Catheter-Based Radiorefrequency Renal Denervation Lowers Blood Pressure in Obese Hypertensive Dogs

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BACKGROUND
Obesity-induced hypertension appears to be due, in part, to increased renal sympathetic activity. Catheter-based renal denervation (RD) has been reported to lower arterial blood pressure (BP) in humans with resistant hypertension, many of whom are obese. This study was performed to assess the impact of radiofrequency–induced RD on renal function, BP, renal norepinephrine (NE), and histology of nerves along the renal artery in obese, hypertensive dogs, an experimental model that closely mimics cardiorenal and metabolic changes in obese hypertensive humans.

METHODS
After control measurements of cardiovascular and renal function were obtained in obese dogs fed a high-fat diet, bilateral RD was performed using the St. Jude Medical EnligHTN RD system. After RD, BP was measured continuously for 8 weeks, and glomerular filtration rate (GFR) was measured biweekly for 6 weeks. At the end of the study, renal arteries were collected for histological analysis, and kidneys were obtained for NE measurement.

RESULTS
Eight weeks after RD, systolic BP fell from 157 ± 5 mm Hg pre-RD to 133 ± 3 mm Hg (P < 0.01), and mean arterial pressure decreased by 9 mm Hg compared with pre-RD (P < 0.01). There were no significant changes in GFR. Renal nerve injury was most prevalent 0.28–3.5 mm from the renal artery lumen. RD caused injury in 46% of the renal nerves observed and reduced renal tissue NE by 42% (P < 0.01).

CONCLUSIONS
Catheter-based RD with the St. Jude Medical EnligHTN system lowers BP in obese dogs without significantly compromising renal function.

Keywords: blood pressure; glomerular filtration; hypertension; obesity; renal denervation.

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Hypertension is one of the most frequent chronic diseases worldwide, affecting approximately 25% of the adult population.1 Treatment of hypertension has relied heavily on pharmacological interventions. Although antihypertensive drug therapy is effective in many patients, up to 10% of patients have resistant hypertension that is not adequately controlled by pharmacological treatment. Resistant hypertension is defined as blood pressure (BP) >140/90 mm Hg, >130–139/80–85 mm Hg in diabetes mellitus, or >130/80 mm Hg in chronic kidney disease while the patient is treated with antihypertension medications, including a diuretic, at maximal or the highest tolerated dose.2 Recently, clinical trials have shown that catheter-based renal denervation (RD) lowers BP in many resistant hypertensive patients.3 Although these results are promising, there are fundamental questions regarding RD that have yet to be answered.

One question is whether RD effectively lowers BP in more common forms of hypertension, such as obesity-induced hypertension. Obesity has rapidly become a major health problem, with more than one-third of all adults in the United States being obese and two-thirds being overweight.4 According to the Framingham Heart Study, 65%–78% of the risk for primary (essential) hypertension is related to excess body weight.4 Although many patients with resistant hypertension are also obese, it is likely that these patients also have substantial target organ injury, which may contribute to their increased BP. There have been no studies, to our knowledge, examining whether catheter-based radiofrequency (RF) ablation of the renal nerves alters renal function and reduces BP in the early stages of obesity-induced hypertension before development of major target organ injury and resistant hypertension.

Previous studies from our laboratory have shown that obesity in dogs, induced by feeding a high-fat diet, causes a 15–20 mm Hg increase in mean arterial pressure (MAP), similar to what is observed in obese humans before developing target organ injury.5 In addition, obese dogs also exhibit cardiovascular, renal, hormonal, and metabolic changes similar to those seen in obese humans.3 We have also shown that obesity hypertension can be markedly attenuated by complete surgical RD in dogs6 or by blocking the sympathetic nervous system with α and β adrenergic antagonists in humans.7

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suggesting that obesity hypertension is caused, at least in part, by increased renal sympathetic activity. Catheter-based RD is thought to cause partial depletion of the sympathetic innervation in the kidney. However, it is not known whether complete denervation of the kidneys is required to reduce or normalize BP in obesity-induced hypertension.

