Role of Glomerular Filtration Rate in Controlling Blood Pressure Early in Diabetes

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Perhaps the most obvious, and least contentious, examples of hypertension caused by the kidneys are renal artery stenosis and diabetic nephropathy, because there are readily identifiable, physical limitations in the ability of the kidneys to excrete sodium in each case. The former is characterized by a global restriction in renal perfusion, and the latter is characterized more specifically by glomerular injury and reduced glomerular filtration rate (GFR), but in each case there must be an increase in arterial pressure to maintain salt and water balance. Thus, in long-standing diabetes, types 1 and 2, a progressive decline in GFR is matched by a reciprocal increase in arterial pressure, which enables maintenance of sodium balance and body fluid volume homeostasis at the expense of deleterious adverse effects of chronic hypertension.

In this framework, decreased GFR in diabetic nephropathy is responsible for imparting a chronic sodium-retaining influence on the kidneys, and hypertension is the counterbalancing natriuretic influence required to maintain sodium balance and sustain life. It, therefore, becomes curious that the early stages of diabetes are characterized by increased GFR and sodium balance, yet blood pressure is normal rather than low. For sodium balance to be maintained at normal blood pressure in the face of the chronic natriuretic influence of elevated GFR, there must be a concurrent sodium-retaining influence. If not, then the natriuretic effect of increased GFR would act unopposed and result in the maintenance of sodium balance at a lower blood pressure, similar to the effect of a diuretic. However, the presence of an underlying salt-retaining influence has been difficult to realize conceptually because of the increase in absolute sodium excretion in diabetes and because normal blood pressure typically does not spur research interest. This review focuses on how sodium balance is maintained at normal blood pressure and increased GFR and how disruption of the mechanisms that sustain that balance influence blood pressure.

Sodium-Retaining Influence Early in Diabetes: Role of the Renin-Angiotensin System

The renin-angiotensin system is our most powerful mechanism for regulating sodium balance in response to variations in sodium intake and/or excretion. It is essential protection against decreases in blood pressure because of decreased extracellular fluid volume, and in diabetes the primary threat is glucose-induced osmotic natriuresis and diuresis. We and others have shown that plasma renin activity (PRA) increases early during the first week of streptozotocin-induced type 1 diabetes in rats, and the increase in PRA occurs even when diabetes is induced in rats with reduced kidney mass and very low baseline PRA and in rats on high and low salt intakes. Miller et al have reported that young diabetic patients under poor glycemic control have a significantly greater drop in arterial pressure after acute losartan administration compared with the response when under good glycemic control, suggesting that angiotensin II (Ang II) is playing a more important role supporting blood pressure under those conditions. Similarly, we have shown that induction of diabetes in rats with chronic angiotensin-converting enzyme inhibition causes arterial pressure to decrease. These data suggest that stimulation of the renin-angiotensin system is compensation for the glucose-induced natriuresis and diuresis at the onset of hyperglycemia and is essential to prevent blood pressure from decreasing.

Postulating a role for Ang II in renal pathophysiology in diabetes has been a challenge historically, because PRA typically is not elevated in sustained diabetes. Even studies that show early increases in PRA have reported a return to normal levels by the second week of diabetes. However, there now is considerable evidence for significant activation of an intrarenal renin-angiotensin system in chronic diabetes, independent of any measurable increase in circulating renin or Ang II. This provides one explanation for a continued sodium-retaining influence even after circulating Ang II levels have normalized. Another intriguing mechanism for promoting sodium retention in diabetes is tubular glucose itself. Hyperglycemia in diabetes increases proximal tubular sodium reabsorption more than can be accounted for by glomerulotubular balance alone, suggesting that it is a primary event. Thus, there is evidence that Ang II and perhaps glucose itself impart a sustained sodium-retaining influence on the kidneys in diabetes.
Then why is Blood Pressure not Increased?

It is important to return to the initiating event, as well as the initial question. Hyperglycemia is the initial event, and this causes significant natriuresis and diuresis even in animals with reduced kidney mass that do not have an increase in GFR. Thus, the body is threatened with volume loss and decreased blood pressure. Stimulation of the renin-angiotensin system is a compensatory response to prevent blood pressure from decreasing and to help restore sodium balance.

With sustained diabetes, intrarenal Ang II generation continues that action. The initial question was: why is blood pressure not decreased in the face of chronically elevated GFR? Our hypothesis is that Ang II provides a counterbalancing antinatriuretic influence, such that sodium balance is maintained at normal blood pressure. However, while studying the effect of NO on blood flow and blood pressure early in diabetes, we observed that, without NO, there was no increase in GFR (Figure 3). Moreover, there was hypertension that was Ang II dependent.

Thus, when diabetes was induced in rats treated chronically with Nω-nitro-l-arginine methyl ester (l-NAME), GFR did not increase, and mean arterial pressure increased above the l-NAME baseline blood pressure (Figure 4). When we used tempol to block superoxide chronically in l-NAME–treated rats, we found that the increase in GFR during diabetes was restored, and the hypertension was prevented.

