Renal autoregulation and passive pressure-flow relationships in diabetes and hypertension

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Hill JV, Findon G, Appelhoff RJ, Endre ZH. Renal autoregulation and passive pressure-flow relationships in diabetes and hypertension. Am J Physiol Renal Physiol 299: F837–F844, 2010. First published July 21, 2010; doi:10.1152/ajprenal.00727.2009.—We investigated renal hemodynamics in isolated, perfused kidneys from rat models of diabetes and hypertension. Autoregulation and passive vascular responses were measured using stepped pressure ramps in the presence of angiotensin II (pEC50) or papaverine (0.1 mM), respectively. Male diabetic heterozygote m(Ren2)27 rats were compared with three male control groups: nondiabetic, normotensive Sprague-Dawley (SD) rats; nondiabetic, hypertensive heterozygote m(Ren2)27 rats; and diabetic, normotensive SD rats. Kidney function (proteinuria, creatinine clearance) was monitored before induction and at monthly intervals. Vascular function was measured in vitro in rats of induction age (6–8 wk) and at 2 and 4 mo postinduction. Renal flow correlated with age, but not diabetes or the Ren2 gene. Kidney weight-specific and body weight-specific renal flow differed between diabetic and nondiabetic rats because diabetic rats had higher kidney but lower body weights. Kidneys from all groups showed effective autoregulation in the presence of angiotensin II. The autoregulatory pressure threshold of m(Ren2)27 rats was higher, and the autoregulation pressure range was wider, compared with SD rats. When vascular smooth muscle activity was blocked with papaverine, pressure-flow responses differed between groups and with time. The m(Ren2)27 rat groups showed higher renal vascular resistance at lower pressures, suggesting greater vascular stiffness. In contrast, diabetic SD rat kidneys demonstrated reduced vessel stiffness. Flow was impaired in diabetic m(Ren2)27 rats at 4 mo, and this correlated with a decline in creatinine clearance. The results suggest that the characteristic late decline in renal filtration function in diabetes- and hypertension-related renal disease follows changes in renal vascular compliance.

Diabetic nephropathy (DN) is the most common cause of end-stage renal failure (ESRF) in the Western world (24). Clinical progression of DN follows a relatively well-defined course characterized by early microalbuminuria, renal hyperfiltration and hyperperfusion, and increased capillary permeability to macromolecules. DN occurs late in diabetes, generally becoming apparent 15–25 yr after onset (8). However, glomerular basement membrane thickening begins less than 2 yr after onset of diabetes and is followed by mesangial matrix expansion. The final stage leading to ESRF is a progressive decline in glomerular filtration rate (GFR) (8, 24). Progressive deterioration of renal function is commonly due to diabetes and hypertension, both separately and together. The causes of hypertension are multifactorial and diabetes is characterized by multiple potential mediators of progressive renal injury, including hyperglycemia, hypertension, endothelial dysfunction, an upregulated renin-angiotensin system, and increased oxidative stress (10, 24). Both diabetes and hypertension affect renal hemodynamics. Renal perfusion is tightly controlled by autoregulation, which is broadly defined as the ability of an organ to maintain flow in response to varying systemic blood pressures. Although autoregulation is critical to both GFR and renal blood flow, glomerular pressure homeostasis is also an important consequence of modulation of afferent arteriolar tone. Glomerular hypertension disrupts glomerular structure (27), while glomerular hypotension reduces the transglomerular pressure gradient and filtration pressure in turn modifying tubular flow and reabsorption.

Taken together, these observations suggest that vascular modification and altered vascular control are early features, which may contribute to progression of DN. We addressed this hypothesis by examining renal hemodynamics in a proposed model of DN, the male diabetic heterozygote m(Ren2)27 rat (D-Ren2) (16, 17). Three groups expressing subsets of the multiple deleterious factors present in the D-Ren2 model were used as controls: the nondiabetic heterozygote m(Ren2)27 rat (N-Ren2), which is a model of fulminant hypertension, the diabetic Sprague-Dawley rat (D-SD), a model of type 1 diabetes, and the nondiabetic Sprague-Dawley rat (N-SD), a normal control. We monitored kidney vascular and nephron function over 4 mo in each group. Renal function was determined by measuring creatinine clearance and proteinuria, and renal vascular hemodynamics were investigated using isolated kidney perfusion in vitro. The glomerular pathologies observed in a subset of these animals have been described (1).

