Renal Morphological Changes After Sinoaortic Denervation in Dogs

Claudine Orfila, Christine Damase-Michel, Jean-Claude Lepert, Jean-Louis Montastruc, Jean-Michel Suc, Paul Montastruc, and Jean-Pierre Girolami

The present study investigates morphological renal lesions in sinoaortic-denervated dogs 1 (n=6) and 18 (n=5) months after sinoaortic denervation compared with sham-operated controls (n=8). After 1 month, a marked hyalinization and moderate thickening of the media of arterioles and small interlobular arteries were observed. These changes associated with edema and intimal thickening led to a narrowing of the lumen. In glomeruli, increase of mesangial matrix was focally present in all cases and associated with mesangial proliferation. In four of six cases, some glomeruli appeared retracted, with a large urinary space. A focal area of interstitial fibrosis occurred in just one case. After 18 months, similar but more pronounced vascular lesions were present, with marked hyperplasia of the media. Glomerular changes were characterized by mesangial lesions associated with focal glomerular sclerosis and thickening of Bowman’s capsule. Tubulointerstitial lesions were more prominent in this group, with the presence of tubular epithelial changes and casts. Focal interstitial fibrosis, infiltrates, or both were demonstrated in all cases. These morphological lesions were associated with an increase in arterial blood pressure, proteinuria, and natriuresis and a decrease in urinary kallikrein. These results show that chronic sinoaortic denervation in dogs is associated with renal lesions similar to those observed in other well-established experimental and clinical hypertensive states. (Hypertension 1993;21:758–766)

KEY WORDS • hypertension, experimental • dog studies • microscopy, electron • kidney • denervation

Among the various models of experimental arterial hypertension, one consists of denervation of the arterial baroreceptors.1 By this surgical approach, hypertension has been induced in dog,2,3 rabbit,4 and rat.5 The mechanism of this experimental hypertension is still being discussed, and it may involve an increase in norepinephrine turnover and biosynthesis already reported in rabbits with neurogenic hypertension.6 To our knowledge, renal modifications in this model of hypertension have received little attention. A recent report concerning urinary kallikrein excretion after chronic sinoaortic denervation in conscious dogs7 has shown that urinary kallikrein excretion, which is of renal origin, is reduced after 32 weeks, thus suggesting renal dysfunction in this model of hypertension. With respect to the renal kallikrein-kinin system, a large number of reports8 suggest a close relation between the decrease in renal kallikrein excretion and the development of hypertension. Although no causal relations have been clearly established between the decrease in urinary kallikrein excretion and the onset of hypertension, a decrease in urinary kallikrein excretion is a significant marker of established hypertension. Because the kidney is a key organ in the long-term control of blood pressure, ascertainment of renal damages could provide other evidence for the persistence of high blood pressure.

An association between kidney disease and hypertension was reported by Bright9 as early as 1836. More recently, the overriding dominance of the kidneys in long-term regulation of arterial pressure and in hypertension has been demonstrated by clinical and experimental studies.10 In both primary and secondary human hypertension, persistence of abnormally high levels of blood pressure is associated with the progression of vascular disease in many organs, including the kidney.

To further document the possible renal effect of high blood pressure associated with arterial baroreceptor denervation, we investigated the renal morphology in this experimental model. To achieve this, we studied the renal morphological changes occurring in a neurogenic hypertensive model in two groups of dogs: one group was studied 1 month after surgery and the second 18 months after surgery; these groups were compared with sham-operated controls.

