Mean transit time as an index of cerebral perfusion pressure in experimental systemic hypotension

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Mean transit time as an index of cerebral perfusion pressure in experimental systemic hypotension

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Abstract
Early diagnosis of cerebrovascular disease requires the accurate identification of brain regions with compromised cerebral perfusion pressure (CPP). Current clinical measures of CPP are invasive and lack regional information. Dynamic contrast-enhanced imaging provides a means of looking at regional cerebral hemodynamics. The purpose of this study was to determine if any of the parameters associated with dynamic contrast-enhanced imaging could be used as an index for CPP under graded systemic hypotension in a rabbit model. Cerebral blood flow (CBF), cerebral blood volume, mean transit time (MTT), and cerebrovascular reserve (CVR) were measured using Computed Tomography Perfusion in three groups: normotensive ($\text{n} = 14$), mild hypotensive ($\text{n} = 9$), and moderate hypotensive ($\text{n} = 6$). MTT demonstrated the strongest correlation with CPP ($\rho = -0.642, P < 0.05$). CBF was the only other parameter to demonstrate a statistically significant correlation ($\rho = 0.575, P < 0.05$). CVR is gaining momentum for diagnosing cerebrovascular disease; however, the technique requires patients to be given a hemodynamic challenge, which could aggravate symptoms and even trigger stroke. The results of this study suggest that the use of MTT, not requiring hemodynamic manipulation, is more sensitive to subtle changes in CPP, as would occur in the early stages of cerebrovascular disease.

Keywords: cerebral perfusion pressure, mean transit time, dynamic contrast enhanced imaging, cerebrovascular reserve, cerebrovascular disease

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1. Introduction

Cerebrovascular disease is the third leading cause of death in North America. The disease often culminates in major events, such as stroke, that result in death, generally after a long-term gradual degradation in cerebrovascular health. There is an opportunity to significantly reduce the incidence of stroke (and other major events) if cerebrovascular disease could be diagnosed in its earlier stages; however, early symptoms are subtle. One predominant hallmark of cerebrovascular disease is a regional decrease in cerebral perfusion pressure (CPP) downstream from a site of pathological origin. As such, a reliable and clinically applicable surrogate of regional CPP would be of substantial benefit to the diagnosis and treatment of cerebrovascular diseases. In this study, the potential for non-invasive hemodynamic imaging parameters to act as surrogates of CPP was investigated in the context of ischemic CVD diagnosis.

Current critical care monitoring practice employs invasive intracranial pressure (ICP) probes to directly measure CPP. This technique carries a risk of infection and bleeding, and fails to provide regional information. Thus, indirect measurements that are sensitive to regional hemodynamic compensatory mechanisms brought about by disturbed CPP must be used to distinguish areas of the brain at risk. Measurements of cerebrovascular reserve (CVR) and mean transit time (MTT) are two hemodynamic imaging parameters that have been proposed to be sensitive to disruptions in CPP (Démostis et al 2000, Eskey and Sanelli 2005, Sette et al 1989). CVR reflects the dilatory capacity of cerebral arterioles and is determined as the ratio of cerebral blood flow (CBF) or cerebral blood volume (CBV) at baseline to that after administration of a vasodilatory stimulus (i.e. hypercapnia or acetazolamide). Despite the clinical acceptance of CVR as a marker of CPP in cerebrovascular disease, a major drawback of the technique is its reliance on stressing the vasodilatory capacity of the brain, a procedure that may precipitate a stroke in patients with compromised hemodynamics, and that may also be impractical in patients with already elevated ICPs. Comparatively, the measurement of MTT does not require hemodynamic manipulation of the patient and can be mapped regionally throughout the brain clinically using a number of imaging approaches, including contrast-enhanced magnetic resonance imaging (Sorensen et al 1999), positron emission tomography (Sette et al 1989) and, as focused on in this study, computed tomography (CT) Perfusion (GE Healthcare, Waukesha, WI). Under conditions of normal CPP, CBF and CBV are tightly coupled; however, this strict coupling is disrupted under conditions of reduced CPP. By the central volume principle, MTT is the ratio of CBV to CBF (Meier and Zierler 1954), making it particularly sensitive to any disturbances in the coupling between the parameters (Gibbs et al 1984, Sette et al 1989). The purpose of this study was to compare CT Perfusion measurements of both MTT and CVR over a range of CPP in a rabbit model.