These studies suggested that, without the increase in GFR, the sodium-retaining actions of Ang II predominated and required an increase in arterial pressure to maintain sodium balance.

However, that hypothesis was based on correlating changes in GFR and blood pressure in rats infused chronically with...
L-NAME, and NO obviously does much more in the body than influence GFR. To test the role of GFR in diabetes without blocking NO synthesis, we used surgical reduction of nephron mass to provide a mechanical limitation to GFR. It is critical to know the distinction between this model and the 5/6 nephrectomy model used most often in rat studies. The 5/6 model most often used is an infarction model created by removing 1 kidney and tying off branches of the contralateral renal artery. It is known to have increased renin secretion for 1–4 weeks postinfarct and to be highly linked to induction of renal inflammatory and immune system cascades that have been shown to induce and mediate sustained increases in blood pressure. Surgical reduction of renal mass, on the other hand, which is what we used, was compared with the 5/6 nephrectomy model by Griffin et al. and shown to be protected from the injury-mediated hypertension. This is a low-renin model that is normotensive on low-salt intake. We reported that GFR did not increase in those rats on induction of diabetes and, similar to earlier reports, they became hypertensive over the 7-day diabetic period (Figure 1, closed triangles), with blood pressures returning to control levels when intravenous insulin was used to restore normoglycemia. Moreover, despite low baseline renin, PRA increased significantly during diabetes, and chronic angiotensin-converting enzyme inhibition prevented the hypertension (Figure 1, open triangles).

**Link Among GFR, Ang II, Sodium Balance, and Arterial Pressure Early in Diabetes**

Sustained hyperglycemia induces natriuresis and decreases sodium balance. Our data in normal and reduced kidney mass rats, with or without increased GFR or Ang II, show that induction of diabetes increases urinary sodium excretion similarly in each case and that daily sodium balance is restored within several days in each case (Figure 2), regardless of which response to diabetes is missing or blocked. The difference is the arterial pressure at which sodium balance is restored. Thus, if GFR and Ang II both increase, as occurs normally, mean arterial pressure remains normal. Likewise, if neither increases, as when diabetes is induced in reduced kidney mass rats with chronic angiotensin-converting enzyme inhibition, arterial pressure also does not change. However, if GFR increases but Ang II does not, then mean arterial pressure falls, and the decrease in arterial pressure provides the antinatriuretic influence that opposes increased GFR and restores sodium balance. If Ang II increases but GFR does not, as occurred in the rats with 70% reduction in kidney mass, then hypertension ensues, and the increased arterial pressure is required to offset the sodium-retaining actions of Ang II and enable restoration and maintenance of sodium balance. That response is similar to what we measured when diabetes was induced in L-NAME-treated rats, but in that case we hypothesized that the failure of GFR to increase in that model was attributable, at least in part, to Ang II-mediated constriction of the afferent arteriole in the absence of NO.

**Mechanism for the Increase in GFR in Diabetes**

There is no consensus on the mechanism for the increase in GFR, but there is good evidence that NO may be involved. NO derived from neuronal NO synthase (nNOS) has been implicated in particular, and indeed blockade of nNOS has been shown to attenuate the increase in GFR in diabetes, but issues of experimental model, the level of oxidative stress, and the time after induction of diabetes play a major role in that assessment, and our results with chronic L-NAME treatment and measurements in conscious, undisturbed animals corroborate the nNOS blockade findings, although they do not distinguish between NO isoforms.

However, the role of NO to increase GFR is not as straightforward as simply having a direct vasodilatory action on the afferent arteriole explain the phenomenon. Although the potential contribution of that mechanism is not discounted, whether it is through endothelial NO synthase or nNOS-derived NO, the constitutive expression of nNOS in macula densa cells raises the possibility that NO may mediate afferent arteriolar vasodilation through its effect to attenuate sodium chloride transport at the macula densa. That would lead to vasodilation, at least in large part, by signaling a reduction in the tubuloglomerular feedback (TGF) vasoconstrictor signal. However, that effect of NO could be due either to actions that are similar to the effect of furosemide, in which afferent arteriolar resistance decreases as a function of decreased macula densa transport primarily along the normal TGF curve (which would mean moving leftward along the control TGF line in Figure 5, because blocking macula densa transport essentially is sensed similar to a decrease in tubular flow), or an effect to blunt the sensitivity of TGF, which means that the TGF curve is shifted (as shown by the upper dashed line in Figure 5). NO has been shown to blunt TGF sensitivity and the consequence of that action is that, for any given level of sodium chloride delivery to the macula densa, there is a lesser TGF signal for constriction of the afferent arteriole.
Decreased TGF sensitivity, therefore, can increase GFR. In an effort to shed light on how TGF and renal autoregulation in general may contribute to renal vasodilation early in diabetes, we used transfer function analysis of our 18-hour daily renal blood flow and arterial pressure records collected from chronically instrumented rats during baseline conditions and through the onset and maintenance of diabetes. We showed that the onset of diabetes increased transfer function gain, ie, increased transmission of arterial pressure power to renal blood flow power, throughout the frequency range analyzed, suggesting that there was a generalized change in the renal vasculature on induction of diabetes (Figure 6). However, there was evidence in particular of blunted TGF, as shown by the changes in transfer function gain within the dashed oval in Figure 6. Moreover, our follow-up study showed that chronic L-NAME treatment, which prevented the increase in GFR, also completely prevented the diabetes-induced shifts in transfer function gain. Although the role of endothelial NO synthase versus nNOS cannot be determined from those studies, these results, using unique, 24 h/d methods for chronic renal blood flow measurement, strongly implicate NO in diabetes-induced renal vasodilation and increased GFR. In addition, they suggest that an effect to blunt the sensitivity of the TGF mechanism may play a role.

