Incidence of Unreliable Automated Computed Tomography Perfusion Maps

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Introduction: Despite the increasing national adoption of automated computed tomography perfusion (CTP) to select thrombectomy patients 6 hours after last known well, reliability issues have been anecdotally reported. Unreliable diagnostic tests add time and confusion to a process that requires efficiency. Our study aims to critically assess an automated CTP program in a contemporary cohort of patients presenting with large vessel occlusion (LVO) in the extended time window by evaluating the rate of unreliable automated CTP maps and whether this influences clinical outcomes. *Methods:* A retrospective review of consecutive thrombectomy candidates undergoing CTP imaging in the extended time window was performed. All automated CTP maps using RAPID software (iSchemaView, Menlo Park, CA) were assessed for reliability. Clinical outcomes were compared between patients with and without reliable RAPID reports. *Results:* Ninety-nine consecutive thrombectomy candidates underwent automated CTP imaging from February 2017 to December 2018. Of these, 78 (79%) had LVO determined by CT angiographyand were included in the study population. Automated CTP maps were unreliable in 13% of cases as a result of motion artifact (n = 3) and contrast bolus flow issues (n = 7). Heart failure was more frequent in patients with unreliable studies. Clinical outcomes did not significantly differ between patients with and without unreliable studies. *Conclusions:* Thirteen percent of CTP maps generated by automated software were unreliable, with an increased frequency among patients with heart failure. Given the rate of unreliable automated CTP maps, further studies are warranted to not only establish the true necessity of currently available CTP software, but also more reliable methods to select patients for thrombectomy presenting in the extended time window.

Key Words: CT perfusion—automated neuroimaging—acute ischemic stroke—extended time window—mechanical thrombectomy

Introduction

Randomized clinical studies have demonstrated that select patients with anterior large vessel occlusions (LVO) may benefit from thrombectomy after 6 hours from last known well or with unknown time of symptom onset.[1-2] The automated computed tomography perfusion (CTP) software used in these trials (RAPID, iSchemaView, Menlo Park, CA) estimated an infarct core and salvageable penumbral cerebral parenchymal tissue. While these studies were used to prove the effectiveness of thrombectomy in the extended time window, concerns exist with regard to its generalizability. Published study results may be susceptible to underreporting the occurrence of patients who did not fit inclusion criteria, including those with unreliable studies. Additionally, automated software must be purchased, is not widely available, and can at times be difficult to interpret. Recent guidelines have incorporated automated CTP imaging to select stroke patients for endovascular thrombectomy when presenting

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after 6 hours from last known well or with unknown time of symptom onset.[3] As more medical centers consider investing in this software, we sought postmarket feasibility data. Our aim was to critically assess an automated CTP program in a large, contemporary cohort of patients presenting with LVO in the extended treatment window by evaluating the rate of unreliable studies and their influence on clinical outcomes.

Methods

Patient Population

We retrospectively reviewed an urban, tertiary care, academic comprehensive stroke center database identifying consecutive patients who underwent automated CTP imaging in the evaluation and management of acute anterior large vessel occlusive strokes from February 2017 through December 2018.

Patient demographics, past medical history, presenting National Institutes of Health Stroke Scale (NIHSS) score, and Alberta Stroke Program Early CT Score (ASPECTS) were reviewed and recorded. LVO site was identified by CT angiography (CTA). In our cohort, LVO was defined as occlusion of the internal carotid artery, or middle cerebral artery M1 and M2 segments. CTP imaging was used to select stroke patients for thrombectomy who presented in the extended time window: 6 hours after symptom onset or with an unknown time of symptom onset.[1-2]

Among patients who underwent thrombectomy, outcomes among patients with and without reliable automated CTP maps were compared. The following time stamps were recorded: last known well (or unknown time of symptom onset), stroke activation, arrival to the hub hospital (if transferred), groin puncture, and time to recanalization. Technical success of thrombectomy was determined by time from groin puncture to recanalization, stent retriever passes, and self-adjudicated modified thrombolysis in cerebral infarction score.[4] Outcome was determined by discharge destination; dichotomized as favorable or unfavorable. Discharge home or to an acute rehabilitation facility (as opposed to a skilled nursing facility, hospice, or death) was considered to be a favorable outcome.[5-9]

Imaging Protocol and Analysis

Head and neck CTA imaging was performed following bolus injection of 80 mL of Isovue 370. Axial 1 mm sections were obtained from the aortic arch to the vertex. Multiplanar maximum intensity projection reconstructions were obtained. Pre- and post-infusion axial 5 mm sections were obtained through the brain. LVO site was identified by CTA.

