The Value of MR Perfusion in Acute Ischemic Stroke

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ABSTRACT:
BACKGROUND:
Stroke is a clinical diagnosis that refers to sudden onset focal neurological deficit of presumed vascular origin. MR perfusion (MRP) provide a rapid, quantitative, and easily interpretable visual assessment of the penumbra.
OBJECTIVE:
To study the value of MR perfusion in acute ischemic stroke within 1st 24hr.
PATIENTS AND METHODS:
Diffusion weighted images (DWI) and perfusion weighted images(PWI) were obtained in 30 ischemic stroke patients within 24 hours after symptoms onset. Perfusion diffusion mismatch (PDM) was analyzed by automated software that aligned apparent diffusion coefficient (ADC) defect with mean transient time (MTT) or time to maximum (Tmax) map.
RESULTS:
Type I (PWI>DWI) in (7) patients (23%), type II (PWI=DWI) is the main pattern described in (20) patients (67%)**.** Average rCBF ratio was significantly reduced in the ischemic core (0.28±0.14) as compared to the normal brain tissue (0.51±0.14). Average rCBV ratio was significantly decreased in the ischemic core (0.35±0.15) as compared with the normal brain (0.90±0.88). MTT value was significantly higher in the infarct core (7.6 sec±0.92) than in the normal brain tissue (4.3sec±0.32)**.**
There was significant reduction in average rCBF ratio in the penumbra (0.54±0.14) in comparison with normal brain tissue (0.66±0.14). A non-significant reduction in average rCBV ratio within penumbra (0.84± 0.29) in relation to normal brain tissue (0.98±0.25). MTT value in the penumbra was significantly higher (4.6sec±0.45) than in the normal brain tissue (4.07sec±0.18).
CONCLUSION:
Type II PDM pattern was the dominant pattern in patient with acute ischemic stroke in the 1st 24 hours. Salvageable penumbra in type I PDM described in (78%) of patients. rCBF in penumbra was higher than ischemic core and lower than normal brain and was the most useful parameter in defining ischemic penumbra and for follow up of patients with acute ischemic stroke.
KEYWORDS: Perfusion MRI, acute ischemic stroke

INTRODUCTION:

Stroke is a medical emergency that refers to sudden onset focal neurological deficit that attributed to acute focal brain injury by vascular cause [1]. Stroke is one of the major causes of mortality and significant morbidity worldwide. In the United States, a stroke occurs every 40 seconds, and a death from stroke occurs every 4 minutes [2]. Neuroimaging supports clinical diagnosis; aids follow up, and guides management of patients with acute ischemic stroke (AIS), especially those with AIS due to large vessel occlusion [3]. Although the initial goals of imaging were to exclude intracranial hemorrhage (ICH), imaging goals evolved to include parenchymal and vascular imaging to identify patients with a small infarct core and large vessel occlusion for the major endovascular therapy (ET) stroke trials [4].

In spite of that DWI is valuable in assessing for infarct core, perfusion imaging is the most typically utilized method to image the penumbra, magnetic resonance perfusion (MRP) techniques provide a quick, quantitative, and easily interpretable visual assessment of the penumbra [5]. The most commonly adapted technique is dynamic susceptibility contrast (DSC) imaging, which relies on susceptibility changes that cause signal loss on T2*weighted image result from administration of a gadolinium-based contrast agent, that passes through cerebral circulation including capillaries ,atime-signal intensity curve is created. This then undergoes mathematical post-processing to yield perfusion maps of the brain, which provide information of clinical utility[6]. PWI also offers a way to assess the core infarct using CBV. Although CBV has been shown to offer good correlation with DWI and final infarct volume [7].

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Accurate assessment of the penumbra is challenging due to the requirement to accurately determine the interface between the core and penumbra, as well as penumbra and areas of benign oligemia. Currently, the most widely utilized threshold to determine penumbral tissue is TMax in the range of 4 to 6 seconds [8, 9]. If there is a significant difference between the imaging core and penumbra, that is, DWI/PWI mismatch, restoration of perfusion to this penumbral tissue results in clinical recovery. In general, a mismatch volume of more than 20% is generally accepted as an indicator of penumbral presence [10].

