The rats were in a stable condition with constant BP and HR, which were maintained throughout the whole experiment and the baseline readings for MAP, HR, CBP, and MBP are summarized in Table 1.

There is no significant alteration in the cortical or medullary blood perfusion after intramedullary infusion of vehicle over a period of time compared with the baseline values in both normotensive and hypertensive groups (the data not shown).

It was noted that the basal level of MAP in the SHRSP was significantly higher than that observed in Wistar rats ($P < 0.05$). The values in both strains before the infusion of saline were (MAP in SHRSP = 136 ± 4 mmHg, MAP in Wistar = 108 ± 4 mmHg; $n = 10$; $P < 0.05$) and after the saline infusion (MAP in SHRSP = 131 ± 5 mmHg, MAP in Wistar = 104 ± 6 mmHg).

In the SHRSP, renal medullary interstitial infusion of vehicle into CMB had no significant effect on either CBP (154 ± 5 PU vs. 159 ± 5 PU; $n = 10$) or MBP (56 ± 4 PU vs. 55 ± 5 PU; $n = 10$; data not shown).

The CBP of SHRSP was close to the average CBP values in Wistar rats and was also relatively stable over the period of intramedullary infusion of vehicle. However, it was notable that MBP was significantly lower in SHRSP in comparison to Wistar rats (56 ± 4 PU vs. 81 ± 8 PU, $n = 10$; $P < 0.05$); CBP and MBP in Wistar rats were similarly unaffected by intramedullary infusion of vehicle.

Effect of renal medullary interstitial infusion of L-NAME on cortical blood perfusion and medullary blood perfusion in stroke-prone spontaneously hypertensive rats versus Wistar rats

The baseline data for MAP, HR, CBP, and MBP in these groups of experiments are summarized in Table 1. It can be seen that L-NAME (10 μg/kg/min) significantly increased the MAP in both SHRSP and Wistar rats [SHRSP = 130 ± 3 mmHg before L-NAME, 144 ± 4 mmHg after L-NAME; $P < 0.05$, $n = 10$: Wistar = 110 ± 4 mmHg before L-NAME, 124 ± 3 mmHg after L-NAME; $P < 0.05$, $n = 10$, Figure 1]. Although HR remained stable in both groups.

Renal interstitial infusion of L-NAME into CMB caused no significant changes to CBP in both SHRSP and Wistar rats.

In contrast to the effects on CBP, infusion of L-NAME into CMB decreased MBP in the SHRSP rats by 18% ±5% ($P < 0.05$, $n = 10$). This L-NAME-induced reduction in MBP was greater than that seen in Wistar rats (12%±4%, $n = 8$, $P < 0.05$), but there was no significant difference in the magnitude of the reduction between the two strains [Figure 2].

DISCUSSION

The SHRSP is now widely accepted as a good animal model of genetic hypertension.[22] In this respect, it displays characteristic symptoms of diseases such as increased peripheral resistance,

atherosclerosis, nephrosclerosis, and associated renal structural changes, which are comparable to the hypertension-associated pathology in humans.[23,24] Furthermore, the hypertensive characteristics displayed by SHRSP also exacerbate with age, which also mirrors the human condition.[23,25]

As hypertension has been associated with renal damage, the study of genetic models of hypertension and their corresponding renal function and reaction to renal ischemia is of the upmost importance.[26] Therefore, the SHRSP, the model of hypertension, was selected to investigate the impact of hypertension on renal perfusion and function before and after a period of intramedullary infusion of drug that inhibited enzyme involved in reducing the level of oxidative stress in the kidney.

