Frequency modulation of renal myogenic autoregulation by perfusion pressure

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Wang X, Loutzenhiser RD, Cupples WA. Frequency modulation of renal myogenic autoregulation by perfusion pressure. Am J Physiol Regul Integr Comp Physiol 293: R1199–R1204, 2007.—Recent studies of renal autoregulation have shown modulation of the faster myogenic mechanism by the slower tubuloglomerular feedback and that the modulation can be detected in the dynamics of the myogenic mechanism. Conceptual and empirical considerations suggest that perfusion pressure may modulate the myogenic mechanism, although this has not been tested to date. Here we present data showing that the myogenic operating frequency, assessed by transfer-function analysis, varied directly as a function of perfusion pressure in the hydronephrotic kidney perfused in vitro over the range from 80 to 140 mmHg. A similar result was obtained in intact kidneys in vivo when renal perfusion pressure was altered by systemic injection of Nγ-nitro-L-arginine methyl ester (L-NAME). When perfusion pressure was not allowed to increase, L-NAME did not affect the myogenic operating frequency despite equivalent reduction of renal vascular conductance. Blood-flow dynamics were assessed in the superior mesenteric artery before and after L-NAME. In this vascular bed, the operating frequency of the myogenic mechanism was not affected by perfusion pressure. Thus the operating frequency of the renal myogenic mechanism is modulated by perfusion pressure independently of tubuloglomerular feedback, and the data suggest some degree of renal specificity of this response.

RENALE AUTOREGULATION IN INTACT kidneys is mediated by the myogenic mechanism and by tubuloglomerular feedback (TGF). These two mechanisms operate on the same actuator, vascular smooth muscle of the afferent arteriole. Whereas the myogenic mechanism senses a variable that is local and related to perfusion pressure, TGF senses tubular transport in the distal nephron, a variable that is downstream to all other components of the combined system. Thus there is strong reason to expect the two systems to interact, and a number of recent studies have in fact shown modulation of the myogenic mechanism by TGF.

Several laboratories have shown transfer of information from TGF to the myogenic mechanism by using both in vitro (19) and in vivo experiments (3, 13). These laboratories addressed changes in the efficiency of autoregulation that resulted from their experimental maneuvers. Another approach has been taken by Marsh and colleagues (9, 10, 15). Using double-wavelet analysis of pressure-flow time series (15) combined with model-based interpretation, these authors have shown that TGF can modulate the frequency of the myogenic mechanism (9, 10). One limitation of all these studies has been that the potential effects of perfusion pressure have not been addressed. There is information in the literature showing that the frequency of vasomotion, a phenomenon presumably related to myogenic autoregulation, varies directly with perfusion pressure in several vascular beds (11, 18). There is also strong evidence for pressure dependency of the magnitude of interaction between TGF and the myogenic mechanism (12).

In the current study, we made use of several existing data sets to examine modulation of the myogenic mechanism by perfusion pressure. We are aware of only one study in which dynamic renal autoregulation was systematically assessed at multiple mean perfusion pressures (1). That study employed isolated, perfused hydronephrotic kidneys and showed that the dynamics of myogenic autoregulation in vitro are consistent with the dynamics of the faster mechanism in vivo. Although the hydronephrotic kidney may not be an ideal preparation with which to study dynamics, it has significant advantages. Perfusion pressure is determined solely by the investigator, it lacks TGF, and it is perfused with a defined medium. Thus there can be no modulation by TGF, and unspecified “factors” are unlikely to play any role. Here we use these data to demonstrate frequency modulation of the myogenic mechanism by renal perfusion pressure. The conclusions drawn from these experiments were confirmed in vivo by studies in which blood pressure was elevated by nonselective inhibition of nitric oxide synthases.

METHODS

All experiments received approval of the Animal Care Committee at the Sir Mortimer B. Davis-Jewish General Hospital (in vivo studies) or of the University of Calgary (in vitro studies) and were conducted under the guidelines promulgated by the Canadian Council on Animal Care. Rats had free access to water and food at all times before the acute experiments.