AIMS OF THE STUDY:
To study the value of MR perfusion in acute ischemic stroke at specific time window (1st 24hr) and to determine parameters that distinguish regions of brain infarction from those that will survive despite hypoperfusion.

PATIENTS AND METHODS:
Study design: was cross sectional analytic study conducted on 30 patients with acute ischemic stroke within the 1st 24 hr. after the onset of symptoms. The study was conducted on 30 patients (19 Males, and 11 Females, 35-65 years old) with acute ischemic stroke between December 2019 and December 2020. The study was done in Al-Imamain Al-Kadhemain Medical City/ Baghdad/ Iraq.

Inclusion criteria: patients with clinical diagnosis of acute stroke within the 1st 24 hr. and restricted pattern on DWI. **Exclusion criteria:** lacunar stroke, hemorrhagic stroke and hemorrhagic transformation of ischemic stroke, stroke more than 24 hrs, patients with contraindicated to Gd contrast, patients with general contra-indication to MRI and when the results of MRI are non-conclusive.

Ethical consideration: the study was approved by the scientific committee of the Iraqi board of Diagnostic Radiology. An oral informed consent was obtained from all patients included in the study, MR exam was explained to patients prior to the exam.

Imaging protocol: all patients were examined by 3T MR Scanner (Achieva, Philips medical system, Netherland). Full clinical history was taken from the patients. Then MR examination was done in the supine position using standard head coil with the following imaging protocols:

1. T1 weighted images: was acquired with axial fast field echo FFE, repetition time (TR) =260ms, echo time (TE) =30ms, flip angle=70-110°, 24 slices, slice thickness =4mm with no inter slice gap, pixel size 0.45mm×0.45mm, 214x 143mm field of view, 400x 298 acquisition matrix reconstructed to 512x512 matrix, Scan time for T1 imaging was approximately 30 .

2. T2 weighted images:was axial spin echo (SE), repetition time (TR) =2245-3000ms, echo time (TE) =80ms, flip angle =90°, 24 slices, slice thickness =4mm, with 1mm gap, pixel size 0.45mm×0.45mm, 184x119mm field of view, 400x255 acquisition matrix reconstructed to 512x512 matrix, flip angle =90°, Scan time for T2 imaging was approximately 1.84min.

3. T2 FLAIR:was coronal spin echo (SE), repetition time (TR)=11000 -2800ms, echo time (TE) =120 ms, slice thickness =4mm, flip angle =20°, 24 slices,slice thickness =4mm, with 1mm gap, pixel size 0.45mm×0.45mm, 214x143mm field of view, 240x139 acquisition matrix reconstructed to 512x512 matrix, Scan time for T2 FLAIR imaging was approximately 1.16 min.

4. DWI:was acquired with an axial gradient -Echo sequence with multiple different diffusion sensitivity of b-values = from 0-1000 s/mm2, repetition time (TR) =7000–10 000ms, echo time (TE) minimized to 123 ms; twenty-six 5mm slices, pixel size 0.9375mm×0.9375mm, 22×22cmfield of view, 128×128 acquisition matrix reconstructed to 256×256 matrix), flip angle, 90°, scan time was approximately 48s. ADC map was generated automatically by post-processing software.

5. PWI: done by DSC MR perfusion scans method using Gradient-echo-planar imaging sequence (GRE-EPI), which comprised single shot EPI to reduce scan time and give high sensitivity for T2* effect which will maximize T2* weighting (shortest TR is used for higher temporal resolution), however sufficiently long to minimize T1 influence (TR 1532-1648 ms), TE sufficiently

long for good T2*-weighting (TE 35-40 ms); large EPI factor was used (about 45) to obtain large water fat shift (WFS), SPIR for fat suppression and to reduce WFS is one of components of GRE-EPI, field of view (240×240 mm); matrix (128×128); slice thickness, 5mm; gap1mm, Flip angle 75,voxel size 2.5x2.5x5. IV contrast (0.1-0.2 mmol/kg GadopentetateDimeglumine (Magnevist®) 0.5 mmol/mL (20ml) was injected into an antecubital veinusing power injector via 18- or 20-gauge catheter at high rate (3-7ml/sec) followed by saline flush of at least 25ml (20-30ml). The pre-contrast EPI scan was followed by a DSC perfusion scan

(single shot, GRE-EPI). The total number of images was 40 (10 pre contrast and 30 post contrast). Scan time for perfusion imaging was (2-2.5 min).