Methods

Sinoaortic Denervation

Nineteen male dogs (mean age, 2.0±1.3 years) weighing 12–25 kg (INSERM farm) were used in the experiments and were divided into control (n=8) and sinoaortic-denervated (SAD) groups. Renal morphology was studied 1 (SAD 1, n=6) and 18 (SAD 18, n=5) months after sinoaortic denervation. Controls were
submitted to sham operation, and renal morphology was studied 1 (sham 1, n=4) and 18 (sham 18, n=4) months later. As previously reported by Damase-Michel et al,11 sinoaortic denervation needed two successive surgical procedures. After being anesthetized with chloralose (80 mg/kg i.v.), the animals were intubated through the trachea and ventilated with a Palmer (London) respirator on the day of the first procedure. The carotid arteries and sinus were isolated after lateral neck incision on the right side under sterile surgical conditions. The carotid sinus nerve was identified and transected with ophthalmic cautery. Then, by sectioning of the common artery and both internal and external carotids, the carotid bifurcation was destroyed. Hering's nerve was sectioned and Cyon's nerve was isolated, identified by electrical stimulation (afferent activation induces bradycardia, hyperpnea, and hypotension), and sectioned over 4 cm to prevent any reinnervation. Both vagal and sympathetic fibers in the vagus were maintained intact during this surgical procedure. Seven weeks later, the same surgical technique was used for the left side. The failure of norepinephrine (0.5, 1, and 2 μg/kg i.v.) and phenylephrine (0.1, 1, and 10 μg/kg i.v.) to induce bradycardia after bilateral carotid and aortic sinus nerve section demonstrated the effectiveness of baroreceptor denervation. Moreover, nitroglycerin (1, 3, 10, and 30 μg/kg i.v.) induced a dose-dependent decrease in blood pressure without any change in heart rate in SAD dogs. These tests were performed just after and every month after sinoaortic denervation. The dogs were kept in individual cages under normal diet. All investigations reported in this article were conducted in conformity with the guiding principles in the care and use of animals.

Biochemical Plasma Assays

Plasma catecholamines were measured before surgery and 1 and 18 months later by high-performance liquid chromatography with electrochemical (amperometric) detection.12 Briefly, fresh blood was collected (from a catheter introduced into the femoral artery 1 hour before to prevent any stress) over lithium heparin via a Gould P23ID transducer. Heart rate was measured using a heart period meter triggered by blood pressure. These measurements were repeated after sinoaortic denervation. Therefore, the values after sinoaortic denervation were compared with those obtained under resting conditions (before sinoaortic denervation), each animal serving as its own control. The cardiovascular parameters were always measured after a rest period of 30 minutes.

Urinary Parameters

Before urine was collected, the animals were acclimatized for 3 days in individual cages, and the urine volume of the following 2 days was measured. Urinary samples were collected on two consecutive days but separate 24-hour periods to minimize kallikrein degeneration by urinary proteases. Urinary kallikrein activity was estimated by the kininogenase activity as previously described.13 Urinary sodium concentration was determined with a flame photometer. Urinary protein was measured by the sulfosalicylic method.14

Blood Pressure and Heart Rate Measurement in Conscious Dogs

Several days before any experiment, animals were trained to stand still for 3–4 hours on a Pavlov table and become accustomed to blood sampling. Blood pressure was measured by means of a catheter introduced into the abdominal aorta with dogs under local anesthesia (xyloca ine 5%) and connected to a Honeywell recorder via a Gould P23ID transducer. Heart rate was measured using a heart period meter triggered by blood pressure. These measurements were repeated after sinoaortic denervation. Therefore, the values after sinoaortic denervation were compared with those obtained under resting conditions (before sinoaortic denervation), each animal serving as its own control. The cardiovascular parameters were always measured after a rest period of 30 minutes.

Morphological Observations

At the end of the observation periods (1 or 18 months), SAD and control dogs were killed by an overdose of intravenous pentobarbital. For light microscopy, renal tissue was fixed by immersion in buffered picric acid–parafomaldehyde fixative (Zamboni’s fixative plus 1% glutaraldehyde) for 4 hours at room temperature. The tissue was then embedded in paraffin after dehydration. Sections were stained with Masson’s trichrome. For electron microscopy, renal tissue was fixed in 2% glutaraldehyde, washed in HCl-cacodylate buffer postfixed in 2% osmium tetroxide, and embedded in Epon 812. Thin sections were stained with uranyl acetate and lead citrate and examined in a Hitachi electron microscope. Semithin sections were stained with periodic acid–Schiff methanamine silver (Jones) and observed by light microscopy.