2. Methods

2.1. Animals and anesthesia

All procedures were approved by the institutional review board at the University of Western Ontario. Studies were conducted on male New Zealand White rabbits weighing 2.5–3.5 kg. Prior to all scans, anesthesia was induced with 3–5% isoflurane, followed by ketamine (3.0 mg kg$^{-1}$) and diazepam (0.3 mg kg$^{-1}$) boluses to facilitate intubation. During scanning, anesthesia was maintained with isoflurane (2.75%), and vecuronium bromide (0.15 mg kg$^{-1}$) was used during acetazolamide (ACZ) challenge to suppress spontaneous respiration caused by increased arterial CO$_2$ tensions. During each scan, physiological parameters were measured and maintained within normal ranges when possible. Another catheter was inserted into a
femoral artery for continuous monitoring of blood pressure and for collection of arterial blood samples for gas and glucose determinations. At all times during the experiment (excluding the ACZ challenge), arterial pCO$_2$ was maintained between 38 and 42 mm Hg by adjusting the respiratory rate. Blood glucose was kept between 3 and 8 mmol l$^{-1}$ by constant infusion of a 25% dextrose solution into a femoral vein. A water-heating blanket was used to maintain a rectal temperature between 37.5 and 38.5 $^\circ$C. Arterial pH, mean arterial pressure and heart rate were also monitored.

2.2. Acetazolamide time course

To ensure ACZ produced a CBF response in rabbits that was measurable and reproducible, CBF and CVR responses to ACZ were investigated in a group of normotensive (normal mean arterial pressure) rabbits ($n = 15$). Basal hemodynamic parameters (CBF, CBV and MTT) were determined by averaging results of two CT Perfusion scans, separated by 10 min, which were collected just prior to i.v. infusion of 20 mg kg$^{-1}$ ACZ (Sigma-Aldrich, St Louis, MO). Subsequent scans were performed at 5, 15, 25, 40 and 60 min post-ACZ infusion to assess the temporal course of the hemodynamic response. CVR was calculated as the percentage increase in CBF at 25 min after the administration of ACZ over basal levels (this time point was chosen because on average it was the point at which the largest change in CBF was observed—see figure 2). One week later, this procedure was repeated in ten of the 15 rabbits to assess the reproducibility of CT Perfusion measurements and the hemodynamic response to ACZ (scanning protocol was truncated to 25 min post-ACZ infusion).

2.3. Intracranial pressure with varying mean arterial pressure

The ability to utilize MAP as a direct surrogate of CPP within the physiological confines of this study was investigated in a separate group of rabbits ($n = 8$), to avoid the disruptive and invasive effects associated with direct CPP measurement via an ICP probe. ICP was measured directly via an intraventricular cannula under normotensive conditions on the first day and under hypotensive conditions on day 2. Chronic implantation of the intraventricular cannula was done with the animals under 3–5% isoflurane anesthesia. The scalp over the superior aspect of the skull was excised to expose an area between the coronal sutures bregma and lambda. A guide cannula (C313G/FS, Plastics One, Roanoke, Virginia) was stereotaxically implanted into the right lateral ventricle of the brain and secured. For continuous monitoring of ICP, an internal cannula (CS313/FS), coupled to a pressure transducer, was fitted to the guide cannula. Hypotension was induced by an i.v. infusion of prostaglandin E$_1$ (PGE$_1$, alprostadil, 500 $\mu$g ml$^{-1}$) at 3.0 $\mu$g kg$^{-1}$ min$^{-1}$. With this level of infusion, a large range of MAP in the group was established, owing to intersubject physiological variability.