Image interpretation & Placement of ROIs:MR images were interpreted by a sophisticated software dedicated for measuring and quantification MR perfusion parameters. Dynamic susceptibility curves produced due to the passage of paramagnetic contrast agent were converted to dynamic tracer concentration data. The dynamic tissue concentration curves at each voxel were then deconvolved with an arterial input function AIF using the model-independent (model free) singular value decomposition (SVD) method to create parametric perfusion maps (MTT, rCBF, rCBV).Three ROIs were placed manually using an ellipse which positioned at the rCBF map: 1st ROI: covered the ischemic core as detected from the DWI,2nd ROI: covered the penumbra surrounding the ischemic core identified on perfusion diffusion alignment map, and 3rd ROI: covered the adjacent normal brain tissue at same territory. All ROIs then were mirrored to the contralateral, unaffected hemisphere to obtain rCBF and rCBV ratios for each patient in all three ROIs. MTT value was calculated separately in seconds, rCBF and rCBV were obtained automatically by dividing the mean signal intensity value of each abnormal region in the affected hemisphere by the mean signal intensity value of the corresponding contralateral normal hemisphere, and the interpretation was done by 2 experienced radiologists.

Automated measurements of diffusion-perfusion mismatch: automated system was used for diffusion perfusion mismatch interpretation. This system computes DWI/PWI mismatch automatically using infarct core segmentation of ADC maps and perfusion deficits segmented from MTT maps. This method is to visually rate the PWI-derived parametric maps and DWI as generated by MRI console software.

Statistical analysis: was performed using Microsoft Office Excel 2016. Descriptive data presented in the form of mean and standard deviation. Paired t test was used to estimate the significance of difference between the mean rCBF, rCBV and MTT in normal versus infarct core, and penumbra respectively. Pearson's correlation was used to assess the correlation between the time since onset of symptoms and rCBF, rCBV, and MTT in the infarct core. P-value of <0.05 was considered statistically significant.

RESULTS:

Demographic data: thirty acute ischemic stroke patients (mean age 51 ± 6.9-year-old; range 35 to 65 years; 19 (63%) males ,11(37%) females, with male: female ratio = 1.7:1 were enrolled. Regarding vascular territories: 4 patients (13%) had infarction in ACA territory,15 patients (50%) had infarction in MCA territory and 11 patients (37%) had infarction in PCA territory.

Patterns of perfusion diffusion mismatch: type I (Target mismatch: PWI>DWI) in (7) patients (23%), type II (Matched: PWI=DWI) is the main pattern described in (20) patients (67%), type III (inverse mismatch: PWI<DWI) pattern was in (2) patients (7%), and type IV (PWI -ve, DWI+ve) in only 1 patient (3%). no type V (PWI +ve, DWI -ve), VI (PWI -ve, DWI -ve) nor VII (malignant mismatch: PWI or DWI > 100ml) were described in this study.

MR perfusion Parameters of the infarct core: average rCBF ratio was significantly reduced in the ischemic core (0.28 ±0.14, range, 0.16-0.61) as compared to the normal brain tissue (0.51±0.14, range,0.36 to 0.84) with a P value of <0.01.Average rCBV ratio was significantly decreased in the ischemic core (0.35±0.15, range, 0.16-0.88) as compared with the normal brain (0.90±0.88, range 0.56 to 1.2) with a P value of 0.0018. Mean MTT value was significantly higher in the infarct core (7.6 sec±0.92, range, 6.2-9.0 sec) than in the normal brain tissue (4.3sec±0.32, (range, 3.8to 4.8sec) with a P value <0.01, these findings were shown in table 1.

Table 1: Mean rCBV, rCBF, and MTT between normal and infarction core.