The impact of catheter-based RF RD on the renal nerves at various distances from the renal artery lumen also remains unclear. Most previous studies have focused on where renal innervation terminates in the kidney, rather than the distribution along the renal artery where catheter-based RF denervation procedures occur. Recently there was a report of renal nerve distribution along the renal artery, including distance of the nerves from the renal artery in human cadavers. Our study not only identified the renal nerves and their proximity to the renal artery lumen but also determined the efficacy of RD using a catheter-based RF method. We also assessed the chronic effects of RF-induced RD on BP and renal function in obese dogs.

METHODS

Experiments were performed on chronically instrumented male mongrel hounds (n = 13) that were conditioned before the study. Nine dogs underwent bilateral RD, and experiments were designed so that each dog served as its own control for the BP, plasma hormones, and renal function measurements. The other 4 dogs served as the controls for renal norepinephrine (NE) measurements and histological analysis. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center and were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the guidelines of the Animal Welfare Act.

High-fat diet

Throughout the study, dogs were fed 3 cans per day (13 oz per can) of a sodium-deficient diet (H/D; Hill’s Pet Products, Topeka, KS) which provided approximately 7 mmol/day sodium and 65 mmol/day potassium. Cooked beef fat (0.5 to 0.9 kg/day) was added to the regular diet. When the dogs achieved a 50%–60% increase in body weight, approximately 5 weeks after starting the high-fat diet, the amount of fat in the diet was reduced to maintain a stable body weight. Sodium intake was kept constant at approximately 76 mmol/day by adding sodium chloride to the food until catheters were implanted to begin a 0.9% saline infusion at a rate of approximately 460 ml/day. This model of obesity created by feeding dogs a high-fat diet closely mimics the cardiovascular, renal, hormonal, and metabolic changes observed in obese human subjects.

Catheter implantation

After at least 5 weeks of high-fat diet, Tygon (Norton Plastics, Akron, OH) catheters were implanted, under isofluorane anesthesia, in the femoral arteries and veins for measurement of arterial BP and blood sampling, respectively. All catheters were tunneled subcutaneously, exteriorized in the scapular region, and filled with heparin solution (1,000 USP U/ml). After surgery, the dogs were permitted to recover, antibiotics were administered daily, and rectal temperatures were monitored to ensure that the dogs were afebrile throughout the studies.

After a recovery period of 1–2 weeks, the dogs were placed in individual metabolic cages in a quiet, air-conditioned room with a 12-hour light/dark cycle and fitted with harnesses containing pressure transducers (Argon, Athens, TX) mounted at the level of the heart. Arterial pressure signals were recorded on a polygraph (model 7D; Grass Instruments, Quincy, MA), sent to an analog-to-digital converter, and analyzed with a digital computer, using software developed in our laboratory. Analog signals from the polygraph were sampled in bursts of 12 seconds/minute, 24 hours/day, and digitized data were processed for determination of systolic BP (SBP), diastolic BP (DBP), and mean arterial BP and heart rates. The average arterial BP and heart rate for each day were calculated from values recorded during an 18-hour period between 2 pm and 8 AM. All routine care of the dogs (including feeding and cage cleaning), studies of renal function, and blood sampling were performed between 8 AM and 2 PM.

One of the venous catheters was connected to a roller infusion pump (Wiz pump; Isco Instruments, Lincoln, NE), which delivered approximately 460 ml/day of sterile isotonic saline solution. The saline solution was pumped through a disposable filter (0.22 μm, Cathivex; Millipore, Bedford, MA). Total sodium intake, including the food and the intravenous saline infusion, was maintained constant at approximately 76 mmol/day throughout the study.

Experimental protocol/control period

After the dogs were placed in metabolic cages and the intravenous infusions were started, 7–14 additional days were allowed for the dogs to achieve sodium balance and for stable control measurements to be acquired. During the control period, the dogs were trained to lie quietly while blood samples were obtained from the arterial catheters and studies of renal function were performed.