A semiquantitative score was used to evaluate the degree of damage according to the method of Raji et al.16 A minimum of 20 glomeruli (range, 20–100) in each specimen were examined, and the severity of the lesion was graded from 0 to 4+ according to the percentage of glomerular involvement; the injury score was obtained by multiplying the degree of damage (0 to 4) by the percentage of glomeruli displaying the same degree of severity. The extent of the injury for each individual tissue specimen was then obtained by the addition of these scores. Similarly, scoring of vascular damage was performed using the same method, replacing glomeruli with arterioles and interlobular arteries. Presence of interstitial fibrosis and infiltrates was semiquantitatively evaluated and graded from 0 to 4+: 0 = absence, 1+ = very mild focal presence, 2+ = mild focal presence,
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Proteinuria was even higher after 18 months (3.4±0.5 g/L, p<0.05). In contrast, marked proteinuria appeared compared with control values.

Plasma Renin Activity and Catecholamine Assays

Urinary Kallikrein Activity and Natriuresis

Plasma renin activity was decreased at the end of the study (p<0.05) and was normal 18 months later. One and 18 months after sinoaortic denervation, urinary kallikrein activity exhibited a significant increase compared with control values (p<0.05). On the other hand, urinary kallikrein activity was lower than control values after 18 months. Urinary sodium excretion exhibited a permanent increase from the first month (p<0.05) to the end of the study (p<0.05) compared with control values.

Proteinuria

No significant proteinuria was detected in control animals. In contrast, marked proteinuria appeared (1.0±0.1 g/L) 1 month after sinoaortic denervation and was even higher after 18 months (3.4±0.5 g/L, p<0.05).

TABLE 1. Cardiovascular and Plasma and Urinary Parameters in Sham-Operated and Sinoaortic-Denervated Dogs Before and After Surgical Procedure

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated dogs</th>
<th>Sinoaortic-denervated dogs</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1 month (n=4)</td>
<td>18 months (n=4)</td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>155±3</td>
<td>155±5</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>65±5</td>
<td>66±5</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>76±6</td>
<td>79±8</td>
</tr>
<tr>
<td>Norepinephrine (nM)</td>
<td>1.34±0.09</td>
<td>1.36±0.15</td>
</tr>
<tr>
<td>Epinephrine (nM)</td>
<td>0.86±0.04</td>
<td>0.85±0.06</td>
</tr>
<tr>
<td>PRA [(ng/hr)/mL]</td>
<td>1.22±0.14</td>
<td>1.20±0.12</td>
</tr>
<tr>
<td>UKal [(µg/min)/mg creatinine]</td>
<td>0.65±0.09</td>
<td>0.63±0.11</td>
</tr>
<tr>
<td>UNaV [(mmol/day)/kg]</td>
<td>0.56±0.20</td>
<td>0.53±0.19</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; PRA, plasma renin activity; UKal, urinary kalliWrein activity; UNaV, urinary sodium volume excretion. Values are mean±SEM.

* p<0.05.

Results

Data concerning blood pressure, heart rate, catecholamine assays, plasma renin activity, urinary kallikrein activity, and natriuresis are presented in Table 1.

Blood Pressure and Heart Rate

Sham operation did not change systolic and diastolic blood pressures and heart rate measured 1 or 18 months later. One and 18 months after sinoaortic denervation, systolic and diastolic blood pressures and heart rate were significantly increased (p<0.05 compared with resting values).

Plasma Renin Activity and Catecholamine Assays

Plasma renin activity was decreased at the end of the first month (p<0.05) and was normal 18 months later. In contrast, plasma catecholamine levels were transiently increased 1 month after sinoaortic denervation compared with control values (p<0.05).

Urinary Kallikrein Activity and Natriuresis

During the first month after sinoaortic denervation, urinary kallikrein activity exhibited a significant increase compared with control values (p<0.05). On the other hand, urinary kallikrein activity was lower than control values after 18 months. Urinary sodium excretion exhibited a permanent increase from the first month (p<0.05) to the end of the study (p<0.05) compared with control values.

