Hypertension in Page (cellophane-wrapped) kidney is due to interstitial nephritis

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Background. Cellophane wrapping of the kidneys (Page kidney) induces perinephritis and hypertension, assumed to be due to renal ischemia resulting from parenchymal compression by the fibrous hull surrounding the kidneys. We investigated if interstitial nephritis, rather than plasma angiotensin activity, played a role in the development of hypertension in the Page kidney model.

Methods. We followed for 7 weeks rats with bilateral cellophane wrapping of the kidneys that received 20 mg/kg/day of the immunosuppressive antiproliferative drug mycophenolate mofetil (MMF) (two-kidney wrap/MMF) ($N = 10$) or vehicle (two-kidney wrap) ($N = 10$), and sham-operated rats ($N = 10$).

Results. The two-kidney wrap group had progressive increment in blood pressure, inflammatory damage occupying 25% to 50% of the renal tubulointerstitial region and increased number of angiotensin II–positive cells, angiotensin II content, and oxidative stress in the kidney. MMF treatment prevented the development of hypertension and renal inflammation without modifying the perinephritic hull or the increment it induced in the intrarenal pressure. The plasma levels of angiotensin II were similar in the two-kidney wrap group, the two-kidney wrap/MMF group and the sham-operated animals and unchanged from baseline, despite the blood pressure increase in the two-kidney wrap group.

Conclusion. Our results indicate that renal wrap hypertension is unrelated to plasma angiotensin II levels and related to the inflammatory damage caused by the external compression of the kidney.

In 1939, Page [1] described a model of hypertension caused by perinephritis induced by cellophane wrapping of the kidneys. He postulated that the fibrocollagenous hull formed around the kidney as a reaction to the cellophane would compress the organ and stimulate the secretion of pressor substances, thus resembling the hypertension obtained by constriction of the renal arteries in the classic Goldblatt experiments [2]. Subsequently, Grollman [3] presented a method of inducing hypertension that he considered to be less complicated than constriction of the renal artery and more reliable than the cellophane wrapping of the kidneys, a figure eight ligature encompassing both kidney poles. The hypertension induced by cellophane wrapping and by figure eight wrapping of one or both kidneys are generally assumed to have the same pathophysiology. As stated in a recent review of the clinical conditions capable of causing what is widely known as “Page kidney,” external compression of the organ causes renal hypoperfusion, ischemia, and activation of the renin-angiotensin system (RAS) [4].

However, the participation of the circulating RAS in pathogenesis of hypertension in the Page kidney has not been confirmed and several findings suggest that other mechanisms may play a more determinant role. First is the observation that the reduction in dietary sodium prevents and corrects hypertension in the renal wrap hypertension [5, 6], in contrast to the lack of effects of sodium restriction in the angiotensin-driven Goldblatt hypertension [7, 8]. Second are the observations of Haywood, Williams, and Ball [6] who found that, in animals given a normal sodium diet, angiotensin antagonists did not correct the early nor the late hypertension in the one-kidney figure eight wrap model. Finally, the studies of Hart et al [9] recently reported that plasma angiotensin II levels are unchanged during the progressive development of hypertension and that volume load is the prevailing stimulus in the early stages of renal wrap hypertension. In addition, various clinical reports [10–13] indicate that relief of the compression of the renal parenchyma may not correct the hypertension, while removal of the kidney is usually successful. The later observations suggested to Sterns et al [13] that “parenchymal scarring” rather than parenchymal compression may play a more significant role in the persistence of hypertension.