		Mean	Standard deviation	P-value
rCBF (ratio)	Normal	0.51	0.142	<0.01
	Infarct core	0.28	0.134	
rCBV (ratio)	Normal	0.90	0.885	0.0018
	Infarct core	0.35	0.154	
MTT (seconds)	Normal	4.37	0.326	<0.01
	Infarct core	7.66	0.923	

MR perfusion parameters in the penumbra: there was significant reduction in Average rCBF ratio in the penumbra (0.54±0.14, range 0.38 to 0.71) in comparison with normal brain tissue (0.66±0.14, range,0.36 to 0.84) (P value 0.0011). A non-significant reduction in Average rCBV ratio within penumbra (0.84±0.29, range 0.43-1.4)

in relation to normal brain tissue (0.98±0.25, range 0.5-1.2) (P value of 0.1). Mean MTT value in the penumbra was significantly higher (4.6sec±0.45, range 4-5.2sec) than in the normal brain tissue (4.07sec±0.18, range 3.8-4.4sec) (P value 0.005), these findings were shown in table 2.

Table 2: Mean rCBV, rCBF, and MTT between normal and penumbra in type I PDM.

		Mean	Standard deviation	P-value
rCBF (ratio)	Normal	0.66	0.143	0.0011
	Penumbra	0.54	0.140	
rCBV (ratio)	Normal	0.98	0.259	0.11
	Penumbra	0.84	0.296	
MTT (seconds)	Normal	4.07	0.189	0.005
	Penumbra	4.60	0.458	

The mean interval between stroke onset and first MRI assessment was 17.2hr (range 4-24hr). Patients divided into 2 groups, 1st group: patients presented within less than 12hrs and 2nd group: those presented after 12hrs, table 3 shows the relation between PDM pattern and time since onset of symptoms: 9 patients (30%) presented within less than 12 hrs: Type I PDM was the most

dominant pattern seen in 7 (78%) patients, 1 (11%) patient shows type II PDM pattern, and 1 (11%) showed type IV PDM, no type III was described. Twenty one patients (70%) presented >12 hrs.: type II PDM was the most dominant pattern in this group represent 19 (90%) patients, 2 (10%) patients show type III PDM pattern, no type I or IV were described.

Table 4: Patterns of PDM in relation to time since onset of stroke.

	PDM type	12 hours since onset		>12 hours since onset	
		No.	%	No.	%
PDM type	I	7	78%	0	0%
	II	1	11%	19	90%
	III	0	0%	2	10%
	IV	1	11%	0	0%
TOTAL		9	100%	21	100%

In the infarct core there was significant negative correlation between rCBF ratio and time since onset (figure 1A). There was significant negative correlation between rCBV ratio and time since

onset (figure 1B). There was non-significant positive correlation between MTT and time since onset in the infarct core (figure 1C).
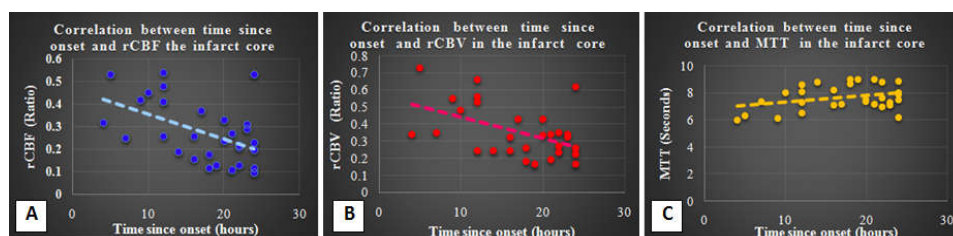