Renal denervation

After 1–2 weeks of control measurements, the dogs underwent bilateral RD using the St. Jude Medical EnlightHTN system (St. Jude Medical, St. Paul, MN). The system consists of an RF ablation generator and an RD catheter. The generator delivers RF energy for RD in a temperature-controlled mode through the catheter. The catheter has an expandable basket with 4 electrodes. The basket is designed with 2 sizes, and it expands from 3 to 6 mm and from 5 to 8 mm, respectively, to cover the range of renal artery diameters and to create 4 lesions at each ablation location. The dogs were given prophylactic analgesia and anesthetized with isofluorane, and a guide catheter was placed in the left carotid artery. Under fluoroscopic guidance, the guide catheter was advanced to the renal artery ostium, and angiograms were obtained to determine the size of the renal artery. Then the RD catheter was advanced into the renal artery, the catheter basket was...
expanded, and the guide catheter was pulled back to the aorta. The RF energy was applied, and ablations were made along the renal artery, starting from the bifurcation and repositioned toward the ostium for additional ablations if the main renal artery length permitted ablations at multiple sites. The average power delivered was 4.6 watts, and the average temperature measured from the electrodes was 65 °C. After the RF ablations, renal angiograms were obtained again to confirm the patency of the artery. The procedure was repeated in the contralateral renal artery to achieve bilateral RD. After RD, dogs were returned to the metabolic cages for hemodynamic and renal function measurements for 8 weeks.

Of the 9 dogs that underwent RD, 3 dogs had atypical renal anatomy. One dog had dual renal arteries, and only 1 of the renal arteries underwent RD. Two dogs had early bifurcations, with the main renal artery length <10 mm. These 3 dogs were excluded from the data analysis.

**Analytical methods**

Glomerular filtration rate (GFR) was estimated from the total clearance of 125I-iothalamate (Glofil; Iso-Tex Diagnostics, Friendswood, TX) biweekly as described previously. The distribution space of 125I-iothalamate was used as an index of extracellular fluid volume. Plasma renin activity was measured by radioimmunoassay (RIA) using 125I-labeled angiotensin I (New England Nuclear, Boston, MA) and polyclonal rabbit antihuman antibody (Arnel Products, New York, NY). Plasma insulin concentrations were measured by RIA (Diagnostic Products, Los Angeles, CA). Renal tissue NE values were measured using high-performance liquid chromatography. At the end of the 8-week period, the dogs were anesthetized, and 6 pieces of renal cortex tissue were collected per kidney, quickly weighed, and placed in liquid nitrogen. Samples were then homogenized in glutathione and ethylenediaminetetraacetic acid (EDTA) buffer and centrifuged to remove cell parts, and the supernatant was collected and frozen. All steps were performed on ice or in a refrigerated centrifuge.

**Histological analyses**

At the end of the 8-week period, the left and right renal arteries, from the aorta to the kidneys, were collected. The renal arteries were cut into equal transverse sections from the aorta to the kidney, fixed, and embedded in paraffin. This resulted in 6–13 blocks depending on the length of the renal artery. Five-micron sections were taken from all blocks processed. Sections of the main renal artery were assigned to 1 of 3 areas: near the bifurcation (close to the kidney), the middle section, and near the ostia. All sections were stained with hematoxylin and eosin. The observer was blinded to the source of tissue in the sections. Sections were examined for the total number of nerves, number of injured nerves, and the distance measured from nerves to the renal artery lumen-intima interface.

**Statistical analyses**

Control BP and renal function data obtained for dogs before the RD period were compared with data obtained for the same dogs after the RD by using analysis of variance and Dunnett’s t test for multiple comparisons. Histologic data for obese RD dogs and obese dogs without RD were compared using the Mann–Whitney rank sum test. Statistical significance was considered at a value of \( P < 0.05 \).

**RESULTS**

**Body weight, BP, and GFR data**

Before the high-fat diet, the dogs weighed 22.0 ± 0.6 kg. At the end of the 5-week high-fat diet the dogs weighed 31.5 ± 1.0 kg. At the end of the experiments, the dogs weighed 37.0 ± 1.3 kg, representing a 66% weight gain compared with their lean weights. SBP fell from 157 ± 5 mm Hg during the control period to 133 ± 3 mm Hg 8 weeks after RD (\( P < 0.01 \) (Figure 1). There was a slight but insignificant decrease in DBP from 88 ± 2 mm Hg to 86 ± 2 mm Hg after RD (Figure 1). RD reduced MAP by 9 mm Hg at the end of the experimental period (Figure 1). All of the dogs had decreases in MAP ranging from −2 mmHg to −14 mmHg. Figure 2 shows the weekly BP changes. MAP and SBP dropped quickly the first 2 weeks after RD and then remained reduced over the next 6 weeks. There were no significant changes in heart rate (control: 96 ± 3 vs. RD: 100 ± 6 beats per minute) or GFR (control: 90.5 ± 4.9 vs. RD: 89.3 ± 4.0 ml/minute after RD (Figure 3).
Renal NE, hormonal, and blood data