Proteinuria

No significant proteinuria was detected in control animals. In contrast, marked proteinuria appeared (1.0±0.1 g/L) 1 month after sinoaortic denervation and was even higher after 18 months (3.4±0.5 g/L, p<0.05).
FIGURE 2. Top panel: Bar graph shows fibrohyalinosis of the media expressed by a scoring system. m, Month; SAD, sinoaortic-denervated dogs. *p<0.02, †p<0.05 vs. sham 1 month; ‡p<0.01 vs. sham 18 months. Bottom panel: Bar graph shows thickening of the intima expressed by a scoring system. *p<0.01, †p<0.01 vs. sham 1 month; ‡p<0.01 vs. sham 18 months.

demonstrated (Figure 6, top panel). In one case, capsular fibrosis (Figure 6, bottom panel) was present. The presence of glomerular collapse (p<0.02) and capsular fibrosis (p<0.05) was significant compared with controls. In two cases, a hyperplasia of juxtaglomerular apparatus was observed (Figure 7).

Tubulointerstitial alterations were moderate and characterized by the presence of localized fibrosis and infiltrates in two cases (Figure 8).

In sham 18, moderate vascular lesions occurred. When compared with sham 1, a medial fibrosis (p<0.02; Figure 2, top panel) and a moderate thickening of intima (p<0.01; Figure 2, bottom panel) were observed. Some glomerular changes were demonstrated: an increase of mesangial matrix (p<0.02; Figure 5, top panel) and a slight thickening of Bowman's capsule (p<0.01; Figure 6, bottom panel). No significant difference was present in interstitial tissue (Figure 8).

Eighteen months after sinoaortic denervation, the vascular changes were characterized by a more extensive fibrohyalinosis of arterioles and small arteries in all cases (Figure 2). Changes in medial and intimal lesions were significant compared with sham 18 (p<0.01). A narrowing of the lumen was also caused by edema and thickening of the media. In two of five cases, the media contained numerous nuclei, indicating that some of the thickening observed is the result of hyperplasia (Figure 9, top panel). Furthermore, interlobular arteries showed elastic fragmentation and reduplication of elastic lamina (Figure 9, bottom panel). These changes were not observed in SAD 1.

The glomerular changes were more intense in SAD 18 than in SAD 1 (Figure 5, top panel; Figure 6). Diffuse increase of mesangial matrix associated with focal proliferation was observed in all cases (p<0.05; Figure 5, top panel). More frequently, the glomerular tuft showed hyalinization at the vascular pole (Figure 10, top panel) and segmental mesangial thickening. Glomeruli were collapsed (p<0.01; Figure 6, top panel), with marked intracapsular fibrosis (p<0.01; Figure 6, bottom panel) and wrinkling of the basement membranes, which appeared thickened, forming a mass of basement membrane (Figure 10, bottom panel). In less severe cases, there was some irregular mesangial sclerosis and adherence of the glomerular tuft to the parietal epithelium. A proliferation of fibrosis tissue of Bowman's capsule caused its thickening in four cases.

FIGURE 3. Top panel: Photomicrograph shows typical arteriolar lesions with severe hyaline thickening of the wall and narrowing of the lumen 1 month after sinoaortic denervation. Bottom panel: Photomicrograph shows arteriolar lesion with clear space in the wall and a red blood cell in the lumen 1 month after sinoaortic denervation. Masson's trichrome, ×361. Bar=50 μm.

A striking progression in tubulointerstitial lesions was also observed in SAD 18 compared with sham 18 ($p<0.001$, Figure 8) and SAD 1 ($p<0.01$, Figure 8). In all cases, interstitial fibrosis was present. A patchy chronic inflammation was demonstrated, mainly in some peritubular areas (Figure 11). In one severe case, dilated tubules containing amorphous or metachromatic casts and sclerosed glomeruli were present inside increased fibrous connective tissue and mononuclear interstitial infiltrates.

**Electron Microscopic Findings**

No marked changes were present in sham 1 (Figure 12, top left panel). No significant vascular lesion was demonstrated. A very mild focal increase of mesangial matrix was observed in one case of sham 18.