Figure 1: Scatter chart showing: A: significant negative correlation between rCBF and time since onset R=-0.5, P=0.005. B: showing significant negative correlation between rCBV and time since onset R=-0.49, P=0.006. C: showing non-significant positive correlation between MTT and time since onset R= 0.32, P=0.08
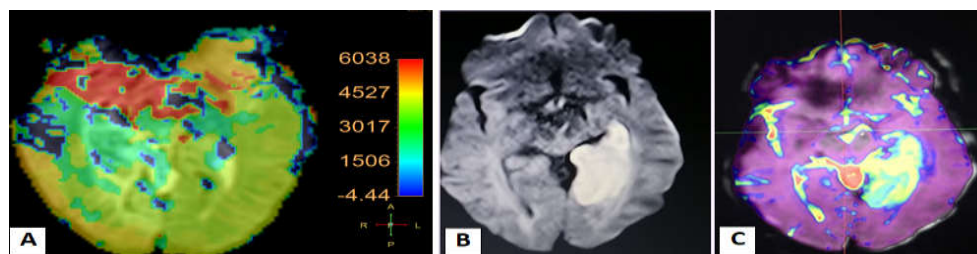
Figure 2A: years old male presented with confusion 4hours before MR exam. showing MTT map of ischemic core with surrounding penumbra MTT for core=6.0s, penumbra=4.7s and normal brain tissue =4.5s. B and C: 56 years old male presented with slurred speech 18 hours before MR exam. (A) shows DWI with acute left PCA infarction figure (B) shows PWI for the same patient describe type II PDM (PWI=DWI).
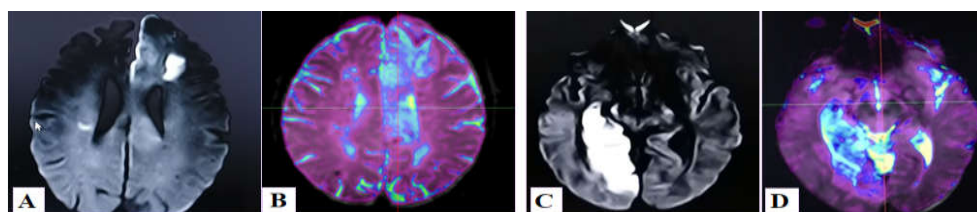

Figure 3: A and B: 49 years old male presented with right sided hemiplegia within 6 hours before MR exam. (A): shows DWI with acute left ACA infarction.(B) shows PWI for the same patient describe type I PDM (PWI>DWI). C and D: 52 years old male presented with left sided hemiparesis within 23hours before MR exam. (A)shows DWI with acute right PCA infarction.(B) shows PWI for the same patient describe type III PDM (PWI<DWI).
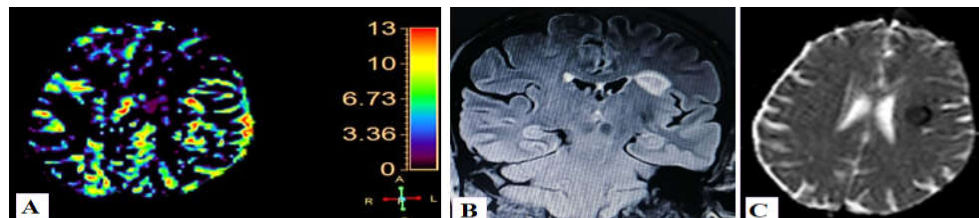

Figure 4: 50-year-old female presented with sudden onset headache within 6hours before MR exam. (A) FLAIR image. (B) ADC map with acute MCA infarction. (C) shows PWI (MTT=3.4s) for the same patient describe type IVPDM (PWI-ve, DWI +ve).

DISCUSSION:

MR perfusion had been increasingly applied for the evaluation of hyperacute and acute stroke. In acute ischemic stroke, perfusion imaging increases diagnostic accuracy, aid treatment target identification, and provide prognostic information about functional outcome. Moreover, perfusion imaging can identify patients who benefit from reperfusion beyond the conventional time window [11].

In this study the mean age of affected patients was 51 years old with a male: female ratio of 1.7:1.

This results were similar to those reported by Gür-Özmen et al [12] and Hong et al [13] stated that the acute ischemic stroke predominantly affects middle aged adults , and males are slightly more commonly involved than females. MCA vascular territory was the most frequent territory to be involved in acute ischemic infarction in this study and represent (50%) of the patients. Similar findings were seen in a previous study done by Zhu et al [14].

In this study type II PDM pattern was the predominant type, it was seen in 23 patients out of a total of 30 (67%) and defined as match pattern, this result was similar to findings in a previous studies done by Gür-Özmen et al [12] and Bang et al [15] that found this PDM was the main pattern in diabetic patients. Another study done by Chen et al [16] performed within 1st 6 hours on 150 patients found that type I PDM was the most common pattern representing (49-70%), this difference can be explained by the fact that (70%) of patients in this study presented after 12hrs of stroke onset and (30%) of patients presented within the first 12 hours, discrepancies between the extent of abnormality on PWI and DWI are supposed to depend predominantly on time from stroke onset to MRI scanning. In the current study, type III PDM represents only (7%) and type IV represents (3%) of patients. A study done by Chen et al [16] found type III in 34% of their patients and type IV in 24%, this difference can be explained by the fact that these types of mismatch was frequent in small subcortical ischemic stroke and single small artery occlusion and infarct core may develop beyond the initial hypoperfusion area and these groups of patients were excluded in the current study. Another explanation for type III PDM, that at the late time point (>6 hours post-infarct), there is probably already irreversible tissue damage to the stroke region. This could be one reason for a larger lesion in DWI than in PWI.

