is not possible with this technique. Thus increases in sympathetic activity occurring only at night, for example, would be missed. Nevertheless, the results are convincing because the NE spillover values were similar on any experimental day and were quite reproducible. Also, our findings are consistent with a study performed in sheep showing that mild mineralocorticoid hypertension is not associated with global sympathoexcitation (39). Furthermore, some studies have shown that NE spillover and muscle sympathetic nerve activity are actually decreased in humans with mineralocorticoid hypertension (40, 44). Even though we did not see an increase in global sympathetic activity, it does not exclude the possibility that specific regional increases in sympathetic activity contribute to hypertension development (20, 21). Also, it is possible that, as reported previously (1, 56), the vascular reactivity to NE is increased in this model and that a “neurogenic pressor effect” is occurring with normal levels of sympathetic activity.

Since NE clearance did not change in either group after DOCA administration, we conclude that overall neuronal and extraneuronal uptake of NE were not affected by DOCA treatment. The prejunctional $\alpha_2$-adrenergic receptors (ARs) at the sympathetic nerve terminal mediate feedback inhibition of NE release (35). Data from various studies indicate that $\alpha_2$-receptor function is impaired in human hypertension (5, 6) and various models of experimental hypertension (37, 41, 53, 58). Nerve stimulation-evoked NE release was attenuated in DOCA-salt arteries treated with yohimbine ($\alpha_2$-AR antagonist), while it failed to decrease after UK-14304 ($\alpha_2$-AR agonist) in DOCA-salt arteries compared with their normotensive controls, suggesting an impairment in function of prejunctional $\alpha_2$-receptors (37). We did not observe an increase in whole body NE spillover or a change in NE clearance between DOCA and Sham groups. Therefore, we conclude that in our mild DOCA-salt hypertension model either $\alpha_2$-AR function is normal or reduced $\alpha_2$-AR function only occurs in some vascular beds.

The majority of NE is taken up by the prejunctional norepinephrine transporter (NET) (10). Previous reports indicate that neuronal NE reuptake may be impaired in hypertension because of altered NET function (10, 14, 15). However, NET protein is elevated in the vasculature and sympathetic ganglia of DOCA-salt hypertensive animals compared with those from normotensive, sham-operated control animals (38). Since NE clearance was not different between the hypertensive and normotensive animals in our study, we conclude that NET function in our hypertensive animals was not impaired. Further studies are necessary to confirm this hypothesis. It also is important to note that there is some controversy about the relative importance of neuronal versus nonneuronal uptake of NE (11, 12).

Increased SNA during the development of hypertension is not uniform; it varies in timing and intensity in different vascular beds (16, 43). The role of the renal sympathetic nerves in the development of hypertension is controversial. It is well known that changes in renal SNA affect renal vascular resistance, renin release, and sodium and water balance (8). Renal NE spillover is increased in human essential hypertension compared with normotensive control subjects, suggesting that renal SNA is elevated (47). Also, it has been reported recently that catheter-based renal denervation by radio frequency ablation caused a substantial decrease in blood pressure in human hypertensive patients with resistant hypertension (34). Osborn and colleagues (25) recently demonstrated that intact renal nerves are crucial for the development of the traditional DOCA-salt model of hypertension, because RDX significantly attenuated hypertension development. Several other investigators have reported similar findings (4, 28, 49).

During the pretreatment period blood pressure was slightly lower in the RDX group compared with the Sham-DX group (~3 mmHg), but the difference between the groups was not statistically significant. More importantly, RDX did not affect the development of hypertension during DOCA treatment. One important caveat to this finding is that the relatively high levels of NE found in the denervated kidneys may indicate either less than complete RDX or significant reinnervation during the course of the study. Thus it is possible that the failure of RDX to affect hypertension development in our model was due to inadequate or nonsustained loss of renal sympathetic input. Nevertheless, our findings are consistent with one earlier study showing that renal nerves are not necessary for the development or maintenance of standard DOCA-salt hypertension in rats (9). Katholi et al. (27) also showed that renal nerves are only important in the early established phase of standard DOCA-salt hypertension and play a diminished role during the later phase. In one previous study, it was concluded that attenuation of DOCA-salt hypertension development was due to reductions in sodium and water intake in renal denervated rats (25). We found that rats in both the groups in our study drank similar amounts of saline during the control period and on days 7, 14, and 21 after DOCA administration. The reason for the differences in the two models is not clear.