Although the vascular and glomerular ultrastructural changes observed in SAD 1 and SAD 18 were similar, they were more prominent in SAD 18. An increase of hyaline basement membrane material occurred inside the intima and media of small vessels. In rare cases, a reduplication of elastic lamellae was demonstrated. In some cases, a marked thickening of the intima was associated with swollen endothelial cells, leading to narrowing of the lumen (Figure 12, top right panel). Collagen fibers were demonstrated in the periadventitia. In glomeruli, a reduplication of Bowman's capsule was observed together with capsular thickening and splitting. A deposition of collagen associated with granular inclusions was observed inside the thickened capsule. Capillary basement membranes showed irregular thickening, with structural granular material trapped inside the basement membranes. The foot processes of the podocytes were focally confluent (Figure 12, bottom left panel). The mesangial matrix was increased, with prominent extensions of cytoplasmic processes, and contained large amounts of hyaline material. Focally, areas of mesangial hyperplasia were demonstrated. In some glomeruli, the capillaries were collapsed and the basement membranes wrinkled, with an increase in the lamina densa (Figure 12, bottom right panel).

**Discussion**

In this study, we describe the renal morphological findings observed in dogs 1 and 18 months after sinoaor-
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Renal Changes in Sinoaortic-Denervated Dogs

Bar graph shows tubulointerstitial lesions expressed by a scoring system. m, Month; SAD, sinoaortic-denervated dogs. *p<0.001 vs. sham 18 months, †p<0.01 vs. SAD 1 month.

Figure 8. Bar graph shows tubulointerstitial lesions expressed by a scoring system. m, Month; SAD, sinoaortic-denervated dogs. *p<0.001 vs. sham 18 months, †p<0.01 vs. SAD 1 month.

Shunt

As early as 1 month after sinoaortic denervation, animals exhibited renal changes compared with normotensive control animals. Vascular lesions were characterized by a thickening of walls associated with hyalinization of the media, edema, and narrowing of the lumen. Similar vascular lesions have been described in cases of benign human essential hypertension. It has been demonstrated that the thickening and reduction in the arteriolar lumen are caused by accumulation of

Figure 9. Top panel: Photomicrograph of small artery shows medial hyperplasia and red blood cells in the lumen 18 months after sinoaortic denervation. Bottom panel: Photomicrograph of small artery shows reduplication (multilayering) of elastic membranes and the presence of red blood cells almost completely filling the lumen 18 months after sinoaortic denervation. Jones’s stain, ×361. Bar=50 μm.

Figure 10. Top panel: Photomicrograph of glomerulus shows segmental hyalinization of the floculus 18 months after sinoaortic denervation. Bottom panel: Photomicrograph shows marked glomerular collapse with contraction of the tuft, enlargement of Bowman’s space, and wrinkling of glomerular basement membranes. The basement membrane of Bowman’s capsule is thickened and laminated 18 months after sinoaortic denervation. Jones’s stain, ×228. Bar=50 μm.

Figure 11. Photomicrograph shows marked interstitial fibrosis and mononuclear interstitial periarteritic infiltrate. Small artery shows mild hyperplasia of the media 18 months after sinoaortic denervation. Masson’s trichrome, ×361. Bar=50 μm.
granular and amorphous material in the intima. Lipids, including lipofuscin, may also be demonstrated. The term “hyalin” means an accumulation of lipids of hematogenous origin\textsuperscript{19,20} and an increase in basement membrane.\textsuperscript{21}

Reduplication of the elastic membrane, which appeared thickened and showed several concentric layers, was another vascular lesion, more prominent in the group of animals studied 18 months after sinoaortic denervation. This finding was also reported in cases of human benign hypertension.\textsuperscript{19} Several factors could be involved, such as thickening of the basement membranes of the endothelial and smooth muscle cells, formation of new collagen, and accumulation of lipids. The presence of mature collagen fibers in the media and perivascular tissues has already been reported.\textsuperscript{18}

Moreover, we also observed the presence of an increase in mesangial matrix sometimes associated with a focal hyperplasia. A previous study\textsuperscript{22} in human essential hypertension reported that mesangial changes in hypertension were characterized by a diffuse increase in matrix, proliferation of cells of the glomerular tuft being more prominent in malignant nephrosclerosis.\textsuperscript{23}