The possibility that renal interstitial inflammation could be playing a role in the hypertension caused by
cellophane wrapping of the kidneys was attractive to us because of previous investigations from our group have explored the relationship between hypertension, renal immune cell infiltration and oxidative stress (reviewed in [14]). In these studies we have shown that strategies leading to the reduction of the infiltration of lymphocytes and macrophages results in improvement in oxidative stress and hypertension in acquired and in genetic models of hypertension and, in particular, in the prevention of salt-sensitive hypertension [15–17]. Therefore, this investigation was designed to evaluate the role of the renal interstitial inflammation in the pathogenesis of the hypertension associated with the Page kidney model. We found that blood pressure was unrelated to plasma angiotensin II levels. Tubulointerstitial damage with accumulation of lymphocytes and macrophages, increased angiotensin II–positive cells and angiotensin II content, and augmented lipid peroxidation, reflecting oxidative stress, were all demonstrated in the cellophane-wrapped kidneys. Administration of the immunosuppressive anti-inflammatory drug mycophenolate mofetil (MMF) did not modify the formation of the fibrous capsule surrounding the kidney but reduced the inflammatory damage, angiotensin activity, and the oxidative stress of the kidney and prevented the development of hypertension.

METHODS
Experimental design

Male Sprague-Dawley rats (Instituto Venezolano de Investigaciones Científicas, Los Teques, Venezuela) were used in the experiments. They were housed in institutional animal facilities and had free access to standard rat food (100 to 120 μEq sodium) (Protinal, Valencia, Venezuela) and tap water. Animals were acclimatized to the animal facilities for 1 week, conditioned to handling and blood pressure determinations, and randomly divided in two experimental groups and a control (sham-operated) group. Experimental groups had bilateral cellophane wrapping of the kidneys and received daily 20 mg/kg body weight of MMF (two-kidney/MMF group) \((N = 10)\) or vehicle (two-kidney wrap group) \((N = 10)\) by gastric gavage. MMF was given suspended in 500 μL of water by vigorous agitation immediately before administration as described in previous communications [14–18].

Rats were followed for 7 weeks after the cellophane wrapping of the kidneys. Systolic blood pressure was determined weekly by tail-cuff plethysmography (ITTC, Life Scientific Instruments, Woodland Hills, CA, USA) as described in previous communications [14–18]. To rule out potential gastrointestinal adverse effects of MMF that would reduce dietary intake and thereby influence blood pressure, food consumption was monitored and the weight of the rats was determined at baseline, at 3 weeks, and at the end of the experiment (7 weeks) when animals were euthanized. At the time of sacrifice, intrarenal pressure was determined, the fibrous hull surrounding each kidney were removed and weighed and the kidneys were then harvested for histologic and immunohistologic studies and determination of angiotensin II and malondialdehyde (MDA) content.

Plasma creatinine and 24-hour urinary protein excretion were determined at baseline, at 4 weeks and 7 weeks after kidney wrapping.

Surgical procedures

Under general anesthesia (diazepam/ketamine) kidneys were exposed by a midline laparotomy and included in cellophane bags made from cellophane sheets, as described by Page [1] taking care that renal pelvis, ureter, and the vascular pedicle were completely free and undisturbed. Sham-operated animals only had manipulation of the kidneys.

Intrarenal pressure determinations

Hydrostatic pressure of the kidneys inside the fibrous hull caused by the cellophane wrap was determined by direct intrarenal fine-needle manometry at the time of sacrifice in five rats from each group. The method has been used by others [19], as well as us [20], to estimate intrarenal pressure during acute rejection in transplanted kidneys. Briefly, a 23 gauge scalp vein set with a three-way connection to a column of sterile 0.9% saline solution was inserted inside the renal parenchyma prior to the removal of the cellophane-induced fibrous hull. Immediately after insertion of the needle and assuring free communication with the saline column, measurements were taken. The height above the kidney at which the saline column stopped flowing toward the kidney was considered representative of the intrarenal pressure in centimeters of H₂O. There were no significant differences in paired measurements in right and left wrapped kidneys. Because it was technically easier, we chose to evaluate intrarenal pressure in the left kidney. Three determinations in separate areas of the kidney (after testing that needle and the system were patent in each instance) were made in each animal and their average was considered to represent the intrarenal pressure.