Materials and methods

All experimental work was approved by the Animal Ethics Committee, University of Otago-Christchurch. Four groups of male rats were compared in a 2 × 2 experimental design of 2 rat strains and presence/absence of diabetes. The two strains were male normotensive Hannover Sprague-Dawley (SD) and heterozygote m(Ren2)27 rat (Ren2) produced by crossing SD females with homozygote m(Ren2)27 males. Note that “SD” and “Ren2” are used to denote both diabetic and nondiabetic animals of each strain and the prefix “D−” or “N−” is used to refer specifically to diabetic or nondiabetic animals, respectively. Rats were housed in cages on sawdust, fed standard rat chow (Weston Milling, Rangiora, New Zealand), and had unlimited access to tap water. Diabetes was induced at 6–8 wk of age using streptozotocin (55 mg/kg iv; Applichem GmbH, Darmstadt, Germany) after overnight fasting; nondiabetic rats were inducted into the study at the same age. Diabetic rats had blood glucose monitored weekly (Accu-check Advantage II glucose monitor, Roche Diagnostics). One to four units of insulin (Protophane, Novo Nordisk Pharmaceuticals) were administered 3 times per week to support nutrition while maintaining blood glucose around a target of 27 mmol/l.

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Each group (n = 14–18 animals) was monitored immediately preinduction (time 0) and before in vitro experiments. Groups lasting 4 mo were also monitored at monthly intervals. Body weight and systolic blood pressure (SBP), using tail sphygmomanometry (PowerLab System, AD-Instruments, Dunedin, New Zealand), were measured. A tail vein blood sample was collected in a heparinized tube, and the plasma was stored at −20°C for creatinine analysis. The rats were then placed in metabolic cages for 24 h with food and water ad libitum. Consumed food and water and urine volume were measured. Untreated urine samples were frozen at −20°C for later creatinine and protein determination.

In vitro experiments using isolated, perfused kidneys (after Cowin et al. 1999) were performed at 0, 2, and 4 mo. Briefly, rats were anesthetized (60 mg/kg pentobarbital sodium, Pentobarb300), heparinized, and given an osmotic diuretic (500 U/ml heparin + 0.1 g/ml 10% mannitol, 0.7 ml/100 g rat body wt iv), followed by cannulation of the right ureter (3-cm polyethylene tubing, 0.61-mm OD, 0.28-mm ID) and right renal artery (20- or 22-gauge iv catheter; Surflo, Terumo, Philippines). Continuous renal perfusion with autologous blood was maintained throughout the entire procedure to minimize hypoxia. Kidneys were perfused with 37°C recirculating Krebs-Henseleit buffer containing 6.7% bovine serum albumin, 5 mM glucose, 20 amino acids, and 1 μCi of [14C]inulin, and gassed with 95% O2-5% CO2. Renal artery perfusion pressure (pressure transducer; Abbott, Sydney, Australia) and flow (SN22 flow probe, T106 flowmeter; Transonic Systems, Ithaca, NY) were measured. Mean renal artery perfusion pressure was held constant using a process controller (West Process Controller, model 2075; West Division, Gulton Industries, Schiller Park, Chicago, IL) which regulated the speed of a peristaltic pump (Watson Marlow Bredel pump, Falmouth, UK). Data were collected digitally (MP100 and “AcqKnowledge” software, Biopac Systems, Goleta, CA) and recorded on a desktop computer. Kidneys were given a 20-min equilibration period before starting experiments.

The first experimental protocol determined angiotensin II (ANG II) dose-response curves for each group (n = 6–12/group) to determine the ANG II concentration required for preconstricting kidneys in later experiments. Kidneys were perfused at constant pump speed at an initial mean perfusion pressure of 110 mmHg. ANG II was infused into the circuit before the arterial cannula, in half-decade increments starting at 1 μM. Renal vascular resistance (RVR) data were used to find the sensitivity (EC50 concentration at which a 50% maximum effect was obtained) and magnitude of the response (absolute increase in RVR) to ANG II.