Other glomerular changes such as thickened and wrinkled glomerular capillary walls could result from ischemia. This has also been reported in cases of human arterial hypertension.\textsuperscript{19,20} A thickening of Bowman’s capsule was observed; this finding was previously reported in humans by Jones,\textsuperscript{21} who described collagen that was laid down by the parietal epithelial cells to form fibrous or fibrocellular crescents. In our study, we also observed increased cellularity of the juxtaglomerular apparatus. This observation has also been reported in human hypertension of less than 1 year’s duration.\textsuperscript{24}

In the literature, these granular cells are hyperplastic and hypergranulated compared with normal cells.\textsuperscript{25}
Focal tubulointerstitial lesions were scarcely present in the group of 1 month SAD dogs, but they were more marked and diffuse in animals studied 18 months after sinoaortic denervation. Tubular atrophy and interstitial fibrosis with chronic inflammatory infiltrates occur also in human hypertension. Bohle et al reported morphometric studies indicating a marked increase of mature collagen fibres in the interstitium.

Some studies suggest that structural alterations are basically the same as hypertension. Glomerular changes such as an increase in mesangial cell matrix size occur during the course of aging as well as sclerosis of the renal arteries and arterioles. In aging rats, interstitial fibrosis is associated with chronic inflammatory infiltrates. Although all these features could be common to hypertension and aging, in our work, the control group of animals was paired for age, and no significant glomerular, vascular, or tubulointerstitial changes were observed.

The lesions observed after sinoaortic denervation show some similarities to those found in spontaneously hypertensive rats. These rats exhibit marked vascular lesions as fibrinoid necrosis, sclerosis, and pericapsular fibrosis of glomeruli, characteristic of alterations described in human essential hypertension. When compared with other models of hypertension, it seems that the response of blood vessels depends on animal species. For instance, in Goldblatt’s model, no sclerosis occurs in vessels of dogs even after 8 years of hypertension. On the other hand, in rabbits there is a considerable increase in the ratio of wall thickness to arteriolar diameter.

In our model, we did not observe a malignant phase with arteriolar fibrinoid degeneration and necrosis, which is observed in dogs with severe impairment of renal function and hypertension in Goldblatt’s model. These severe morphological changes were also described in dogs after unilateral renal artery constriction and in wrapped kidney according to Page’s model in both rabbits and rats. On the contrary, hypertension induced by injection of platelet aggregates or Sephadex was associated with microembolic renal lesions. The intrarenal structural changes resembled human benign hypertension.

Previous studies during 4-hour recording sessions from our laboratory have shown that after sinoaortic denervation, blood pressure and heart rate remained elevated. The development of hypertension after sinoaortic denervation is associated with an increase in sympathetic tone. This result is in agreement with several previous data showing that this enhancement in plasma catecholamine level is strongly correlated with a decrease in leukocyte, cardiac, or renal β-adrenergic receptor number. Moreover, we observed a decrease in plasma renin activity and a transient rise in urinary kallikrein activity, which were already reported in this model. It can be suggested that these changes could be linked to the sympathetic hyperactivity and subsequent decrease in β-adrenergic receptors. This hypothesis is consistent with the observations of Albetini et al who, in conscious rats and Girolami et al in rat kidney cortical slices, who suggested that kallikrein release is inhibited by a direct adrenergic effect.

In contrast, the role of circulating catecholamines is not exclusive to the maintenance of high blood pressure, because these parameters (as well as leukocyte or cardiac adrenergic receptors) returned to normal values 18 months after sinoaortic denervation, whereas blood pressure remained elevated. During this second period of hypertension, urinary kallikrein activity and renal β-adrenergic receptor number appeared to be reduced. This change in urinary kallikrein activity is in agreement with most of the data previously reported during hypertensive states in either humans or experimental models.

In conclusion, sinoaortic denervation in dogs is rapidly associated with progressive renal damage. These changes are similar to renal alterations described in hypertensive states either in experimental models or in humans. During the long-term study, these changes became aggravated, especially the glomerular and tubulointerstitial lesions, and could perpetuate the hypertensive state itself. It could be interesting to investigate in these dogs a putative protective effect on the occurrence of renal lesions of antihypertensive drugs known to decrease blood pressure in this model.

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