Plasma and renal angiotensin II

Determination of plasma angiotensin were done in 2 mL blood samples obtained at baseline, at 3 weeks, and at 7 weeks (sacrifice) after kidney wrapping. Plasma was collected in chilled tubes containing an inhibitor mixture [50 μL 0.3 mol/L ethylenediaminetetraacetic acid (EDTA) and 2.5 μL 0.5 mol/L 1,10-phenantroline per mL] and determinations of plasma angiotensin II were done by enzyme-linked competitive immunoassay using
commercially available kits (Peninsula Laboratories, Inc., San Carlos, CA, USA) after extraction in C18 Sep columns following the procedure recommended by the manufacturer. The minimal detectable concentration is 0.03 ng/mL assay tube and the intra- and interassay variations are 5 ± 2% and 12 ± 3%, respectively.

Renal angiotensin II was determined following the guidelines of Durvasula et al [21] in five kidneys of each group that were removed after perfusion with cold saline solution. Briefly, the renal cortex was immediately excised, cut in small pieces, and placed in a solution at 2°C containing 20 mmol Tris HCl (pH 7.40), 10 mmol/L of EDTA, 5 mmol/L, ethyleneglycolte-traacetic acid (EGTA), and protease inhibitor cocktail one tablet per 10 mL (Roche, Molecular Biochemicals, Indianapolis, IN, USA). Tissues were homogenized by pulse sonication in ice and then centrifuged at 16,000 × g for 15 minutes at a temperature of 2°C [21]. Supernatants were collected in cold propylene tubes and placed at −20°C until the determination of angiotensin II was done. Angiotensin II was determined by enzyme-linked competitive immunoabsorbent assay after extraction in C18 Sep columns (Peninsula Laboratories, Inc.) using a 10 point standard curve (0 to 10 ng/mL assay tube). Intra- and interassay variation were 10 ± 8% and 28 ± 5%, respectively. Results are expressed in fmol/g of renal cortex. Recovery of angiotensin II added prior to extraction was 77 ± 7.5% for blood and 84 ± 12% on renal cortical homogenates.

Renal MDA and glutathione (GSH) content

Determinations of MDA and GSH content were done in one of the kidneys harvested at the time of sacrifice by the method of Ohkawa, Ohishi, and Yagi [22] and Beutler, Duron, and Milkus [23], respectively. MDA and GSH were measured in supernatants of kidney slices placed in a cold mixture of 100 mmol/L KCl and 0.003 mol/L EDTA, homogenized and centrifuged at 600g. Specific details of this methodology in our laboratories have been published previously [24].

Histology and immunohistology

Histology was studied by light microscopy in paraffin-embedded kidney sections fixed in Methyl Carnoy and stained with periodic acid-Schiff (PAS), hematoxylin and eosin, and trichromic stains. Glomerulosclerosis was graded and scored as described by Raji, Azar, and Keane [25] and detailed previously [14–17]. Tubulointerstitial damage was scored using a 0 to 5 scale depending on the extent of areas with tubular dilatation, interstitial infiltration and fibrosis (0, no changes; grade 1, <10%; grade 2, 10% to 25%; grade 3, 25% to 50%; grade 4, 50% to 75%; and grade 5, 75% to 100%), determined in successive fields examined in the entire cortical and jux-tamedullary areas suited for evaluation of each biopsy, using computer assisted image analysis (Olympus BX51 System Microscope and DP70 microscope Digital camera, with software of Sigma Pro, Leesburgh, VA, USA).

Avidin-biotin-peroxidase methodology [26] was used to study to identify lymphocytes (CD5-positive cells), macrophages (ED1-positive cells), and angiotensin II–positive cells.

Glomeruli and tubulointerstitial regions were evaluated separately and results were expressed as positive cells per glomerular cross section (gcs) and positive cells per mm², respectively. All studies were done in a blinded fashion.