The first study employed six hydronephrotic kidneys. The details of creation of hydronephrotic kidneys, of in vitro perfusion, of perfusate composition, and of experimental procedures for this experiment have been reported previously (1). Data (including renal artery pressure and perfusate flow) were acquired at 3 Hz for 400 s at each mean pressure. Random fluctuations in perfusion pressure were introduced manually as described previously (1). Average perfusion pressure was increased successively from 60 to 80, 100, 120, and 140 mmHg. Data segments of 1,024 points (341 s) were subjected to linear trend removal and were low-pass filtered. Pressure-flow transfer functions were computed on 256-point overlapping segments with a frequency resolution of 0.01172 Hz.

Subsequent experiments were performed in vivo and involved measurement of blood flow in the left renal artery or in the superior
mesenteric artery of rats anesthetized by isoflurane. In all cases, the vascular bed under study was denervated. The details of surgical manipulation, drug administration, and experimental procedures are given in one or more of references (1, 20, 21) as noted specifically below. \( \text{\textsuperscript{\textdegree}N\textendash} \text{nitro-L-arginine methyl ester (L-NAME; 10 mg/kg iv; Sigma)} \) was injected after the control period.

In 22 Wistar rats, blood pressure and renal blood flow (RBF) were acquired before and after injection of L-NAME (2, 20, 21). In seven Wistar rats, L-NAME was given during intravenous infusion of atrial natriuretic factor (15 μg/kg plus 15 μg·kg\(^{-1}·\text{h}^{-1}\)) (21). In all of these animals, blood pressure was allowed to increase after L-NAME and autoregulation was driven by spontaneous fluctuation of blood pressure. Similarly, blood flow in the superior mesenteric artery was acquired before and after L-NAME in 17 Wistar rats (2). Pressure-flow transfer functions were computed on 256-point overlapping segments with a frequency resolution of 0.01172 Hz. RBF dynamics and mesenteric blood flow dynamics from these experiments have been reported elsewhere (2, 21).

Six experimental series employed Brown Norway (\( n = 10 \)), Sprague-Dawley (\( n = 9 \)), Wistar (\( n = 7 \) and 9), Long-Evans (\( n = 9 \)), and Wistar Kyoto (\( n = 6 \)) rats. In these studies, an initial period at spontaneous blood pressure was followed successively by a control forcing period and a second forcing period after intravenous injection of L-NAME. Blood pressure was forced by a supraprenal aortic clamp driven by a program that operated as a servo controller to regulate femoral arterial pressure and to add noise. By design, renal perfusion pressure in the control (forced) and L-NAME periods was the same or similar. Pressure-flow transfer functions were computed on 512-point overlapping segments with a frequency resolution of 0.0039 Hz. RBF dynamics, and the effects thereon of L-NAME, from these experiments have been reported previously (20, 21).

Pressure and flow signals were acquired and analyzed as reported previously (1, 2, 5, 20, 21). Briefly, perfusion pressure and blood and perfusate flow were measured over periods of at least 400 s. Transfer functions based on the fast Fourier transform were used to determine the relationship between perfusion pressure and perfusate or blood flow. Transfer functions acquired from the renal circulation routinely show a resonance peak in gain that is generated by the myogenic mechanism, and for the purpose of this study the location of this peak was defined to be the operating frequency of the myogenic mechanism. In each record, the resonance peak was identified visually from a plot of gain vs. frequency over the interval from 0.1 to 0.3 Hz (to 0.4 Hz in vitro). A second assessment of operating frequency was also used. Under pressure-passive conditions, admittance phase in a denervated organ is normally close to zero. Operation of an autoregulatory mechanism causes a phase peak that is coincident with the interval of gain reduction. We defined the initiation of the phase peak as follows. Baseline (pressure-passive) phase was taken to be the average in the interval of 0.4–0.6 Hz (0.5–0.75 Hz in vitro) and the peak as the maximum value in the interval from 0.1 to 0.3 Hz (0.1 to 0.4 Hz in vitro). The “phase-rise frequency” at which phase first was \( \geq \text{baseline} + (\text{peak} − \text{baseline})/2 \), that is, one-half the total phase rise, was used as an index of the initiation of the myogenic phase peak.

Differences between experimental periods were assessed by paired \( t \)-tests in two-period experiments and in the remaining experiments by one-way repeated-measures ANOVA (Statistica version 5.5; Statsoft, Tulsa, OK). Contrast analysis was used to test whether there were differences between consecutive periods. \( P < 0.05 \) was considered to indicate a significant difference. Results are presented as means ± SE.