Control groups

These groups were used to evaluate the BP, HR, MBP, and CBP responses to the infusion of vehicle into the CMB in both SHRSP and Wistar rats, and these groups were considered as control groups against the other groups that received a drug mixed with the vehicle, so we could judge whether the effect originated from the drug or from the vehicle. It was evident
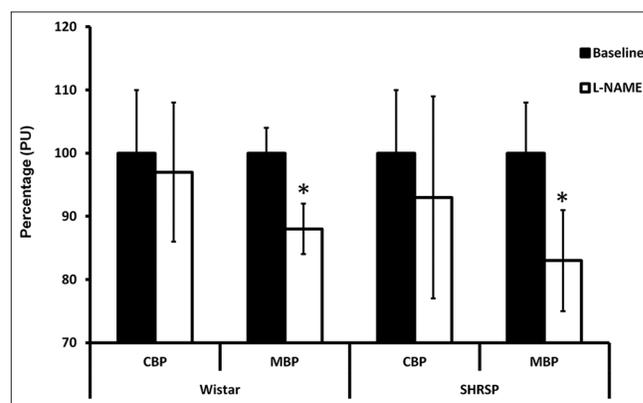

Figure 1: Histogram demonstrating the effect of L-NAME on CBP and MBP in Wistar rats relative to SHRSP ($n = 10$ for each data point). Data analysis was performed using Student's paired t-test within the group and two-way ANOVA between the groups. *Significant difference between the L-NAME treated group and the respective baseline ($P < 0.05$) (at column width)

Table 1: Baseline values of mean arterial pressure, cortical blood perfusion, medullary blood perfusion, and heart rate

Parameter	Wistar		SHRSP	
	Vehicle	**L-NAME**	**Vehicle**	**L-NAME**
n	10	10	10	10
Baseline MAP (mmHg)	108±4	114±3	136±4*	130±3*
Baseline CBP (PU)	150±19	112±11	154±5	115±12
Baseline MBP (PU)	81±8	76±3	56±4*	65±5*
Baseline HR (beats/min)	374±17	321±17	268±23*	237±16*

Values obtained from vehicle and L-NAME treated groups of SHRSP and Wistar rats before any infusion. Statistical analysis was performed using a two-way ANOVA test. *$P<0.05$, when baseline values of SHRSP were compared with those of Wistar rats. MAP: Mean arterial pressure, CBP: Cortical blood perfusion, MBP: Medullary blood perfusion, HR: Heart rate, SHRSP: Stroke-prone spontaneously hypertensive rats
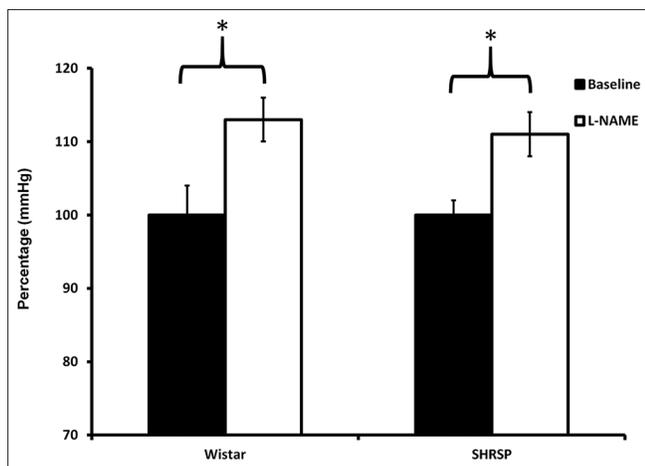
Figure 2: Histogram demonstrated the effect of L-NAME on BP of SHRSP and Wistar rats. * indicates $P < 0.05$, significantly different from the baseline ($n = 10$ for each data point). Statistical analysis was performed using Student's paired t-test within the group and two-way ANOVA between the groups (at column width)

that over the periods of measurements, perfusions and the other parameters remained relatively unchanged in each group indicating that the preparation was stable, and the vehicle had no action on all the parameters.

There were significant differences between the baselines of cortical perfusion and medullary perfusion. The cortex was shown to have a higher level of red cell flux than that obtained from the medulla, which is in accordance with the understanding that the renal cortex has a greater concentration of blood vessels and therefore a higher perfusion than the medulla.

The previously mentioned findings were consistent with observations from earlier studies on Wistar and SHRSP in our laboratory[19,21,27] that findings plus the stability of all the parameters over the whole period of the control study provided a strong evidence regarding the reliability of our current experiments.

The second part of this study was to examine the effect of the acute inhibition of the NOS enzyme and analyze the outcome to assess its underlying contribution to tone of the renal vasculature in SHRSP and Wistar rats.

