Severe Hypertension Induces Disturbances of Renal Autoregulation

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To study if the severity of hypertension could be associated with disturbances of the autoregulation of renal blood flow and glomerular filtration, we compared the renal hemodynamic and functional responses to acute blood pressure reductions of a group of patients with moderate essential hypertension (n=10) with those of a group of patients with severe hypertension (n=10). Blood pressure was reduced to normal levels by a stepwise infusion of sodium nitroprusside, and effective renal blood flow (by 131I-hippuran), glomerular filtration rate (by endogenous creatinine clearance), and filtration fraction were determined. After acute blood pressure normalization, effective renal blood flow and glomerular filtration rate were significantly reduced in patients with severe hypertension (-41.6±8.3% and -44.7±6.8%, respectively; p<0.01 for both) but not in those with moderate hypertension (+4.9±9.1% and +6.2±13.3%, respectively; NS). Filtration fraction remained unchanged in both groups. These results show that severe but not moderate essential hypertensive patients have a displacement to the right of the lower limit of the renal autoregulation curve due to impaired vasodilation to maintain adequate renal blood flow during acute reductions of blood pressure. This impairment may be due to anatomic or functional defects of preglomerular vessels, or to both. Furthermore, the inability to maintain adequate glomerular filtration in these circumstances shows that patients with severe hypertension also have an impaired ability to adjust postglomerular vasomotor tone in the face of reductions in glomerular blood flow. (Hypertension 1992;19[suppl II]:II-279-II-283)
or extracellular volume contraction. Except for blood pressure levels, both groups of patients were comparable by age, sex, duration of hypertension, and renal function. (Table 1). Patients were admitted to the University Hospital of Escola Paulista de Medicina for a period of 2 days before the study. On the day of study, patients had a bladder catheter positioned for urine collection, and two veins in the arm were punctured for infusions. Blood collections were obtained from peripheral veins, and blood pressure was determined by an automatic sphygmomanometer at regular intervals. An equilibration period of 40 minutes was allowed before the study was begun. The study consisted of five periods: a 30-minute control period, three periods of 20 minutes during which sodium nitroprusside was infused at increasing doses (ranging from +2% to −77%, resulting in an average reduction of 41.6±8.3%). In contrast, only three of 10 patients with MH had such diminutions in ERPF.

Comparisons between the two groups were made by the Student’s t test, and comparisons between values obtained during the various periods of the studies were performed by one-way analysis of variance for repeated measurements, associated to the Duncan’s multiple range test. 10 Correlations were analyzed using the Spearman’s method, and associations were tested by Fisher’s exact test. Results are shown as mean±SEM.

**Results**

With the graded sodium nitroprusside infusions, blood pressure (systolic/diastolic) was reduced in MH patients from control values of 170.4±3.2/107.9±3.0 to 132.5±3.3/89.0±1.4 mm Hg, and in SH patients from 197.8±9.2/127.3±3.6 to 138.7±3.5/92.5±1.6 mm Hg. In MH patients, no significant changes were noted in ERPF (from 395.2±38.5 to 392.8±27.9 ml/min/1.73 m²) or in glomerular filtration rate (from 123.1±10.9 to 122.5±7.7 ml/min/1.73 m²). In contrast, in SH patients, ERPF and glomerular filtration rate did not change with the two lower doses of sodium nitroprusside (Figure 1) but decreased significantly at the third dose (from 375.5±55.6 to 222.5±50.6 ml/min/1.73 m², p=0.0087, and from 104.7±10.9 to 62.4±10 ml/min/1.73 m², p=0.0083, respectively) (Figure 1). No significant changes were noted in filtration fraction in either group (SH, from 31.9±2.1% to 31.9±1.7%; MH, from 30.6±3.1% to 32.1±3.1%). Renal vascular resistance did not change significantly in SH patients (from 0.311±0.058 to 0.495±0.150 AU, p=0.14768), but its decrease was of borderline statistical significance in MH patients (from 0.206±0.020 to 0.161±0.011 AU, p=0.07530).