RD lowered renal cortex NE levels by 42% overall (210 ± 48 pg/g kidney for control kidneys vs. 121 ± 19 pg/g kidney for RD kidneys; P < 0.01). There was a correlation of renal tissue NE with mean arterial BP reduction (r = 0.73; P = 0.08) as well as with SBP reduction (r = 0.74; P = 0.07), with greater BP reductions occurring with lower tissue NE content (Figure 4); however, the correlations did not reach statistical significance. Table 1 shows that there were no significant changes in plasma protein, plasma sodium, plasma renin activity, plasma aldosterone, plasma cortisol, or plasma insulin levels. There was a small but significant increase in plasma potassium concentration (control: 3.9 ± 0.1 mEq/L vs. RD: 4.5 ± 0.1 mEq/L; P < 0.01). There was also a decrease in hematocrit (control: 42 ± 1% vs. RD: 35 ± 1%; P < 0.05).

Histology and distribution of renal nerves

Sections of the renal artery were examined to determine the distance of the renal nerves from the luminal-intima border and the extent of denervation. Renal nerves were found as close as 0.28 mm and as far as 6.3 mm from the renal artery lumen-intima interface. Seven percent of the nerves were found between 0.28 mm and 1.0 mm from the artery lumen, 61% were found between 1.0 mm and 2.5 mm, 20% were found between 2.5 mm and 3.5 mm, and 12% were found between 3.5 mm and 6.7 mm. Figure 5 shows the cumulative percentage distribution of renal nerves from the renal artery lumen-intima interface. Eighty-five percent of the renal nerves were found within 3.5 mm of the renal artery lumen-intima interface. Approximately 46% of renal nerves observed exhibited injury due to the RD procedure (n = 101 of 220). Injury was found at nearly all distances from the artery lumen but was
most prevalent from 0.28 mm to 3.5 mm, with 90% of the injured nerves being found in this range. Renal nerve injury was found dispersed along the length of the renal artery, with signs of injury occurring in 49% of the nerves observed near the bifurcation, in 38% of the nerves observed in the main renal artery, and in 63% on the nerve observed near the ostium. Injury to the renal nerves was assessed as peri-neural fibrosis, necrosis, and neuron loss (Figures 6 and 7). These samples were examined approximately 8 weeks after RD; therefore some smaller injured nerves may have degenerated and become unobservable.

DISCUSSION

Catheter-based RD was effective in reducing renal NE levels and lowering BP in obese, hypertensive dogs. All dogs had decreased MAP, a ≥10 mm Hg decrease in SBP, and a slight decrease in DBP, GFR, plasma insulin concentration, and heart rate were not significantly altered by RD.

Renal tissue NE content was reduced in all RD dogs, with an average decrease of 42% compared with control dogs. There are currently no reports, to our knowledge, that show the level of RD needed to reduce BP by a determined amount. Most previous RD studies have either performed surgery to achieve near complete RD or have used RF ablation methods to produce partial RD but have not quantified the actual level of denervation. Although this study was not designed specifically to quantify the level of denervation, the reduction in renal NE levels observed in RD dogs corresponds well with the histological analysis of renal nerve injury. There was a correlation of renal tissue NE with MAP reduction, as well as with SBP reduction, although this was not statistically significant. The 42% average reduction in renal NE levels in this study was similar to reductions in NE spillover in humans undergoing RF ablation of the renal nerves.\(^\text{13}\)