Antisera

Anti-CD5 and anti-ED1 monoclonal antibodies (Biosource, Camarillo, CA, USA) were used to identify lymphocytes and macrophages, respectively. Rabbit anti-human angiotensin II antiserum with cross-reactivity to rat angiotensin II (Peninsula Laboratories, Inc.) was used to identify angiotensin II–positive cells and specificity of the staining was tested by preincubating the antibody with human angiotensin II as described in a previous communication [27]. Secondary biotin-conjugated affinity-pure antibodies with minimal reactivity to rat serum proteins were purchased from Accurate Chemical and Scientific Co. (Westbury, NY, USA). Nonrelevant antibodies were used for negative control studies.

Statistical analysis

Results were analyzed with analysis of variance using a commercially available statistical package (Instat, GraphPad R, San Diego, CA, USA) and significant differences defined with Tukey post tests. Results are expressed as mean ± SD and differences are considered significant when P < 0.05.

RESULTS

Renal function and body weight

There were no significant changes in plasma creatinine concentration or in urinary protein excretion. Plasma creatinine (mg/dL) was similar at baseline (two-kidney wrap group = 0.43 ± 0.12 and two-kidney wrap/MMF group = 0.35 ± 0.12), at 4 weeks (two-kidney wrap group = 0.41 ± 0.16 and two-kidney wrap/MMF group = 0.35 ± 0.12), and at the end of the experiments (two-kidney wrap group = 0.42 ± 0.15 and two-kidney wrap/MMF group = 0.40 ± 0.15). Proteinuria (mg/24 hours) was also similar at baseline (two-kidney wrap group = 6.0 ± 2.3 and two-kidney wrap/MMF group = 3.5 ± 1.0), at 4 weeks (two-kidney wrap group = 7.2 ± 5.4 and two-kidney wrap/MMF group = 2.6 ± 1.7), and at the end of the
Fig. 1. Systolic blood pressure (SBP) changes after kidney cellophane wrapping. The mycophenolate mofetil (MMF)-treated group (2K-wrap + MMF) (○) maintains a blood pressure at similar levels than the sham-operated group (□), in contrast with the progressive elevation of the blood pressure in the untreated kidney wrap group (2K-wrap) (■). Values are mean ± SD. *** P < 0.001 vs. the rest.

Blood pressure
Blood pressure findings are shown in Figure 1. The two-kidney weight group experienced progressive increments in systolic blood pressure beginning 1 week after cellophane wrapping of the kidneys and reached values of 157 ± 6.18 mm Hg after 7 weeks. In contrast, the blood pressure in the two-kidney wrap/MMF group remained at baseline values as did in the sham-operated control group.

Intrarenal pressure and the fibrous hull surrounding the kidney
Intrarenal pressure at the end of the experiment was 7.6 ± 4.0 cm H$_2$O in the sham-operated group and was significantly (P < 0.01) elevated in the two-kidney wrap group (22.3 ± 5.15) and in the two-kidney wrap/MMF group (25.6 ± 5.49). The difference in intrarenal pressure between the untreated (two-kidney wrap) and the MMF treated (two-kidney wrap/MMF) kidney-wrapped groups was not significant (Fig. 2A).

The weight of the fibrous capsule surrounding the kidney was comparable in the right and left kidneys and there were no significant differences between the MMF-treated and the untreated experimental groups (Fig. 2B).

Histologic examination of the fibrous hull did not reveal differences between the MMF-treated and untreated groups.

Plasma and renal angiotensin II
The plasma angiotensin II levels determined at three different time intervals in the experiment were not significantly different in the experimental groups and the control group (Fig. 3A).

The angiotensin II content in the renal cortex is shown in Figure 3B. As shown, the two-kidney wrap group had increased angiotensin II while the two-kidney wrap/MMF group had values that were essentially similar to those in the sham-operated kidneys.