RESULTS

Figure 1 displays renal circulatory dynamics acquired from hydronephrotic kidneys at four different mean perfusion pressures ranging from 80 to 140 mmHg. Figure 1A shows that in all records there was high coherence between perfusion pressure and perfusate flow. The transfer functions are shown in Fig. 1B (admittance gain) and Fig. 1C (admittance phase). At all pressures >60 mmHg, the signature of an autoregulatory mechanism was apparent with gain reduction to <0 dB and an associated positive phase peak. As expected, and as noted previously (1), gain reduction was progressively stronger at higher pressures. The autoregulatory mechanism also operated progressively faster as pressure was increased. This is shown by the progressive right shift of the resonance peak in gain and of the associated rise of phase.

Figure 2 shows the average resonance and phase-rise frequencies plotted against mean perfusion pressure for the six hydronephrotic kidneys together. There were substantial and pressure-dependent increases in the frequency of the resonance peak in gain and in the phase-rise frequency (both \( P = 10^{-5} \)). Contrast analysis showed that the resonance frequency at 80 mmHg was less than that at 120 (\( P = 0.0021 \)) and at 140 mmHg (\( P = 0.0004 \)); the resonance frequency at 100 mmHg was less than that at 140 mmHg (\( P = 0.005 \)). The phase-rise frequency at 80 mmHg was less than that at all higher pressures (\( P = 0.0341, 0.0007, \) and 0.0017 vs. 100, 120, and 140 mmHg, respectively), whereas the phase-rise frequency at 100 mmHg was less than that at 140 mmHg (\( P = 0.0028 \)).
Vasomotion was not apparent at 60 mmHg and appeared at higher pressures. This is shown in Fig. 3, which depicts the power spectra of afferent arteriolar diameter in a single experiment. Oscillation of afferent arteriolar diameter was obvious at 100 mmHg and at higher pressures became more continuous and progressively faster. The low-frequency power (<0.1 Hz) at 120 and 140 mmHg reflects intermittent oscillation. Vasomotion produced a defined spectral peak at all pressures ≥100 mmHg in five of six hydronephrotic kidneys. The frequency of this peak increased from 0.16 ± 0.04 Hz at 100 mmHg to 0.23 ± 0.04 Hz at 120 mmHg (P = 0.053) and to 0.26 ± 0.04 Hz at 140 mmHg (P = 0.042 vs. 100 mmHg; not significant vs. 120 mmHg).

Figure 4 summarizes the results of the in vivo experiments. In all cases, l-NAME caused a profound and very similar reduction of renal or mesenteric vascular conductance. When the renal perfusion pressure was allowed to rise after l-NAME, the peak resonance frequency rose from 0.211 ± 0.007 to 0.254 ± 0.006 Hz and the phase-rise frequency from 0.184 ± 0.007 to 0.248 ± 0.009 Hz (P = 6 × 10^{-7} and P = 3 × 10^{-7} respectively; two-tailed t-test) in 22 previously untreated Wistar rats. Similarly, l-NAME given during infusion of atrial natriuretic factor increased the resonance frequency from 0.229 ± 0.011 to 0.273 ± 0.010 Hz and the phase-rise frequency from 0.199 ± 0.012 to 0.244 ± 0.010 Hz (P = 0.043 and P = 0.046, respectively). In another 17 Wistar rats that were similarly prepared and in which blood flow in the superior mesenteric artery was measured, l-NAME increased blood flow comparably and profoundly reduced mesenteric vascular conductance (P = 8 × 10^{-10}) but did not affect the resonance frequency (control, 0.159 ± 0.007; l-NAME, 0.166 ± 0.006 Hz; P = 0.299, two-tailed t-test) or the phase rise frequency (control, 0.148 ± 0.006 Hz; l-NAME, 0.157 ± 0.004 Hz; P = 0.125).