The reason for the incomplete RD observed 6 weeks after the RF ablation procedure is unclear, but our observations are consistent with previous RF RD studies in humans using renal NE spillover to assess completeness of RD.\(^\text{14}\) One likely explanation for the partial denervation is that a significant fraction of the renal nerves do not enter the vascular adventitia until after branching of the renal artery and are therefore not susceptible to the ablation procedures, which are confined to the main renal artery before it branches. In fact, we recently found in pigs that RF renal nerve ablation in the branches of the renal artery produced a 74% reduction in renal tissue NE content (unpublished data). Another possible explanation is that there may have been some regrowth of the renal nerves by 8 weeks after the procedure was performed when the renal tissue samples were obtained. This seems unlikely because we previously reported that renal NE content was reduced by >99.5% 6 weeks after surgical denervation\(^\text{15}\) and Nomura et al.\(^\text{16}\) also found anatomical evidence for only slight renal nerve regeneration between 12 and 24 weeks after surgical RD in dogs and that regeneration was not functionally or morphologically complete even after

| Table 1. Plasma hormones, sodium, potassium, and hematocrit for 7 dogs before and 6 weeks after renal denervation |
|-----------------------------------------------|-----------------|-------------------|
| Measurement                      | Pre-RD          | RD                |
| Extracellular fluid volume, ml     | 7,968 ± 444     | 7,860 ± 336       |
| Hematocrit, %                     | 42 ± 2          | 37 ± 1*           |
| Plasma protein, g%                | 6.9 ± 0.2       | 7.4 ± 0.1         |
| Plasma sodium, mmol/L             | 148 ± 1         | 147 ± 1           |
| Plasma potassium, mmol/L          | 3.9 ± 0.1       | 4.5 ± 0.1*        |
| Plasma renin activity, ng angiotensin I/ml/hour | 1.09 ± 0.38 | 0.66 ± 0.17         |
| Insulin, µU/ml                    | 42.1 ± 9.1      | 60.95 ± 10.2      |
| Aldosterone, ng/dl                | 4.15 ± 0.59     | 4.66 ± 0.47       |
| Cortisol, µg/dl                   | 1.28 ± 0.34     | 1.25 ± 0.18       |

*Data are mean ± SE. Abbreviation: RD, renal denervation. *P < 0.05 vs. pre-RD.
Therefore, it seems unlikely that significant regrowth of the renal nerves can explain our finding that renal NE content was reduced by only approximately 42% 6 weeks after RF ablation. Regardless of the reasons for the moderate degree of RD produced in our studies, it is clear that even partial RD can cause significant, chronic reductions in BP. Whether more complete RD would produce even greater reductions in BP is unclear.

Sympathetic denervation has been used to lower BP both experimentally in animals and therapeutically in humans. In dogs, surgical RD before the development of obesity markedly attenuates the sodium retention and increased BP that is usually observed as obesity develops. However, surgical RD is not a feasible option for treating many patients with common obesity-associated hypertension. In our study, the much less invasive method of RF RD was effective in lowering arterial BP after obesity was established. The largest change in BP was seen in SBP, which decreased in all dogs, with an average reduction of 24 mm Hg. The reduction in DBP was less pronounced and more variable. These observations, along with our previous studies and studies by Lohmeier et al., indicate that the renal nerves play an important role in mediating renal sodium retention and elevated BP in obesity. Moreover, RF ablation of renal nerves after obesity is established can substantially reduce BP, especially SBP, even with only partial RD. A limitation of our study is that we did not, for practical reasons, include a sham control group. The lack of a sham control group has also been a limitation of clinical studies using RF RD.

In humans, radical surgical sympathectomy of the thoracic nerves and some of the lumbar nerves was once used as a treatment for hypertension when there were no other options. Although providing a method to lower BP, the extensive surgical denervation caused complications that overrode the beneficial effects, and performance of the surgery was ended in the 1950s. Catheter-based RF ablation of the renal nerves may provide a feasible alternative to lower BP without radical surgery. The results of our study indicate that this procedure may be effective in treating relatively mild hypertension associated with obesity, even if RD is only partial.
Catheter-based RD has proven to be an effective treatment in many resistant hypertensive patients. In most of the clinical trials, SBP was required to be >160 mm Hg for patient enrollment. With these high BPs, it is perhaps not surprising that decreasing renal sympathetic activity by RD lowers BP; even though BP is not always reduced to normal values. Clinical trials, including a trial using the EnligHTN RD system, have consistently shown that office BP is lowered by approximately 30 mm Hg and 12 mm Hg for SBPs and DBPs, respectively, in patients with resistant hypertension. In Symplicity HTN-2, catheter-based RD lowered SBP by 24 mm Hg and DBP by 8 mm Hg. An important point is that this large decrease in BP (−33/−12 mm Hg SBP/DBP) in the Symplicity HTN-2 trial was measured using standard office BP procedures. When 24-hour ambulatory BP was measured in a subgroup of patients with resistant hypertension, the BPs were still lower than in the control group, but the difference was much less (−11/−7 mmHg SBP/DBP) when compared with decreases in office BP measurements.