In the second protocol, renal autoregulation and the passive pressure-flow response were measured using stepwise increases in perfusion pressure while monitoring perfusate flow (after 12). Initial perfusion pressure was set at 70 mmHg, and increased in 15-mmHg steps (held constant for 3 min per step) up to 220 mmHg (or to 190 mmHg for 4-mo D-Ren2). Three pressure ramps were performed: 1) a control/equilibration ramp (nothing added), 2) in the presence of ANG II (infused at EC50 concentration to facilitate and measure autoregulation), and 3) in the presence of papaverine (0.1 mol/l) to abolish vascular smooth muscle (VSM) tone and measure the passive pressure-flow response. Flow, RVR (= pressure/flow), and change in conductance (ΔG = Δflow/Δpressure between consecutive pressure steps) were measured or calculated at each perfusion pressure. ΔG is the slope of the G vs. pressure curve (i.e., ΔG/ΔP: analogous to velocity vs. acceleration Δv/Δt). ΔG is zero if G does not change with an increase in P (c.f. acceleration is zero if velocity does not change with time). ΔG indicates how G (and its inverse R) changes with P (c.f. acceleration indicates how velocity changes with time). Thus, with an increase in pressure does the vessel stretch (ΔG > 0; indicating compliance), contract (ΔG < 0; c.f. constriction or autoregulation), or maintain constant G (ΔG = 0; indicating high vessel stiffness). This is analogous to an elasticity stress/strain curve, where the stress is perfusion pressure and the strain is how the vessel responds. ΔG was used as an index of vascular stiffness (degree of deformation due to pressure). Indexes of autoregulation (AR, ARI, ARr) as used in previous studies (12, 23, 26) were considered as alternatives to ΔG but were found to be unsuitable for comparing autoregulation over different pressure ranges or when the initial RVR was not constant.

The following autoregulatory values were determined for each group: the lowest perfusion pressure at which autoregulation was apparent (lower autoregulatory threshold (LAT); the intersection of the preautoregulatory slope and the autoregulatory slope was determined for each kidney individually, and the next highest measured pressure was defined as the LAT for that kidney), the efficiency of autoregulation (the ability to maintain near constant flow as demonstrated by proximity of ΔG to 0), the optimal autoregulatory range (the perfusion pressure range over which the lowest ΔG was maintained), and optimal pressure (the pressure in the center of the optimal autoregulatory range). At the end of each experiment, kidneys were blotted dry before being weighed.

Chemical analyses. Creatinine in both urine and plasma was measured by HPLC (modified from 30). Briefly, 20% methanol:80% acetonitrile solution was used to dilute and deproteinize the samples. After centrifugation, the supernatant was injected into an HPLC (alkaline methanol:acetonitrile mobile phase, alumina column) and measured on a UV-absorbance spectrophotometer at 236 nm. Protein was measured using a modified Bradford method (Bio-Rad protein assay).

Statistical analysis. Data are given as means ± SE. A single repeated-measures, two-way ANOVA (time x treatment or pressure x ramp protocol), after appropriate transformation (natural logarithm or square-root) if necessary, was used except in the following cases. IPKR data were analyzed using two consecutive ANOVAs: the first analyzed nondiabetic rats of both strains at 0–4 mo, and the second analyzed the diabetic and nondiabetic animals of both strains at 2 and 4 mo only (since rats could not have streptozotocin for time 0). Post hoc analyses were performed using Fisher’s Protected Least Significant Difference tests. Kidney weight was analyzed using the Kruskal-Wallis test as these data were heteroscedastic. Statistical analyses were carried out using SPSS (SPSS, Chicago, IL) or PRISM (Graphpad Software).