The plasma angiotensin II levels in the two-kidney wrap group were stable, in contrast with the progressive hypertension developed by these rats, as shown in Figure 4. The changes in plasma angiotensin II observed
during the study were unrelated to the changes observed in blood pressure levels (data not shown).

**Light microscopy**

Glomeruli were in general normal or presented mesangial expansion. Glomerulosclerosis (score 0 to 400 range in the method used) was rare and similar in the two-kidney wrap group (6.8 ± 5.56) and the two-kidney wrap/MMF group (4.44 ± 5.83).

Tubulointerstitial damage induced by cellophane perinephritis was prominent in the two-kidney wrap group, occupying 25% to 70% of the renal cortex (3.0 ± 0.77 score). Damage consisted of extensive areas of intense cellular infiltration, with focal areas of fibrosis and occasional dilated tubules. The tubulointerstitial findings in the two-kidney wrap/MMF group, when present, comprised less than 10% of tubulointerstitial areas (1.0 ± 0.51 score) (P < 0.001 vs. the two-kidney wrap group) (Fig. 5A and B).

**Infiltrating cells**

The number of intraglomerular lymphocytes and macrophages was not increased in the experimental groups (<0.7 positive cells/gcs). In contrast, there was significant tubulointerstitial infiltration of lymphocytes (CD5-positive cells) and macrophages (ED1-positive cells) in the two-kidney wrap group. MMF treatment reduced tubulointerstitial immune cell accumulation (Figs. 5C and D and 6). Angiotensin II–positive cells were generally absent in the tubulointerstitial areas of sham-operated rats; however, they were present in the two-kidney wrap group and MMF treatment reduced their numbers (Fig. 7A). The angiotensin II–positive cells were both tubular cells and infiltrating cells (Fig. 7B) and double-staining studies (not shown) demonstrated that 20% to 30% of the infiltrating macrophages stained positive for angiotensin II.

**Renal MDA and GSH content**

Renal MDA content was increased in the two-kidney wrap group and reduced to normal levels by MMF treatment (Fig. 8). The renal GSH content was comparable in the two-kidney wrap group (7.63 ± 2.82 nmol/mg protein) and the two-kidney/MMF group (5.97 ± 2.1).

**DISCUSSION**

The present studies were done to gain insight on the pathogenesis of hypertension associated with the cellophane kidney wrap model of perinephritis. As initially postulated by Page in 1939 [1], the presently accepted views implicate a mechanism similar to the Goldblatt model of renal artery constriction. In the kidney wrap model, renal ischemia would be the consequence of the compression exerted by the perinephritic hull formed in reaction to the cellophane wrapping [4]. The central findings of the present work are (1) the demonstration that
the hypertension is unrelated to the plasma angiotensin II levels, in agreement with the work of Hart et al.\cite{9}; (2) that cellophane perinephritis results in significant tubulointerstitial inflammatory damage; and (3) that suppression of the immune cell infiltration prevents tubulointerstitial damage and hypertension in the Page kidney model, without modification of the mechanical effects of the perinephritic fibrous hull surrounding the kidney.

We selected male rats for this study because female rats are partially protected against renal wrap hypertension\cite{28} and choose the cellophane, rather than the figure eight, kidney wrap model because cellophane wrapping results in a well-defined fibrous hull that can be removed and weighted. In addition, the perinephritic hull resulting from cellophane wrapping has more resemblance to the clinical conditions known as Page kidney (see later). We favored the two-kidney two-wrap model because this model is more reliable in inducing hypertension than the one-kidney wrap model, if the later is not associated with contralateral nephrectomy\cite{1}, and we wanted to avoid superimposed tubulointerstitial inflammation resulting from renal mass reduction.