2.4. Hemodynamic measurements with varying MAP

With the ACZ response characterized and the feasibility of using MAP as surrogate of CPP justified within the physiological confines of this study, a third study was performed. Rabbits were randomly assigned to one of two groups: normotensive ($n = 14$) and hypotensive ($n = 15$) to investigate the relationship between CPP and the hemodynamic parameters CBF, CBV and MTT over a range of MAPs. The hypotensive group was further separated into two subgroups: a mild hypotensive group ($n = 6$; 1.5 $\mu$g kg$^{-1}$ min$^{-1}$ PGE$_1$ infusion) and a moderate hypotensive group ($n = 9$; 3.0 $\mu$g kg$^{-1}$ min$^{-1}$ PGE$_1$ infusion) to create a larger CPP range. Two baseline CT Perfusion scans were collected from all animals. The hypotensive
Figure 1. CT Perfusion scanning protocol. All groups of animals received two basal scans to measure normal cerebral hemodynamics. After basal scanning was completed, normotensive animals continued with ACZ administration (ACZ Tx) and CVR scans while hypotensive animals received hypotensive treatment (E) and a basal hypotensive scan before ACZ Tx and subsequent CVR scans. Hypotensive treatment lasted the duration of CVR testing for these animals.

2.5. CT imaging

All imaging was conducted on a LightSpeed Plus 4-slice CT scanner (GE Healthcare, Waukesha, WI). Rabbits were placed in the prone position on a custom-made jig and a routine scout was used to localize a 2 cm slab that maximized cortical gray matter volume. The CT Perfusion scanning protocol consisted of a continuous 32 s scan using 80 kVp, 80 mA and 1 s rotation speed while the couch remained stationary. One hundred twenty-five 512 × 512 images were reconstructed with the detail algorithm (reconstruction filter) and with a 10 cm field-of-view at 0.25 s intervals for each of the four 5 mm thick slice locations. The limiting resolution of the detail algorithm is \( \sim 10 \text{ lp mm}^{-1} \) or 0.5 mm. Upon commencement of each scan, a bolus injection of 5 ml of contrast agent (iohexol [Ominpaque], 300 mgI ml\(^{-1}\); GE Healthcare, Piscataway, NJ) was given at a rate of 0.5 ml s\(^{-1}\) into the femoral vein with an automatic injector (Medrad, Indianola, PA).

CT Perfusion calculations and parametric map constructions were based on the central volume principle, relating CBF to the ratio of CBV to MTT (Meier and Zierler 1954). To calculate these parameters from data acquired by CT scanning, blood was rendered detectable by the CT scanner with the injection of contrast agent, as previously discussed, and the deposition (concentration) of the contrast within individual regions of the brain was quantified as an increased CT number (Hounsfield units—HU). Raw data sets were transferred to a GE workstation (GE Healthcare) for calculation of parametric maps using proprietary software (CT Perfusion, GE Healthcare) (Cenic et al 1999).

2.6. Data analysis

Parametric maps were analyzed using a region of interest analysis program developed in our lab using IDL (Research Systems, Boulder, CO). Large regions of interest (ROI) were hand
Figure 2. Graph of CBF response to ACZ in gray matter of control animals. Graph of the CBF (mean ± SD) response to ACZ (20 μg kg⁻¹) for a group of animals (n = 15) under normotensive conditions. CBF at all time points post-ACZ are statistically similar to each other and are significantly greater than basal levels (*p < 0.05).
Figure 3. Reproducibility graph of intra- and inter-test day variability in CBF and CBF response to ACZ. Reproducibility analysis of intra- and inter-test CTP measurements of CBF (basal scans) and inter-test CBF response to ACZ (5, 15, 25 min following ACZ administration). Tests 1 and 2 were separated by 7 days. Intra-test basal CBF measurements were not significantly different and had a CV of 9.0%. Inter-test measurements were also non-significant for basal and post-ACZ time points with a CV of 16.6% and 8.9%, respectively.

Table 1. Pressure measurements with varying MAP.