RESULTS

Evolution of diabetic and m(Ren2) renal disease: in vivo parameters. Diabetic rats ate and drank more than nondiabetic animals (D-/N- ratio: food: 202 ± 3% and water: 511 ± 20%), but body weight was lower (334 ± 14 vs. 529 ± 5 g at 4 mo). Ren2 rats consumed more food (116 ± 2%) and water (130 ± 4%) than SD rats, although body weight was not affected. SD rats had lower SBPs than Ren2 rats (mean of 0–4 mo 125 ± 3 mmHg, respectively; Fig. 1A). Diabetes did not affect SBP in SD rats, but it lowered SBP in Ren2 rats (mean of 0–4 mo 125 ± 3 vs. 189 ± 4 mmHg, respectively; Fig. 1A). Diabetes did not affect SFP in SD rats, but it lowered SFP in Ren2 rats (mean of 1–4 mo: 201 ± 3 vs. 183 ± 3 mmHg in N-Ren2 and D-Ren2, respectively). There was a decline in D-Ren2 SFP with time; SFP was lower at 4 mo than at 1 or 2 mo.

Creatinine clearance (Ccrea) was higher in D-Ren2 rats compared with the other three groups at 1–3 mo; Ccrea was equal in all groups at 4 mo, when there had been a decrease in Ccrea in D-Ren2 rats (Fig. 1B). Plasma creatinine was higher in the nondiabetic groups compared with the diabetic groups, but there was no difference between strains (data not shown). Total creatinine excretion was higher in diabetics compared with nondiabetics and Ren2s compared with SDs during 1–3 mo and increased with age/weight in nondiabetic rats (data not shown).

Diabetes did not significantly increase proteinuria, but from 3 mo some D-Ren2 rats showed extreme proteinuria of greater than 100 mg/24 h (see greater variance at 3 and 4 mo in
D-Ren2 rats; Fig. 1C). This observation suggests that rats with both the Ren2 gene and diabetes had a higher incidence of more extreme proteinuria. Proteinuria was greater in Ren2 rats compared with SD rats from 1 mo for N-Ren2 and 2 mo for D-Ren2. All groups showed an increase in proteinuria between 0 and 1 mo, but no group changed from 1 mo onwards. Protein loss was indexed to UCr as is performed clinically (Fig. 1D). D-Ren2 at time 0 was low due to an age match discrepancy; this did not affect other data. From 1 mo onwards, N-SD rats had the lowest index (exception: D-Ren2 at 1 mo). The highest index was for N-Ren2 rats at 1 mo, when SBP also reached a maximum. A decreasing index after this time is consistent with improved reabsorption and/or reduced glomerular loss. At 4 mo, the urinary protein/creatinine index of D-Ren2 rats was significantly greater than that of N-Ren2, N-SD, and D-SD rats.

Evolution of diabetic and hypertensive renal disease: in vitro evaluation. Wet kidney weights of N-SD and N-Ren2 were similar and increased between 0 and 2 mo (Fig. 2). D-SD rats had larger kidneys than N-SD rats at 2 and 4 mo, whereas D-Ren2 rat kidneys were larger than N-Ren2 rat kidneys at 4 mo only. D-Ren2 rats had larger kidneys than D-SD rats at 4 mo and were the only group to increase kidney size between 2 and 4 mo. The perfusion pressure required to produce urine was higher in N-Ren2 than N-SD at all times (data not shown).

ANG II dose-response data. ANG II sensitivity increased with age in all groups between 0 and 2 and between 2 and 4 mo as shown by the decrease in EC50 (Fig. 3A; P = 0.004). Ren2 rats had a slightly lower sensitivity to ANG II at 2 and 4 mo (13 ± 1 vs. 17 ± 1 pmol/l for SD and Ren2, respectively, P = 0.030), but there was no difference at 0 mo. Diabetes did not affect ANG II sensitivity. Magnitude of response was measured as absolute change in RVR. Initial RVR was not significantly different between groups at either 2 or 4 mo. The magnitude of response to ANG II was similar in the N-Ren2 and N-SD groups at 0 mo (Fig. 3B). However, at 2 and 4 mo, there was an additive effect of diabetes and the Ren2 gene (P = 0.006, P < 0.001, and P = 0.090 for diabetes, strain, and an interaction, respectively), with these combining to increase RVR and presumably reflecting increased VSM constriction.