From baseline to the third dose of sodium nitroprusside, the changes produced in ERPF and glomerular filtration rate were strikingly different between the two groups. In nine of 10 patients with SH, we observed diminutions greater than 10% in ERPF (ranging from +2% to −77%, resulting in an average reduction of 41.6±8.3%). In contrast, only three of 10 patients with MH had such diminutions in ERPF.
(ranging from +58% to −32%, resulting in an average change of +4.9 ± 9.1%). The association of decreases in ERPF and severe hypertension was statistically significant (Fisher's exact test, p = 0.0197). Also, a reduction in glomerular filtration rate of 44.7 ± 6.8% (p < 0.001) was observed in SH patients, but changes of only +6.2 ± 13.3% (NS) were noted in MH patients.

A significant correlation was observed in SH patients between changes in glomerular filtration rate and changes produced in ERPF during the lowering of blood pressure (r = 0.8251, p < 0.0001) and also between the percentage of change in blood pressure and the percentage of change in ERPF (r = 0.4013, p = 0.0279). In contrast, the MH group did not show statistically significant correlations between these parameters.

**Discussion**

In several experimental models of hypertension, the increased blood pressure levels seem to alter the ability of the kidney to autoregulate renal blood flow and glomerular filtration.1-3,11 Studies addressing this issue in human hypertension have been scarce, and their results are in general negative.5,7 In the present study, we observed that SH patients but not MH patients exhibited substantial reductions of ERPF during acute normalization of blood pressure. These reductions were accompanied by decreases of similar magnitude in glomerular filtration. These data clearly reflect impaired renal autoregulation in severe hypertension. This is further illustrated by the observed significant correlation between changes in the variations in mean arterial pressure produced by nitroprusside infusions and the changes in ERPF. Furthermore, the behavior of renal vascular resistance during the test suggests that these autoregulatory dysfunctions in SH patients were a consequence of inadequate vasodilation. In contrast, in the MH group, most of the patients showed renal vasodilation leading to a borderline significant decrease in renal vascular resistance in the group as a whole. Additionally, in contrast to what was found in some studies with patients and animals with renovascular hypertension,7,8 in which alterations in renal autoregulation were evident already at the first step of the gradual reduction in arterial pressure, our patients in the SH group had preserved autoregulatory capacity while blood pressure was still in the hypertensive range. The decreases in renal blood flow occurred only when blood pressure was within the normal limits (Figure 1). This demonstrates that the normal levels of blood pressure were below the lower limits of renal autoregulation in our SH patients, similar to that which occurs with the cerebral circulation.12 Thus, our data strongly suggest that in severe hypertension, the elevated levels of blood pressure induce a displacement of the normal autoregulation curve to the right. They are also in accordance with observations in the spontaneously hypertensive rat3 and in a special strain of genetically hypertensive rats1 in which reductions in renal plasma flow and glomerular filtration rate were detected when diastolic blood pressure was reduced from hypertensive levels to 95 mm Hg.

On the other hand, Omvick et al.6 studying patients with essential hypertension, did not observe any impairment of autoregulation of renal blood flow. The discrepancies of these results with ours may be due to specific characteristics of the patients in the two studies. Our patients had more severe hypertension than the subjects in Omvick's study. The criterion for inclusion of patients in our SH group was that of a diastolic blood pressure equal to or greater than 120 mm Hg, whereas this was the upper limit for mean arterial pressure for inclusion in Omvick's study. Ethnic differences between the two popula-
tions could also account in part for the differences, because black hypertensive patients seem to have more anatomic abnormalities in renal vessels than white hypertensive patients.13

The alterations in renal autoregulation in our SH patients are new observations. With a similar protocol, Textor et al7 have also shown autoregulatory limitations only in patients with physical blood flow constraints to the kidney, such as bilateral renal stenoses or stenosis to a solitary kidney. Our data, however, indicate that disturbances of renal autoregulation can also be identified in patients with severe forms of essential hypertension, but these impairments are of smaller magnitude than those observed in patients with renal stenosis.7 Therefore, this fact shows that patients with severe hypertension can preserve the autoregulatory capacity in the hypertensive range of arterial pressure in contrast with patients with bilateral renal stenosis.