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hypotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>49 ± 11</td>
<td>32 ± 7'</td>
</tr>
<tr>
<td>ICP</td>
<td>9 ± 3</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>CPP</td>
<td>40 ± 12</td>
<td>23 ± 10'</td>
</tr>
<tr>
<td>25 min</td>
<td>45 ± 10</td>
<td>36 ± 7'</td>
</tr>
<tr>
<td></td>
<td>9 ± 4</td>
<td>9 ± 3</td>
</tr>
<tr>
<td></td>
<td>36 ± 12</td>
<td>27 ± 10'</td>
</tr>
</tbody>
</table>

MAP, ICP, CPP (mmHg); mean ± SD; * = significant differences from basal normotensive values (P < 0.05).

3.2. Intracranial pressure with varying MAP

ICP, MAP and CPP measurements made at baseline and 25 min post-ACZ for both MAP states are displayed in table 1. ICP remained steady at 9 ± 3 mm Hg (mean ± SD) both before and after ACZ administration, in both normotensive and hypotensive states. MAP and CPP, both before and after ACZ administration, were significantly lower in the hypotensive group compared to the normotensive group. Since no changes in ICP were observed for any manipulation, MAP was used as a surrogate for global CPP to reduce the invasiveness of further studies.

3.3. Hemodynamic measurements with varying MAP

Physiologic parameters measured at baseline (before ACZ administration) for normo- and hypotensive groups are summarized in table 2. There were no significant differences between the parameters of each group. Significant differences after ACZ injection between groups were only reported for end-tidal CO₂, with a reduction in the moderate hypotensive (35 ± 1 mmHg) group, when compared with the normotensive group (36 ± 1 mmHg) (data not shown). The hemodynamic measurements from CT Perfusion scans are presented in table 3 for the normo- and hypotensive groups. At baseline, CBV was not significantly different between
Table 2. Basal physiological measurements with varying MAP.

<table>
<thead>
<tr>
<th></th>
<th>Normotension</th>
<th>Mild</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>53 ± 12</td>
<td>35 ± 3'</td>
<td>28 ± 6'</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>273 ± 33</td>
<td>259 ± 34</td>
<td>222 ± 31</td>
</tr>
<tr>
<td>Temp (°C)</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>34 ± 4</td>
<td>32 ± 2</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>EtCO₂ (mmHg)</td>
<td>40 ± 1</td>
<td>40 ± 2</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>314.9 ± 31.5</td>
<td>299.2 ± 55.3</td>
<td>288.9 ± 31.2</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>41.8 ± 3.4</td>
<td>41.3 ± 3.3</td>
<td>43.2 ± 3.7</td>
</tr>
<tr>
<td>HCO₃ (mM)</td>
<td>25.7 ± 1.8</td>
<td>25.8 ± 3.6</td>
<td>26.0 ± 2.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.03</td>
<td>7.42 ± 0.05</td>
<td>7.40 ± 0.04</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; HR = heart rate; Temp = temperature; Hct = hematocrit; EtCO₂ = End tidal CO₂; pO₂ = arterial oxygen; pCO₂ = arterial carbon dioxide; HCO₃ = bicarbonate; mean ± SD; * = P < 0.05 compared with normotension.

Table 3. Hemodynamic parametric measurements with varying MAP.

<table>
<thead>
<tr>
<th></th>
<th>Normotension</th>
<th>Mild</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal 25 min</td>
<td>Basal 25 min</td>
<td>Basal 25 min</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>53 ± 12</td>
<td>49 ± 13</td>
<td>35 ± 3'</td>
</tr>
<tr>
<td>CBF (ml/100g/min)</td>
<td>126 ± 11</td>
<td>149 ± 10''</td>
<td>107 ± 7''</td>
</tr>
<tr>
<td>CBV (ml/100g)</td>
<td>2.17 ± 0.21</td>
<td>2.47 ± 0.19''</td>
<td>2.17 ± 0.16</td>
</tr>
<tr>
<td>MTT (s)</td>
<td>1.04 ± 0.08</td>
<td>1.02 ± 0.08</td>
<td>1.21 ± 0.03''</td>
</tr>
<tr>
<td>CVR (%)</td>
<td>16.3 ± 9.0</td>
<td>16.7 ± 8.6</td>
<td>22.0 ± 14.4</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure (mmHg); CBF = cerebral blood flow (ml/100g/min); CBV = cerebral blood volume (ml/100g); MTT = mean transit time (s); CVR = cerebrovascular reserve (% increase above own group basal measurement), * = P < 0.05, ** = P < 0.01 compared with normotensive basal levels.