A total of 50 rats from five normotensive strains in six experimental series were studied in the final protocol. In this experiment, l-NAME was administered systemically to 4 groups of rats after an initial control period. Mesenteric blood flow (MBF) dynamics were assessed in 1st group, and renal blood flow (RBF) dynamics in other 3 groups. In 3 of these groups, shown from left, perfusion pressure (A) was permitted to increase (Spontaneous; all P < 0.001); in 4th group, shown at right (Clamped), renal perfusion pressure was held almost constant by a suprarenal aortic clamp (n = 50; Δ = ±2.7 ± 0.8 mmHg; P = 0.001). B: l-NAME caused profound and similar reduction of conductance in all groups of rats (in all cases P << 10^{-3}). C: l-NAME-induced hypertension increased resonance frequency of renal myogenic autoregulation (n = 22, P = 6 × 10^{-5}, two-tailed t-test; n = 7, P = 0.043, ANOVA) but not that of mesenteric myogenic autoregulation (n = 17, P = 0.199, two-tailed t-test). As shown at right, resonance frequency of renal myogenic autoregulation was not altered by l-NAME when perfusion pressure was not permitted to rise (n = 50, P = 0.636). D: l-NAME-induced hypertension increased phase-rise frequency of renal myogenic autoregulation (n = 22, P = 3 × 10^{-5}, two-tailed t-test; n = 7, P = 0.046, ANOVA) but not that of mesenteric myogenic autoregulation (n = 17, P = 0.125, two-tailed t-test). In presence of l-NAME but absence of a pressure change, phase-rise frequency was unaltered (P = 0.637).

Fig. 2. Frequencies of resonance peak in gain (solid line) and of phase rise (dotted line) increased substantially as renal perfusion pressure was elevated. Standard errors of mean perfusion pressure are not shown, because all were ≤0.4 mmHg. Resonance peaks at 80 and 100 mmHg were slower than those at 120 and 140 mmHg (80 vs. 120, P = 0.0024; 80 vs. 140, P = 0.0004; 100 vs. 120, P = 0.0167; 100 vs. 140, P = 0.005; 120 vs. 140, P = 0.0285). Similarly, phase-rise frequency increased with perfusion pressure (80 vs. 100, P = 0.0341; 80 vs. 120, P = 0.0007; 80 vs. 140, P = 0.0017; 100 vs. 140, P = 0.0028).

Fig. 4. A: l-NAME-nitro-L-arginine methyl ester (l-NAME) was administered systemically to 4 groups of rats after an initial control period. Mesenteric blood flow (MBF) dynamics were assessed in 1st group, and renal blood flow (RBF) dynamics in other 3 groups. In 3 of these groups, shown from left, perfusion pressure (A) was permitted to increase (Spontaneous; all P < 0.001); in 4th group, shown at right (Clamped), renal perfusion pressure was held almost constant by a suprarenal aortic clamp (n = 50; Δ = ±2.7 ± 0.8 mmHg; P = 0.001). B: l-NAME caused profound and similar reduction of conductance in all groups of rats (in all cases P << 10^{-3}). C: l-NAME-induced hypertension increased resonance frequency of renal myogenic autoregulation (n = 22, P = 6 × 10^{-5}, two-tailed t-test; n = 7, P = 0.043, ANOVA) but not that of mesenteric myogenic autoregulation (n = 17, P = 0.199, two-tailed t-test). As shown at right, resonance frequency of renal myogenic autoregulation was not altered by l-NAME when perfusion pressure was not permitted to rise (n = 50, P = 0.636). D: l-NAME-induced hypertension increased phase-rise frequency of renal myogenic autoregulation (n = 22, P = 3 × 10^{-5}, two-tailed t-test; n = 7, P = 0.046, ANOVA) but not that of mesenteric myogenic autoregulation (n = 17, P = 0.125, two-tailed t-test). In presence of l-NAME but absence of a pressure change, phase-rise frequency was unaltered (P = 0.637).
protocol, data were acquired at the same or very similar mean perfusion pressure during the control and L-NAME periods. RBF dynamics from most of these rats have been reported previously (20, 21). Previous analysis showed that these strains had very similar RBF dynamics, with the exception of the Brown Norway rats, which had less efficient myogenic autoregulation, and that the response of RBF dynamics to L-NAME was the same in all strains (20). Similarly, repeated-measures ANOVA of the different strains in the current study showed that all exhibited the same responses of conductance and frequency of the myogenic mechanism. Consequently, the results were pooled for presentation. L-NAME resulted in a small increase in blood pressure from 100 ± 1 to 103 ± 1, which was significant due to the large number of rats (P = 0.001). There was the expected large reduction of renal vascular conductance due to L-NAME (P = 8 × 10⁻²³) but no change in the resonance frequency (control, 0.215 ± 0.004 Hz; L-NAME, 0.213 ± 0.004 Hz; P = 0.636) or in the phase-rise frequency (control, 0.210 ± 0.003 Hz; L-NAME, 0.203 ± 0.007 Hz; P = 0.637).