The intrarenal pressure measured in the sham-operated group in the present study is in the normal range of interstitial hydrostatic pressure reported in studies of Khairibi\cite{29} and Tang, Yu, and Khrabi\cite{30}. The fibrous hull that surrounded the cellophane wrapped kidneys increased the intrarenal pressure about threefold.
at the end of 7 weeks. These findings are in agreement with the studies on Denton and Anderson [31], who reported that renal venous wedge pressure was elevated in the renal wrap model in rabbits. However, it is unlikely that intrarenal pressure per se could be the cause of hypertension since the treatment with MMF did not modify intrarenal pressure or the size of the fibrous hull surrounding the kidney (Fig. 2) and, nevertheless, ameliorated tubulointerstitial inflammation, preserved renal integrity, and prevented the development of hypertension in the two-kidney wrap/MMF group (Fig. 1). In contrast with the findings of others [9], tubulointerstitial injury was prominent. It may be noted that tubulointerstitial inflammation is a more conspicuous characteristic of increased intrarenal pressure than is glomerular damage, since glomeruli were for the most part intact, even when immersed in areas of significant tubulointerstitial dam-

age in the two-kidney wrap group (Fig. 5A). Similar preponderance of tubulointerstitial inflammatory injury is a characteristic of other models of salt-driven hypertension [14–18].

It is unlikely that systemic angiotensin activity plays a significant role in the development of hypertension since angiotensin II plasma levels were comparable in all experimental groups (Fig. 3). Furthermore, in the two-kidney wrap group plasma angiotensin II levels remained steady despite the progressive increment of the blood pressure (Fig. 4). However, stable levels of plasma angiotensin II are physiologically inappropriate in the face of hypertension [32] and prolonged activation of intrarenal...
angiotensin II, as demonstrated in Figure 3B, may have resulted in a down-regulation of extrarenal angiotensin II production.

Our results are in agreement with the previously mentioned studies of Hart et al [9] who also found unchanged levels of plasma angiotensin II in this model as well as with the observation that angiotensin-converting enzyme (ACE) antagonists failed to correct hypertension in rats renal wrap model [6]. In contrast, Denton and Anderson [31] and Siragy and Carey [11] found early increments in plasma renin activity and plasma angiotensin II and that administration of losartan during this period acutely lowers the blood pressure [11]. The same research group [33] found that 3 days after surgery there was a down-regulation of the angiotensin II type 1a receptor expression suggesting increased levels of the ligand. It is possible that when we first tested plasma angiotensin II, the third week after surgery, the levels may have already returned to normal, as is the case in the two-kidney one-clip hypertension, in which the plasma angiotensin II levels are increased at day 7 and return to normal by day 25 after surgery [34]. However, in two-kidney one-clip hypertension, blood pressure increases soon after surgery, while in the cellophane wrap model hypertension develops progressively, as initially reported by Page [1] and confirmed in the present studies (Fig. 1). Therefore, if plasma levels of angiotensin II were increased in the first week or two after surgery they would have been associated with relatively minor hypertensive effects.

In our experiments, hypertension was prevented by MMF treatment that controlled renal inflammation and intrarenal angiotensin II activity and oxidative stress. These findings, taken in context with the progressive, rather than sudden increment in blood pressure, and with the findings previously mentioned that a low-salt diet prevents hypertension in the renal wrap model [5, 6] and that volume load is the primary drive for hypertension [9], strongly suggest that renal sodium retention plays a determinant role in the pathogenesis of hypertension in the Page kidney model.

In contrast to experimental observations, the patients with Page kidney usually have high plasma renin activity in the renal vein of the affected kidney. We did not measure renal vein plasma renin activity but it appears unlikely that it would have been different in the two-kidney wrap group and in the two-kidney wrap/MMF group since, as mentioned before, the mechanical compression of the kidney and the systemic angiotensin II levels were similar. Most of the patients with Page kidney–like conditions in the literature have subcapsular hematomas or cysts (reviewed in [4, 35]) and, more rarely, perinephritis [36]. Therefore, our findings may not be directly extrapolated to those patients. However, it may be noted that seldom is the relief of the compression sufficient to correct the hypertension and nephrectomy is usually needed for this purpose [13]. An additional observation that underscores the physiopathologic differences between renal artery stenosis and the Page kidney is the finding that captopril renography, a test for renal artery stenosis, is negative in patients with Page kidney [37].