groups. Basal CBF and MTT were statistically similar between both mild and moderate hypotensive groups but CBF was significantly reduced (~15%) while MTT was significantly elevated (~16%), in comparison to the normotensive group (P < 0.05). Administration of ACZ did not significantly alter the MAP of any group with respect to their respective basal measurements. The difference between CVR of each group was not statistically significant (range: 16.3–22.0%). Similarly, there were no significant differences in the percentage or absolute increase of CBV in response to ACZ between groups (range: 12.4–13.8%).

Figure 4 displays the correlations between all hemodynamic data and MAP. Both MTT and CBF demonstrated statistically significant Spearman’s rank correlation coefficients of ρ = −0.642 and 0.575, respectively (P < 0.05). Correlations of CBV and CVR with MAP were not significant over the range of pressures tested.
4. Discussion

A non-invasive, regional surrogate of CPP could be a significant aid for early diagnosis of cerebrovascular disease. The results of this study suggest that the hemodynamic parameter, MTT, which can be mapped non-invasively with clinically available CT Perfusion software (GE Healthcare, Waukesha, WI), shows promise as such a surrogate. Within the physiological confines of this study, MTT was found to be a more sensitive surrogate of CPP than a competing technique, CVR, which requires the additional risk of a hemodynamic challenge.

To understand the sensitivity of MTT to CPP, a discussion of the theoretical relationship between cerebral hemodynamics and CPP is warranted. Conventionally, a simplified model of CPP progression separates the disease into three distinct phases (Baron et al. 1989, Derdeyn et al. 2002, Powers 1991, Powers et al. 1987). Stage I is characterized by a decrease in CPP that does not extend outside of the range of autoregulation. Within this stage, CBF is thought to be maintained by compensatory vasodilation (Paulson et al. 1990), which would result in an increased CBV. Stage II is characterized by a larger decrease in CPP, exceeding the autoregulatory window but not resulting in reduced metabolic supply. Within stage II, CBF begins to drop but metabolic rates are maintained by a compensatory increase in OEF. In stage III, CPP decrease exceeds the limits of OEF compensation and metabolism is compromised. Recognition of stages I and II is of the utmost importance for early diagnosis of cerebrovascular disease—stage III is considered severe and is associated with easily recognizable symptoms.

Results from recent studies are beginning to complicate this simplistic view of cerebrovascular disease. For instance, subtle changes in OEF can occur in lieu of vasodilation within the range of autoregulation (a compensatory mechanism once thought only to occur during stage II) (Derdeyn et al. 2002). Furthermore, slight reductions in CBF with decreasing
CPP have also been demonstrated within autoregulation (Dirnagl and Pulsinelli 1990). Both of these effects have made a point of controversy of the assumption that CBV and CPP are correlated within stage I (Grubb et al 1973, 1975, Schumann et al 1998, Zaharchuk et al 1999), and at least one study has demonstrated further increases in CBV can occur even outside of autoregulation (Schumann et al 1998). It is clear that, alone, none of CBF, CBV, or OEF can be considered sensitive markers of CPP since the effects of CPP on each parameter are complex and differ depending on the stage of disease. Instead, more informative parameters are required. The two that were investigated in this study were CVR and MTT. CVR, which reflects the vasodilatory capacity of the cerebrovasculature, is correlated with decreased CPP, but only within autoregulation, since outside autoregulation, vessels should be maximally dilated. As suggested by the results of our study, MTT should be sensitive to CPP both in and out of autoregulation. MTT is the ratio between CBV and CBF, by the central volume principle (Meier and Zierler 1954); hence, during stage I, when CBV is the parameter predominantly affected by CPP, and during stage II, when CBF is the parameter predominantly affected by CPP, MTT will always correlate inversely with CPP, as demonstrated in this study (figure 4). It is important to note that if the validity of the simplified three-stage model does not hold—for example, if both CBF and CBV drop commensurately outside of autoregulation—then the sensitivity of MTT to CPP cannot be assumed.