**DISCUSSION**

The overall finding of this study is that there is a graded increase in the frequency of myogenic autoregulation as perfusion pressure is elevated. This effect is prominent in the isolated perfused hydronephrotic kidney: it is strong in the region of pressure between 80 and 140 mmHg, with little evidence of saturation within the range of pressures examined. In vivo, L-NAME also results in increased frequency of myogenic autoregulation when renal perfusion pressure increases but not when pressure is held at the control level. In contrast, the frequency of myogenic autoregulation in a major splanchnic circulation is unaffected by L-NAME-induced hypertension.

Two assessments of the operating frequency of the myogenic mechanism were performed. In the first, a single observer identified the resonance peak in gain in each individual record. Such analysis permits one to adjust for noise in the record but may of course be subject to conscious or unconscious observer bias. Assessment of the phase-rise frequency is more determinate and less subject to observer bias but is perhaps more susceptible to noise in the record. In the hydronephrotic kidney experiment and in the in vivo experiments in which autoregulation was driven by spontaneous blood pressure fluctuation, i.e., those experiments in which the resonance frequency and the phase-rise frequency varied systematically, 123 pairs of measurements were made. The measurements were highly correlated (r = 0.87; Fig. 2), and as predicted, the resonance frequency was slightly and consistently higher than the phase-rise frequency (0.229 ± 0.062 vs. 0.211 ± 0.060 Hz; means ± SD). Thus we are confident that the analysis can detect systematic changes in the operating frequency of myogenic autoregulation.

The current study used three experimental designs to explore whether perfusion pressure per se affects the frequency of myogenic autoregulation in kidneys. The first study used isolated hydronephrotic kidneys perfused with defined medium. These kidneys were perfused at pressures determined solely by the investigator, ranging from 60 to 140 mmHg. Use of the hydronephrotic kidney precluded any influence of TGF, and a wide range of perfusion pressures provided an excellent test for pressure dependency of myogenic operating frequency, with minor change in renal vascular conductance. In this experiment, both the frequency of the resonance peak in gain and the phase-rise frequency increased progressively with renal perfusion pressure in the range from 80 to 140 mmHg. These assessments were performed at the macroscopic level, whereas previous studies of frequency modulation of the myogenic mechanism have employed single-nephron data (9, 10, 22).

Thus we also observed the emergence and then development of vasomotion in individual afferent arterioles as perfusion pressure was increased. Vasomotion is a microcirculatory phenomenon characterized by intermittent or stable limit cycle oscillation of arteriolar diameter. Like myogenic autoregulation, it occurs in arterioles in which autoregulation is mediated, is elicited by an increase in pressure, and involves cycling of intracellular calcium concentration (16, 23). It must be recognized that although vasomotion is related to autoregulation, its absence is not synonymous with absence of autoregulation. For instance, in the current study the one afferent arteriole that did not display vasomotion nevertheless showed strong autoregulation as its diameter was reduced from 17.4 μm at 60 mmHg to 6.9 μm at 140 mmHg. The observed frequencies of vasomotion are similar but not identical to those of macroscopically determined myogenic autoregulation in the same kidneys. Nevertheless, vasomotion is pressure induced and calcium dependent, and its frequency increases systematically with perfusion pressure in renal afferent arterioles as in cerebral (11) and mesenteric vessels (18). Thus this result too reveals the presence of frequency modulation by perfusion pressure of vasoactivity in the afferent arteriole.

The second design used L-NAME in vivo to increase blood pressure and reduce renal vascular conductance. We and others (2, 4, 13, 17, 20, 21) have shown repeatedly that inhibition of nitric oxide synthase substantially alters RBF dynamics, particularly the dynamics of the myogenic mechanism, and that this effect is independent of blood pressure. We have also shown that inhibition of nitric oxide synthase does not alter the dynamics of mesenteric blood flow (2). Here we wish to differentiate pressure-dependent from nitric oxide-dependent modulation of the frequency of myogenic autoregulation by comparing the responses of RBF dynamics when pressure was allowed to rise, both with RBF dynamics when pressure was held at the control level and with mesenteric blood flow dynamics with elevated pressure.