Perhaps when considering RD as a treatment for hypertension, then degree of renal sympathetic activation should be considered. From published clinical studies, 8%–17% of patients treated with RD are classified as nonresponders who had <10 mm Hg reduction of SBP 6 months after RD. The nonresponder rate was as high as 37% in the crossover group of the Symplicity HTN-2 trial. Assuming effective RD was achieved, it may be that these patients have essential hypertension that is not associated with elevated renal sympathetic activity, and thus RD may not be an effective treatment in these patients.

Another aspect of the clinical trials that should be examined is the occurrence of obesity, which has been shown in experimental animals as well as in humans to be associated with increased renal sympathetic nerve activity. Most of these trials include obese patients with a mean body mass index (BMI) of 30 kg/m². Data from the Framingham study have attributed 65%–75% of the risk for primary (essential) hypertension to obesity. Perhaps the other 25%–35% in Framingham and the 28% of the nonresponder population in RD studies have the lack of sympathetic activation as a common link. Therefore, assessment of factors that are usually associated with increase renal sympathetic activity, such as visceral obesity, may be useful in predicting which patients are more likely to have a significant BP reduction after RD.

Renal tissue NE content was decreased by 42% after RF ablation of the renal nerves in our study. In the human Simplicity HTN I trial, renal NE spillover was measured in a subgroup of 10 patients and found to be decreased by 47%. A possible mechanism by which RD may lower arterial BP is by removing afferent nerve signals from the kidney to the brain. However, the role of the afferent nerves in BP control in obesity or in resistant hypertension is still unclear. Kopp et al. showed that afferent RD alters the ability of the baroreflex to control efferent renal sympathetic nerve activity. Wyss et al. showed that removing the afferent sensory signal attenuated renovascular hypertension in rats. Although our study was not designed to determine the mechanisms by which RD lowers BP, our previous studies have shown that complete surgical removal of renal afferent traffic by dorsal root ganglionection from T10 to L2 did not attenuate obesity-induced hypertension in dogs, the same model of obesity used in this study. These findings suggest that most of the effect of RD on BP in obese dogs fed a high-fat diet can be attributed to removal of renal sympathetic efferent fibers rather than renal afferents.

One goal of our study was to evaluate the distribution of the renal nerves around the renal artery and the effectiveness of RF-based RD to injure those nerves. Our data show that most of the renal nerves (approximately 86%) are located within 3.5 mm of the renal artery luminal surface. Atherton et al. recently examined renal nerve distribution in human cadavers and found that 90.5% of the nerves were located within 2 mm of the artery luminal surface. They stated that some nerve structures extended beyond 2.5 mm; however, their study focused on nerves out to 2.5 mm. We found nerves to be out as far as 6.5 mm from the luminal surface of the renal artery. Although there was some renal nerve injury >3.5 mm from the luminal surface, the majority of the nerve injury (88%) was found within 3.5 mm. Therefore, it appears that the RF signal can cause significant nerve injury approximately 3.5 mm from the luminal surface of the renal artery. Because most of the nerves occur within that area, RF-based RD can be an effective method to injure those nerves.

In conclusion, catheter-based RF ablation of the renal nerves lowers BP in obese hypertensive dogs, which appear to mimic the cardiovascular, renal, and metabolic changes observed in obese, hypertensive humans, without significantly compromising renal function or vascular integrity. The data from this study also indicate that complete RD is not necessary for achieving significant BP reduction in obese hypertensive dogs. The mechanism by which RD lowered BP was not examined in this study but may be due largely to removal of renal sympathetic efferent fibers, corresponding to a 42% decrease in renal NE content as well as injury in 46% of the nerves observed along the renal artery.

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DISCLOSURE

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