L-NAME groups
This study set out to investigate the role of NO in the kidney, particularly on the renal cortical and medullary microvasculature, as NO has been characterized as having potent vasodilator actions and also has been reported to be generated in significant amounts in the renal medulla. It is known that the kidney possesses three distinct NO synthase (NOS) isoforms (iNOS, eNOS, and nNOS); but in this study, a nonselective NO inhibitor was chosen to inhibit the synthesis of NO from the amino acid L-arginine.

Previous studies examined the effect of systemic NO inhibition on systemic and renal hemodynamics and

excretory function have yielded disparate results. There have been reports of increased, as well as unchanged, MAP after L-NAME administration.[28-30] The findings are more divergent in terms of renal hemodynamic and excretory function, ranging from an increase, decrease to no change. [28-31] The variability in these finding probably reflects differences in the experimental preparation, routes, and methods of L-NAME administration. In the present study, the possibility that NO generation may not be efficiently prevented was excluded since the dose of L-NAME used has been shown to be effectively block NOS activity in Wistar rat kidney and to cause an increase in BP and depressed renal plasma flow, after intravenous administration at least in same dose used in our study or higher.[19,28]

The effect of chronic intravenous infusion of L-NAME on BP and intrarenal blood flow had been previously studied and the authors provided clear evidence for the reduction in renal MBP and increase in systemic BP but there was no change in cortical perfusion;[8] the same findings were obtained previously from our laboratory when the L-NAME was administered locally into the CMB of Wistar rats;[19] also, these findings are in agreement with what we currently find in the new set of experiments on Wistar rats. However, the number of animals and the protocol were slightly different but still provided same findings, which indicate that NO plays an important role in regulating the tone of blood vessels in the medullary region.

In SRRSP, where the level of oxidative stress is considered to be very high due to the increased amount of superoxide anion in the medullary region and the increase in sensitivity of the medullary region of SHRSP to ROS,[27] the NO appears to play a similar role in maintaining the stability of blood perfusion in the medullary region of the kidney as same as their action on normotensive rats although a tendency of having more role in hypertensive state was obvious by reducing the MBP in SHRSP by 18% and by 12% in Wistar rats.

Numerous studies have demonstrated that endothelium-dependent vasorelaxation markedly decreases in the hypertensive state and in experimental animal models of hypertension.[32,33] Furthermore, exaggerated production of superoxide anion by the vascular wall has been observed in different animal models of hypertension including SHRSP.[34,35] There is a growing body of evidence that supports the possibility of increased oxidative inactivation of NO by an excess of superoxide and may account for the decrease in available NO and endothelial dysfunction observed in hypertensive rats.[33,36,37]

In the present study, we found that antagonizing NOS with L-NAME reduced MBP significantly in both SHRSP and Wistar rats. These findings suggested that the lower amount of NO found in the SHRSP plays a very important role in the control of vascular tone, which was to counteract the action of superoxide anions. It seems that a small part of the L-NAME given locally did get absorbed into the systemic circulation as it significantly increased the BP in both SHRSP and Wistar rats.

An interesting finding in the present study was the arterial pressure which increased on the acute infusion of L-NAME. The elevation of arterial BP in this case is probably due to a number of different factors; the L-NAME infusion may have initially increased BP because of increased peripheral resistance, as previously described by Gardiner et al.,[38] because we hypothesized that some of the L-NAME reached the systemic circulation. Other predictable reasons for the elevation of BP might be due to sodium and water retention, which has been reported previously,[8,39] while L-NAME given locally to the renal medulla would have effectively blocked the all NOS isoforms, which would prevent any local production of NO, which in turn would lead to vasoconstriction of the medullary blood vessels. This would also reduce the glomerular filtration rate and then reduce the sodium excretion from the kidney.

CONCLUSION

The acute intramedullary infusion of L-NAME into CMB prevented NO production that would cause a reduction in MBP, which may be important in the initiation of sodium and water retention, and leads to hypertension. Whereas cortical blood flow was unaltered by intramedullary L-NAME infusion. This study suggested that the availability of NO in the kidney region plays a major role in the control of renal microvasculature in both SHRSP and Wistar rats equally, regardless to the amount of ROS produced in the region.

Conflicts of interest
There are no conflicts of interest.

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