Autoregulation facilitated by ANG II. ANG II facilitated the best autoregulation, papaverine the least, and control (no additives) ramps were intermediate (Fig. 4). ANG II-facilitated autoregulatory pressure-flow and ΔG curves are shown in Fig. 5. The LAT was higher in N-Ren2 compared with N-SD at all times (Fig. 6A). Diabetes did not affect the LAT in SD rats but significantly decreased LAT in Ren2 rats (Fig. 6A). Qualitatively, LAT and SBP were similar (Fig. 1A vs. 6A) with the exception of the D-Ren2 groups which showed low LAT vs. SBP at 2 and 4 mo. Most rat groups could autoregulate with perfect efficiency with ΔG = 0 over at least one 15-mmHg pressure step (Table 1). The optimal autoregulatory range occurred over higher pressures in the Ren2 groups at 2 mo but
not at 4 mo (Fig. 6B). Diabetes extended the range to lower pressures at 4 mo. The optimal pressure for autoregulation followed a similar trend to LAT, although the pressures more closely approximated SBP with the exception of D-Ren2 (Fig. 6B).

Pressure-flow relationships in the presence of papaverine. At 2 mo, D-SD rat kidneys had higher flow (Fig. 7B) reflecting reduced resistance (Fig. 7E) due to greater distensibility. In contrast, the D-Ren2 group showed reduced distensibility (increased RVR) vs. SD groups at intermediate perfusion pressures (Fig. 7E). At 4 mo, the high flow/low RVR shown by the D-SD group at 2 mo was reduced (Fig. 7, C and F). In addition, the Ren2 groups and nondiabetic groups tend to have a lower flow/higher RVR than the SD and diabetic groups, respectively.

Vessel wall stiffness was assessed from ΔG. At 2 and 4 mo, increasing perfusion pressure from 70 mmHg decreased ΔG in Ren2 groups highlighting that higher pressures were required to maintain flow in the presence of increased wall stiffness (Fig. 7, H and I). This was more obvious in the N-Ren2 group. In contrast, in D-SD kidney, ΔG increased over this pressure range, demonstrating increasing vessel wall compliance; flow also remained high with increasing pressure demonstrating greater conductance. If it is assumed that the N-SD groups are normal, these results suggest that vascular tensile strength is lower in diabetes and higher with the Ren2 gene. This was more obvious at 2 than at 4 mo. At higher pressures, ΔG remained constant, implying a constant RVR and a loss of compliance.

DISCUSSION

Autoregulation. In the present study, assessment of ANG II-enhanced static (vs. dynamic 9) autoregulation showed that the kidneys from hypertensive and diabetic rats retained the ability to maintain blood flow independently of SBP. In kidneys from all 2- and 4-mo diabetic and Ren2 rats, the mean ΔG reached zero. The LAT occurred at a lower pressure at all times in N-SD compared with N-Ren2, which suggests that this threshold is at least partially dictated by the prevailing BP. The
optimal autoregulatory range was extended in N-Ren2 rats. At pressures above this range, ΔG tended to be lower than in N-SD. Both these changes move the absolute autoregulatory range toward hypertensive in vivo pressures, which might be seen as protecting renal structure and function against pressure-induced injury as well as larger fluctuations in glomerular pressure.

Diabetes did not affect LAT in SD rats, but significantly decreased LAT in Ren2 rats, extending the optimal autoregulatory range to lower pressures at 4 mo, which also coincided with a drop in SBP at that time. Both the LAT and the optimal autoregulatory pressure were similar to SBP in most groups (Fig. 1A). The exception was in the D-Ren2 group where the LAT was lower than expected for such high SBPs. This suggests diabetes may impair resetting of the autoregulatory range, as observed in our N-Ren2 group, and previously in spontaneously hypertensive rats (15). Although LAT correlated with mean arterial pressure (MAP) in that study, the LAT threshold was always lower than MAP. This is supported by our observation that LAT thresholds were significantly below measured SBP, which has been previously shown to be well-correlated with MAP in rat models of hypertension (13).