Another hypothesis for increased GFR in diabetes is that it is a consequence of decreased sodium chloride concentration at the macula densa because of a combination of glucose-stimulated proximal tubular sodium reabsorption and the osmotic diuretic effect of tubular glucose. Thus, despite increased total sodium chloride delivery, as reflected simply by the natriuresis, the macula densa senses a decrease in tubular sodium chloride concentration. In other words, it behaves as if one were moving leftward along the control TGF curve in Figure 5, and the macula densa might be viewed anthropomorphically in this sense as being "tricked" by those tubular conditions. In that scheme, therefore, the TGF mechanism is functioning normally and would be mediating dilation of the afferent arteriole through withdrawal of the TGF vasoconstrictor signal in response to decreased tubular sodium chloride concentration. We have invoked this possibility previously, and these osmotic diuretic and sodium transport effects of hyperglycemia also may contribute to the stimulation of renin secretion early in diabetes.

This evaluation of GFR control essentially has tried to explain why, in the face of increased distal tubular flow and total sodium chloride delivery in diabetes, there is not the predicted TGF signal to reduce GFR. Some reports have suggested that TGF is doing exactly that in diabetes, but the weight of evidence that supports a role for NO argues that the TGF vasoconstrictor signal is diminished in diabetes. The effect of NO to impair macula densa transport could accomplish this by moving leftward along the normal TGF curve or by blunting TGF sensitivity. Both actions may occur and have additive or potentiating vasodilator effects, and if there is a decrease in distal tubular sodium chloride concentration because of the proximal tubular actions of glucose, then that also would decrease the TGF vasoconstrictor signal and contribute to the vasodilation. Our data suggest that TGF may be blunted early in diabetes, but that does not exclude the other 2 mechanisms or the possibility that all are involved simultaneously. Finally, our observations that the failure of...
GFR to increase in l-NAME-treated diabetic rats is Ang II and superoxide dependent, suggest that NO also may influence GFR by protecting against Ang II- and/or superoxide-mediated afferent arteriolar constriction early in diabetes.70,71 Thus, if stimulation of the renin-angiotensin system is a normal response to counteract sodium and volume loss early in diabetes, the protective action of NO against Ang II-mediated afferent arteriolar vasoconstriction would be important.

Implications Beyond Type 1 Diabetes

The hypothesis that we have developed is that a balance between the natriuretic effect of increased GFR and the antinatriuretic effect of Ang II is required for sodium balance to be maintained at normal arterial pressure at the earliest stages of type 1 diabetes. The increase in GFR is strongly NO dependent, but whether that is because of independent or combined effects of NO to blunt TGF or protect against Ang II-mediated afferent arteriolar constriction is not known. However, if there is an increase in Ang II and no increase in GFR, then there is an increase in arterial pressure. In the pre-type 2 diabetic, obese state most generally described as metabolic syndrome,72–74 there also is Ang II-dependent hypertension. However, if there is an increase in Ang II and no increase in GFR, then there is an increase in arterial pressure. In the pre-type 2 diabetic, obese state most generally described as metabolic syndrome,72–74 there also is Ang II-dependent hypertension.75–79 However, GFR typically is elevated, which would tend to argue against extrapolating our hypothesis to this condition. On the other hand, impairment of endothelial function also is a characteristic of the obese, metabolic syndrome state,80–84 and if endothelial NO synthase plays a role in the increased GFR in this pre-type 2 diabetic condition, then it is possible that GFR is not increased as much as it should be. Thus, the gradual evolution of hypertension during the progression of metabolic syndrome toward overt type 2 diabetes would be compensation for increased renin-angiotensin system activity that would help maintain sodium balance in the face of a gradual impairment in renal vasodilatory capability. This also is a hypothesis, and with little or no direct experimental evidence, but our work in type 1 diabetes suggests that such a mechanism has the potential to contribute to the development of hypertension in metabolic syndrome.

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References


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