When renal perfusion pressure was permitted to rise after L-NAME injection, either under control conditions or during infusion of atrial natriuretic factor, similar highly significant increases in the resonance and phase-rise frequencies occurred. Using contemporaneous data from similar experiments exploring mesenteric blood flow dynamics (2), we were able to confirm the finding of Léti et al. (6) that the operating frequency of the myogenic mechanism in the splanchnic circulation is not affected by the hypertension induced by L-NAME.

In the final experiments, renal perfusion pressure was controlled and forced by a suprarenal aortic clamp so that only a trivial rise in perfusion pressure occurred subsequent to L-NAME injection. In these experiments, the reduction of renal vascular conductance by L-NAME was comparable with that seen when renal perfusion pressure was allowed to in-
crease and the expected alteration of dynamics occurred (20). Yet in the absence of a change in perfusion pressure, there was no change in either the resonance frequency or the phase-rise frequency, indicating that the change in the previous experiments was induced by the rise of renal perfusion pressure and was not a consequence of the inhibition of nitric oxide synthase or of reduction of renal vascular conductance. Thus it seems extremely unlikely that the pressure dependency of the resonance and phase-rise frequencies is related to activity of nitric oxide synthases. Instead, the results of the current studies are most readily explained by an effect of pressure per se on the afferent arteriole.

There has been little previous study of potential pressure modulation of renal myogenic autoregulation. Yip et al. (22) assessed efferent arteriolar blood flow by spectral, though not transfer-function, analysis of laser Doppler signals acquired at the surface of the kidney. No change in myogenic frequency was apparent when hypertension was induced acutely, although, for reasons unclear at this remove, the myogenic signal in this study was perhaps not optimal. The analysis conflated vasomotion with myogenic autoregulation, and, as noted above, the two phenomena are related, although they are clearly not synonymous. More recently, Just and Arendshorst (3) showed that the rate of myogenic autoregulation in the kidney was increased after 1-NAME. However, the increase was not abrogated by servo control of perfusion pressure and was therefore attributed to an effect of nitric oxide at the vascular smooth muscle.

Although the results do not disclose the mechanism by which increasing pressure makes myogenic autoregulation faster, there is likely a role for the known pressure sensitivity of the afferent arteriolar vascular smooth muscle membrane potential (8) and of intracellular calcium concentration (23). However, this is unlikely to be the whole story, because similar pressure dependency of membrane potential has also been demonstrated in the mesenteric circulation (14). Nevertheless, the present results do indicate that the pressure-dependent variation of myogenic frequency resides within the myogenic mechanism and that TGF is not necessary for its expression. They also suggest some degree of kidney specificity.

One important question is not addressed by the current analysis. That is, how quickly does the modulation occur when perfusion pressure changes? We have no information concerning the rate of change of myogenic frequency, how alteration of perfusion pressure will affect autoregulatory kinetics, or how perfusion pressure will interact with TGF in modulating myogenic autoregulation. Another question that we hesitate to speculate on at present concerns the physiological implications of this feature of the renal myogenic response. Does this phenomenon simply reflect an intrinsic effect of preactivation on myogenic reactivity, or is this an adaptation reflecting a specific need for the renal vasculature to respond faster when renal perfusion pressure is elevated? Would such modulation play a significant role in regard to the efficiency of the preglomerular vasculature in buffering changes in glomerular filtration and preventing the transmission of pressure transients to the glomerulus?

It is also perhaps noteworthy that one can expect interaction between perfusion pressure and TGF in the modulation of the myogenic mechanism. Pressure inputs to TGF are filtered first by the myogenic mechanism and the vasculature and second by the low-pass filter properties of the nephron. Certainly, the contribution of TGF to autoregulation is often intermittent and dependent on fairly large pressure transients. This is often apparent on visual examination of raw pressure-flow data and has been demonstrated explicitly by use of time-varying transfer functions (24). One implication of this time-varying contribution of TGF and its origin in blood pressure would be that modulation of the myogenic mechanism by TGF and by pressure are likely to be correlated in time.

GRANTS

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