The patients were divided according to time of onset of stroke symptoms into those presented within less than 12hours and those presented after 12 hours of onset. in patients presented within less than 12 hrs., type I PDM (78%) was the dominant pattern, the current finding that a mismatch remains present in most patients imaged within 1st 12 hours after stroke onset were in agreement with Copen et al study [17] in which Persistence of mismatch after 9 hours is common and occurs most often in patients with proximal arterial occlusion. Another study done by Henery et al study [18] show similar results in which the patients examined within 1st 48 hours, the type I PDM pattern was seen earlier after stroke onset and fragmented with the time.

In this study, the rCBF, rCBV, and MTT were analyzed for both hypoperfused as well as unaffected contralateral tissue, the mean ratio for rCBF was 0.28 for infarct core and 0.54 for penumbra, Liu et al [19] show approximately similar results with rCBF ratios of 0.27 for infarct core and 0.69 for region of penumbra. Another study done by Grandin et al [20], reported higher rCBF ratios of 0.44 for core and 0.56 for penumbra, this can be explained by the difference in sample size and time of examination from the onset of symptoms.

The mean rCBV ratios of 0.35 for infarct core and 0.84 for penumbra. Mean rCBV ratios did rise in a step-wise manner (0.56, 0.84, and 0.98 for core, penumbra, and normal brain tissue, respectively). No statically significant correlation was observed between the mean rCBV ratios for penumbra and normal brain. Liu et al [19], used similar design of PWI in comparison with SPECT, found that the mean rCBV ratios of the core, the area of infarct growth, and the eventually viable tissue of 0.25, 0.69, and 1.13, respectively, which are in good agreement with the current study. Zaharchuk et al [21] show that the occasional finding of elevated rCBV in the ischemic penumbra demonstrating that in the early stages of ischemia, decreased cerebral perfusion pressure produces vasodilatation and an increase in the CBV. With further decreases in cerebral perfusion pressure, the compensatory vasodilatation reaches a maximum and CBF begins to fall. As the CBF falls, the CBV initially continues to rise but then falls as capillary beds collapse occurs.

MTT ratios were elevated in both ischemic core (7.6sec) and penumbra (4.6sec), these findings were comparable to that of Deutschmann et al [22] that found MTT >6sec indicate infarct core and Tong et al [23] defined the penumbra by MTT of 4-6sec.

Average rCBF and rCBV ratios associated with cerebral ischemic core were highly influenced by the time of measurement in the course of acute ischemia because the development of brain damage depends on both severity and duration of the perfusion disturbance. There is statistically significant negative correlation between an average rCBF and r CBV ratios with the time interval between the onset of symptoms and time of MRI exam findings, similar findings were seen by previous studies done by Hong et al. [13] and singer et al [24]. There was no significant correlation between MTT and time since onset that MTT remained stable over time compared with the unaffected side, with a steeper slope as compared with rCBF and rCBV correlation with the time. These results were in agreement with data obtained from Hong et al. [13]. on the other hand

Rohl et al. study [25] showed significant correlation with more prolonged MTT being associated with more severe ischemia in the course of infarct. This difference can be attributed to that the MTT maps are less helpful because they display circulatory derangements that do not necessarily reflect ischemic change including large-vessel occlusion with collateralization, autoregulation, and reperfusion hyperemia after revascularization .

CONCLUSION:

Type II PDM pattern was the dominant pattern in patient with acute ischemic stroke in the 1st 24 hours. Salvageable penumbra in type I PDM (PWI>DWI) described in (78%) of patients examined within 1st 12hours. rCBF in penumbra was higher than ischemic core and lower than normal brain and was the most useful parameter in defining ischemic penumbra and for follow up of patients with acute ischemic stroke. rCBV in penumbra was variable. MTT was elevated in both penumbra and ischemic core. Both rCBF and rCBV show significant decline with time but MTT show non-significant increase with the time since stroke onset.

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