Our findings could be attributed to distinct anatomic or functional features of the renal vasculature of the group with hypertension. Anatomic factors can be hypothesized because these structural alterations in hypertension were demonstrated in necropsy studies14 of patients with essential, uncomplicated hypertension. Furthermore, in two-kidney one clip hypertensive rats, the kidney not submitted to ischemia has narrower arteriolar lumens and has autoregulation of renal plasma flow readapted to more elevated levels of blood pressure when compared with the ischemic kidney.2 The functional15 and structural16,17 adaptations appear early in the course of hypertension and are progressive, as suggested by Hollenberg et al,4,5 who showed a greater degree of vascular structural changes in severe compared with moderate hypertension. Therefore, the distinct behavior of renal blood flow in our SH patients may be due to the fact that the vascular changes in these patients are dependent on the severity of hypertension. Structural vascular alterations may also be involved in the autoregulatory dysfunction, because it is established that vascular hypertrophy reduces the maximal capacity of vasodilation during renal hyperperfusion.18-21 Thus, anatomic changes may be responsible in part for the shift of the inferior limit of the perfusion autoregulatory curve observed in our SH patients.

However, changes other than structural must also be considered to explain our results. Studies of the cerebral circulation of patients with severe hypertension and of the renal circulation in the spontaneously hypertensive rat have shown that shifted autoregulation curves can be normalized with short-term antihypertensive treatment.3,12 This fact is compatible with functional, rather than structural, disturbances of the vascular bed. The functional events that might account for the changes in autoregulatory adaptation may involve baroreceptors, as shown in other vascular areas22,23 in which restoration of normal function can be observed with reduction of blood pressure in periods of time as short as 6 hours. On the other hand, humoral factors may also be involved in the disturbance of autoregulatory function. The participation of the renin-angiotensin system in this phenomenon has been excluded;2 but the involvement of the renal prostaglandin system may be considered because loss of renal autoregulation in the aged spontaneously hypertensive rat has been observed by the inhibition of this system with indomethacin.23 Finally, biochemical factors of endothelial origin, which are responsible for the control of the local blood flow,24 may also be involved. Substances of endothelial origin with vasoconstrictor function can be liberated when structural alterations are present in a vessel wall25 and may induce alteration of the vascular wall.26 It is reasonable to assume that patients with severe hypertension have greater endothelial damage than those with moderate hypertension, because these patients usually show preserved vasodilator responses to acetylcholine, whereas patients with severe hypertension have no response.4,15

In addition to the disturbances of autoregulation of renal blood flow, our study also shows that patients with severe hypertension have an impaired capacity to regulate the glomerular filtration rate as blood pressure is reduced to normal levels, in contrast with patients with moderate hypertension. These results are also in accordance with those of experimental studies that show diminutions in glomerular filtration rate in cases in which autoregulatory defects of blood flow to the kidney could be detected.1,10 In our SH patients, the intrinsic renal mechanisms responsible for increases in filtration fraction to compensate for reductions in renal blood flow were not operative, resulting in significant reductions in glomerular filtration. This failure could be due to maximally constricted postglomerular vessels, which, as such, are incapable of further increasing filtration fraction, similar to what was described by Ferreira Filho et al27 in patients with congestive heart failure. This possibility can be suggested in analogy to other circumstances such as acute volume depletion, when the postglomerular vasculature is insensitive to regulatory constrictr agents.28 Thus, it is reasonable to speculate that patients with severe hypertension failed to regulate the glomerular efferent arteriolar tone in the face of a potent stimulus such as the diminution of renal blood flow because of insensitive postglomerular vessels, possibly due to prior maximal stimulation.

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