Passive pressure-flow relationship. The vasculature of the kidney can be modelled as a branching tree (18), with the branches narrowing toward the resistance vessels. All vessels have elasticity, defined as the degree to which energy is conserved during a deformation-recoil reaction (31). Stiffness is the resistance to deformation offered by an elastic body; the inverse of stiffness is compliance. As perfusion pressure increases, blood vessels dilate, with more compliant vessels dilating at lower pressures than stiffer vessels. This was observed as a ΔG greater than 0 and a decreasing RVR. Hemodynamic parameters obtained during the papaverine pressure ramps were assumed to be dictated by properties independent of VSM activity, such as the number of nephrons and the diameter, elasticity, stiffness, tortuosity, or wall irregularities of the resistance vessels.

As perfusion pressure increased from 70 mmHg in the presence of papaverine, the RVR of N-Ren2 kidneys decreased, consistent with dilatation of the renal vasculature. Relative to D-Ren2 rat kidneys, ΔG in N-Ren2 rat kidneys decreased at higher pressures (compare D- and N-Ren2 curves up to 115 mmHg; Fig. 7, H and I). This suggests that diabetes increased compliance in Ren2 kidney vessels. We assume ΔG in the SD groups was greatest below 70 mmHg. After an initial decline, ΔG increased in the D-SD group at 2 mo and in both SD groups at 4 mo. This may represent a failure of elastic components in these groups. Conversely, the renal vasculature of Ren2 rats has greater pressure resilience, and compliance may increase with age (see N-SD data from Fig. 7, H vs. I). The present data are supported by the study of Beenan et al. (3) in Wistar and spontaneously hypertensive rats (SHR), at pressures below ~75 mmHg, where resistance was higher in SHR and nondiabetic rats compared with Wistar and diabetic rats, respectively. In contrast, RVR was similar above this pressure. This implies ΔG must have been higher in the SHR and nondiabetic rats immediately below 75 mmHg in order for the resistances to converge. The 2-mo flow data demonstrated that the vasculature of the D-SD group had a relatively high conductance, which suggests an early effect of diabetes.
so much a limit of autoregulation as a strain limit of the VSM. This strain limit probably correlates with VSM volume (fiber mass), suggesting that the upper limit of autoregulation is correlated with VSM volume.

If LAT is modulated by vascular stiffness, the autoregulatory and upper limits of autoregulation are modulated by VSM volume, and the LAT and autoregulatory range/upper limit are correlated, then this suggests VSM volume and vascular stiffness must also be correlated. Thus, the increase in stiffness may be at least partially due to an increase in VSM volume. This may explain why autoregulation tends to be optimal in the pressure range over which the passive-pressure-flow relationship has the highest stiffness (i.e., lowest ΔG).

Resetting of autoregulation is likely to begin from the point at which blood pressure starts to escalate, which is at ~5 wk of age in the m(Ren2)27 homozygote (21). In the present study, 6- to 8-wk-old Ren2 rats required a higher perfusion pressure than their age-matched SD rat counterparts to produce urine (data not shown). This suggests that preglomerular, nonautoregulatory resistance is higher in Ren2 rats at 6–8 wk and that resetting has already begun. Resetting would not be expected to be complete until after blood pressure has peaked, which has been reported to be at 10 wk (2) and is supported by our data (Fig. 1A).

In summary, an increase in vascular stiffness increases the LAT by protecting the VSM from higher pressures, while a decrease in vascular stiffness decreases LAT by reducing VSM protection from higher pressures. An increase in VSM volume increases the autoregulatory range and upper limit of autoregulation, and a decrease in VSM volume (and possibly fiber tensile strength) decreases the autoregulatory range and upper limit of autoregulation, because resistance to strain is VSM volume dependent. In D-SD rats, the LAT falls below systemic pressures (Fig. 6A) and the top of the autoregulatory range is lowered (Table 1) making the kidney susceptible to higher blood pressures. This effect would be exacerbated in D-Ren2 rats due to the presence of hypertension. Loss of autoregulation, and failure to protect glomeruli from hypertension, has been proposed as a factor contributing to progressive nephron loss (6).