The observed insensitivity of CVR to changes in CPP warrants further discussion. It should be noted that the values of CVR we obtained (21.3% on average) were lower than those presented in other experimental designs (Csete et al 2004, Démosis et al 2000), and no effect was observed between CVR and CPP. A potential cause of this observation is that the maximum of the range of CPP investigated in this study was at, or below, the autoregulatory threshold (i.e. in stage II like conditions). This is supported by the statistically significant correlation observed between CBF and CPP combined with the absence of any CPP effect on CBV. Previous studies in rabbits have demonstrated the lower limit of autoregulation to be a MAP of roughly 40 mmHg (Cranston and Rosendorff 1971, Tuor and Grewal 1994), which indicates that the normotensive group in this study was indeed near that limit of autoregulation, and the hypotensive groups were below the limit. The particularly low MAP observed within this study was likely an effect of isoflurane, which was used for anesthesia. Isoflurane has been associated with decreases in MAP (Takenaka et al 2003), resulting from its incitement of peripheral vasodilation (Abe 1993, Iida et al 1998). The cerebral vasodilatory effects of isoflurane may also have played a role in the insensitivity of CVR to changes in CPP, as demonstrated in a canine study (McPherson et al 1989). It should also be noted that despite the limited CVR response observed (figure 2), the reproducibility of the response is much better than what would be expected in patients, since CVR response is sensitive to a number of physiologic conditions that can be highly variable over a population (Dumville et al 1998). This fact accentuates the difficulties of using CVR clinically.

Global measurement of CPP is defined as the difference between the MAP and the ICP (Schumann et al 1998), assuming that the venous backpressure is negligible (Powers 1991). In the presented study, global changes in CPP were achieved by pharmacologically manipulating MAP with two different doses of PGE1. Both hypotensive groups had significantly lower MAP from the normotensive group but were not significantly different from each other, potentially due to the heterogeneous response of individual animals to the two dosages of PGE1. PGE1 was chosen to manipulate MAP because at dosages of \( \leq 3.0 \mu g \text{ kg}^{-1} \text{ min}^{-1} \), the agent has no effect on cerebrovascular tone and does not impair the CVR in rabbits (Miyabe et al 2001, Takenaka et al 2003) and in humans (Abe 1993, Abe and Yoshiya 1993). Interestingly, we found that ICP did not change over the range of MAP tested, which facilitated the use of MAP
as a direct correlate of CPP and allowed us to minimize the invasiveness of surgery in the majority of the experiments. This result has been corroborated by Schumann et al (1998).

This study has provided an animal model for global reductions in CPP causing vasodilation near the maximum physiological dilation of vessels. The inability of reduced perfusion pressure to cause further vasodilation suggested that these areas may be within stage II of hemodynamic failure. Clinically, these areas are known to experience ‘misery perfusion’ and are at the highest risk of ischemic incidents as compensatory mechanisms near exhaustion. These areas would be considered the border zones of chronic hyperperfusion and may be caused by large artery occlusions. Further study is needed to investigate the relationship between CVR and MTT with CPP under conditions that more closely mimic stage I of cerebrovascular disease. The results of this study indicated that MTT measured with CT Perfusion offers a sensitive, regional marker of decreased CPP in a rabbit model of hypoperfusion. Considering that MTT does not require a hemodynamic challenge and may be more likely to be indicative of CPP under stage I and stage II cerebrovascular disease (whereas, CVR is likely only effective under stage I), this study introduces MTT as a promising new candidate for diagnosing cerebrovascular disease.

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