Previous reports indicate that RDX decreases peripheral sympathetic activity in hypertensive animals (29, 30), and catheter-based RDX decreased whole body NE spillover and directly recorded muscle sympathetic nerve activity in a human patient with drug-resistant hypertension (48). To study the effect of RDX on neurogenic pressor activity in the Sham-DX and RDX groups, we measured changes in MAP to acute ganglionic blockade with hexamethonium. The magnitude of the acute depressor response was taken as an index of overall neurogenic pressor activity. We observed that the depressor response was similar in both groups on day 14 but was significantly attenuated on day 21 after DOCA treatment in the RDX group compared with Sham-DX rats. We conclude that
neurogenic pressor activity is decreased in the established phase of hypertension in RDX rats compared with SHAM-DX rats. A possible explanation for this finding is that even partial RDX attenuates afferent renal nerve activity, and therefore decreases global SNA. It has been reported that afferent signals from the kidney project centrally and play an important role in modulating peripheral SNA (8). If increased afferent renal activity stimulated peripheral sympathetic outflow in DOCA-salt animals, then even partial disruption of renal nerves should result in attenuation of peripheral sympathetic activity. Further studies are necessary to confirm that idea. Nevertheless, considering that blood pressure was similar in Sham and RDX rats treated with DOCA-salt, we conclude that increased neurogenic pressor activity is not essential to maintain hypertension in our model. Presumably other blood pressure control mechanisms compensated for loss of neurogenic pressor activity after partial RDX. The decrease in blood pressure observed in human hypertensive patients after RDX, however, indicates that this compensation does not always occur.

Perspectives

Sympathetic activation is common to human and experimental hypertension, but the mechanisms involved and the specific vascular regions affected remain to be elucidated. Our data do not support recent findings that mineralocorticoids are an important cause of sympathoexcitation in hypertension. However, even though global SNA was not increased in our model of mineralocorticoid hypertension, this does not rule out the possibility of increased regional sympathetic activation in one or more vascular beds, perhaps balanced by decreases in other beds. In our model sympathetic activation to the kidneys is not the full explanation, because partial RDX did not attenuate the development of hypertension. Nevertheless, in agreement with earlier studies in experimental animals and recent findings in humans, we showed that partial RDX can reduce overall sympathetic activation to the kidneys is not the full explanation, because partial RDX did not attenuate the development of hypertension. Nevertheless, in agreement with earlier studies in experimental animals and recent findings in humans, we showed that partial RDX can reduce overall sympathetic activation to the kidneys. In our model sympathetic activation to the kidneys is not the full explanation, because partial RDX did not attenuate the development of hypertension. Nevertheless, in agreement with earlier studies in experimental animals and recent findings in humans, we showed that partial RDX can reduce overall sympathetic activation to the kidneys. In our model sympathetic activation to the kidneys is not the full explanation, because partial RDX did not attenuate the development of hypertension. Nevertheless, in agreement with earlier studies in experimental animals and recent findings in humans, we showed that partial RDX can reduce overall sympathetic activation to the kidneys. In our model sympathetic activation to the kidneys is not the full explanation, because partial RDX did not attenuate the development of hypertension. Nevertheless, in agreement with earlier studies in experimental animals and recent findings in humans, we showed that partial RDX can reduce overall sympathetic activation to the kidneys. In our model sympathetic activation to the kidneys is not the full explanation, because partial RDX did not attenuate the development of hypertension. Nevertheless, in agreement with earlier studies in experimental animals and recent findings in humans, we showed that partial RDX can reduce overall sympathetic activation to the kidneys. In our model sympathetic activation to the kidneys is not the full explanation, because partial RDX did not attenuate the development of hypertension. Nevertheless, in agreement with earlier studies in experimental animals and recent findings in humans, we showed that partial RDX can reduce overall sympathetic activation to the kidneys.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