Remodelling. It is likely that structural changes underlie the functional changes observed in this study. In the hypertensive Ren2 rat, RVR in the absence of VSM tone (i.e., in the presence of papaverine in the present studies) was elevated compared with SD rats and there was evidence to suggest increased vascular stiffness. Kidneys from diabetic animals were larger than those from nondiabetic animals, and the passive hemodynamic data suggest the renal vasculature was more compliant.

The same vasoactive compounds that mediate autoregulation and shear-induced dilatation can induce long-term structural

Table 1. Optimal autoregulatory range defined by ΔG = 0

<table>
<thead>
<tr>
<th>Month</th>
<th>N-SD</th>
<th>D-SD</th>
<th>N-Ren2</th>
<th>D-Ren2</th>
</tr>
</thead>
<tbody>
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<td>0</td>
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<td>85–145</td>
<td>115–130</td>
<td>100–175</td>
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<tr>
<td>2</td>
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<td>4</td>
<td>130–145</td>
<td>130–145</td>
<td>85–130</td>
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Where ΔG = 0, flow is constant and autoregulation is “perfect.” Italics are used where ΔG was minimized but remained significantly different from 0; this was assumed to be the optimal autoregulatory range for that group.
and functional changes by acting as mitogenic stimuli. Vasococontractors tend to promote, and vasodilators to inhibit, smooth muscle cell proliferation (22) and they are independently regulated and mediated (9). Hypertensive Ren2 rats may be considered a model of chronic vasoconstriction and diabetes may be considered a model of chronic vasodilation (4). Additionally, endothelial cell gene expression is affected by biomechanical stimulation (11) and this could lead to changes in vascular structure and function. Histological studies of rat preglomerular vessels show a different effect of hypertension (28) and diabetes (29). Structural changes can presumably provide longer-term compensation for biomechanical perturbations induced by hypertension and diabetes, whereas renal autoregulation modulates more acute effects.

The kidneys from the rats in this study showed remarkable phenotypic plasticity in compensating for diabetic and hypertensive hemodynamic perturbations. Diabetic rats regulated flow in a similar manner to age-matched nondiabetic rats even though diabetic animals had lower body and larger kidney weights. It was shown previously that glomerular capillary pressure is preserved in 4-mo-old m(Ren2)27 rats while media thickness was increased and arteriolar diameter decreased in the afferent arterioles (28). This suggests structural changes are protecting glomerular hemodynamics. However, glomerular capillary pressures were elevated by 8 mo, which suggests that these changes can only offer temporary protection.

Transgenic m(REN-2)27 rats and diabetes. The D-Ren2 rat showed a marked decline in GFR between months 3 and 4 (Fig. 1B), and this correlated with lower than expected vascular compliance (Fig. 7I). This suggests that the characteristic decline in renal filtration function in diabetes- and hypertension-related renal disease follows changes in renal vascular compliance. Early hyperfiltration in diabetes is mediated by enhanced proximal tubule reabsorption which reduces sodium concentration at the distal tubule and thereby leads to tubuloglomerular feedback-induced afferent arteriolar vasodilation (5).

Proteinuria was more severe in animals with the Ren2 gene. There may be synergy between the Ren2 gene and diabetes on the incidence of severe proteinuria (Fig. 1C). As protein loss is influenced by filtration (glomerular basement membrane and podocyte integrity) and reabsorption (efficiency of mesangial and tubular reabsorption), protein excretion was normalized to UCr (Fig. 1D), as is now routine in clinical practice. Normalized proteinuria was lowest in N-SD rats, highlighting compromised glomerular protein leakage and/or postglomerular
increased in the presence of the gene. These results point to vascular remodelling as compensation for the hemodynamic sequelae of hypertension and diabetes.

Summary. These data show that autoregulatory capacity remains intact in the presence of both diabetes and the Ren2 gene but that there is a resetting of pressures at which autoregulation is optimal. In the Ren2 rat, the new autoregulatory pressure thresholds do not fully compensate for the high average SBP (200 mmHg). The hemodynamic studies further suggest that diabetes reduced vessel wall stiffness, which was increased in the presence of the Ren2 gene. These results point to vascular remodelling as compensation for the hemodynamic sequelae of hypertension and diabetes.

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

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