We cannot answer from our study when the tubulointerstitial immune cell infiltration starts in this model but its pathogenetic relevance is strongly suggested by the finding that its suppression with MMF treatment prevents hypertension. While MMF has a variety of effects on resident kidney cells (reviewed in [38]) that may contribute to its beneficial effects, the results of the present investigation are consistent with previous studies in a variety of experimental models in which reduction of the inflammatory infiltrate reduces oxidative stress and improves or prevents hypertension (reviewed in [14]) even in experimental models that do not present significant interstitial fibrosis or significant nephron loss [15, 18]. The administration of MMF was well tolerated. Experimental groups that had cellophane wrapping of the kidneys failed to gain weight significantly but the weight was similar in the untreated hypertensive two-kidney wrap group and in the normotensive two-kidney wrap/MMF group. Therefore it is unlikely that dietary factors would be responsible for the prevention of hypertension in the MMF-treated group.

Increased numbers of angiotensin II expressing cells in tubulointerstitial areas were observed in association with interstitial nephritis in the two-kidney wrap group. As in previous reports [14–18], the angiotensin II–positive cells were both proximal tubular cells and infiltrating cells and their numbers were reduced by MMF treatment (Fig. 7). These findings are strengthened by the demonstration that the angiotensin content in the renal cortex was increased by renal cellophane wrapping and reduced
to levels similar to those found in sham-operated rats by MMF treatment (Fig. 3B). Since the intrarenal pressure and perinephritic hull resulting from cellophane wrapping was not modified by MMF (Fig. 2), it is likely that the reduction in intrarenal angiotensin II was also related to the improvement in the interstitial inflammation.

The reduction of renal MDA content observed with MMF treatment (Fig. 8) is not unexpected since lipid peroxidation resulting from unchecked generation of reactive oxygen species would be likely reduced as a consequence of improvement of interstitial inflammation, as has been reported in previous studies [15–18].

The mechanisms involved in the development and maintenance of hypertension associated with renal interstitial inflammation have been recently reviewed [14] and relate to the interplay of angiotensin II activity and unchecked generation of reactive oxygen species that result in a tendency to sodium retention by the kidney. The present studies did not evaluate sodium balance but it is reasonable to assume that the demonstrated increment in renal angiotensin activity and oxidative stress would impose a reduction in urinary sodium excretion until a new balance is achieved at a higher level of blood pressure.

Investigations by several groups have shown that that renal wrap hypertension is temporarily reduced by ablation of the paraventricular nucleus [39], sympathetic blockade [40], and V1 receptor blockade [41]. Particularly relevant to the present work are the investigations of Haywood, Williams, and Ball [6], Hinojosa-Laborde, Guerra, and Haywood [40], and Hinojosa and Haywood [41] who have shown that hypertension is salt sensitive in the renal wrap model and those of Hart et al [9] who determined that volume load, rather than humoral factors, is the prevailing condition in the early phase of hypertension. Our results offer a potential explanation for their findings because, as indicated earlier, salt retention is the expected result of the combined effects of interstitial inflammation and oxidative stress [14]. These factors, driving a tendency to sodium retention, may be responsible, at least in part, for the lack of a natriuretic response to atrial natriuretic peptide in renal wrap hypertension [42].

CONCLUSION

Our results show that the progressive hypertension induced by cellophane wrapping of the kidneys is unrelated to plasma angiotensin II levels and to the mechanical effects of compression caused by the perinephritis. While unchanged plasma angiotensin II levels may be physiologically inappropriate, interstitial inflammation and tubular damage of the wrapped kidneys, likely driven by increased intrarenal angiotensin activity and oxidative stress, appear to play a determining role since correction of these features with MMF administration prevents the increment in blood pressure that is characteristic of this model.

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