Brain CTP imaging was performed after bolus injection of 40 mL of Isovue 370 intravenously with a power injector at a rate of 4 mL/s over a course of 60 seconds. CTP images were acquired from the Siemens scanner and sent to a networked computer running fully-automated RAPID software for postprocessing of cerebral blood flow (CBF), cerebral blood volume, mean transit time, time to maximum residue function (Tmax), and time to drain maps. (RAPID version 4.5.0. iSchemaView, Menlo Park, CA) A perfusion mismatch ratio was defined as hypoperfused lesion volume (Tmax > 6 seconds) divided by ischemic core (CBF < 30%). A perfusion mismatch volume was defined by hypoperfused lesion volume minus ischemic core.[10]

At the study medical center, automated software used to generate CTP maps had been employed for 4 years prior to the initiation of the study. Maps were assessed by the acute stroke team immediately after acquisition with automated interpretation, and at a later time by the neuroradiologist. We defined a reliable RAPID-generated CTP study as the successful automated measurement of Tmax, CBF, and cerebral blood volume volumes using appropriately selected arterial input function and venous output function to provide visual evidence of a core infarct and penumbral tissue in patients with acute ischemic stroke, which could be used by the stroke team to determine patient selection for thrombectomy. Unreliable automated CTP maps were due to motion artifact or contrast bolus flow issues. Reasons for contrast bolus flow issues included cardiac insufficiency, hemodynamically significant carotid stenosis, hemodynamic instability, and adaptive cerebral autoregulatory hemodynamics in the setting of cerebral ischemia. iSchemaView offers immediate expert RAPID tech support vita telephone and e-mail to assist in troubleshooting unreliable studies, however this service was not used in the study.

Statistical Analysis

Continuous variables were reported as a median with an interquartile range (IQR). Categorical variables were reported as proportions. Differences in continuous variables were assessed by the use of the Mann-Whitney U test assuming unequal sample variances. Differences between proportions were assessed by the use of Fisher's exact test. All tests of significance were 2 sided. Differences were considered statistically significant at P less than .05. The Institutional Review Board at our university approved the protocol (18100903-IRB01).

Results

Between February 2017 and December 2018, 99 consecutive patients underwent automated CTP imaging with a suspected acute cerebral LVO. Of these patients, 78 (79%) had LVO determined by CTA and were included in the study cohort. Automated CTP maps were unreliable in 13% of cases (n = 10). Unreliable automated CTP maps were due to motion artifact (n = 3) or contrast bolus flow issues (n = 7). Reasons for contrast bolus flow issues included cardiac insufficiency (n = 3), hemodynamically

significant carotid stenosis (n = 1), hemodynamic instability (n = 1), and adaptive cerebral autoregulatory hemodynamics in the setting of cerebral ischemia (n = 2).

Figure 1 exemplifies the most frequent scenarios in patients with unreliable automated CTP maps: (1a) those associated with delayed perfusion states (cardiac insufficiency, hemodynamically significant arterial stenosis, and global hemodynamic instability) and (1b) those directly related to adaptive cerebral autoregulatory hemodynamics in the setting of cerebral ischemia (luxury perfusion and misery perfusion).

The median age in the study group was 68 years (IQR 57-79 years) and median presenting NIHSS was 19 (IQR 13-23). Forty-four percent of the patients in the sample were female. Median ASPECTS was 8 (IQR 6-9) across all patients. 46% of LVO occurred in the middle cerebral artery M1 segment (n = 34). Fifty-one percent of the strokes were due to a cardioembolism (n = 40).

Table 1 compares the demographics, past medical history, NIHSS, ASPECTS, and stroke etiology of patients included in the study. There were no statistically significant differences in patients with unreliable automated CTP maps (unreliable group) compared to patients with reliable automated CTP maps (reliable group). There was a trend towards statistical significance between groups in patients with a history of heart failure with reduced ejection fraction (30% versus 9%; $P = .09$).[11]

Forty-nine patients in the study underwent thrombectomy for LVO (63%). Median NIHSS was 18 (IQR 12-21) and median ASPECTS was 9 (IQR 7-10). Automated median core volume was 0 mL (IQR 0-21 mL) and median penumbra volume was 151 mL (IQR 81-203 mL). Thirteen of 49 patients received intravenous tissue plasminogen activator (IV-tPA) prior to thrombectomy, all of which had reliable automated CTP maps. Median time from groin puncture to recanalization was 36 minutes (IQR 22-53 minutes) and median number of passes was 1 (IQR 1-2).

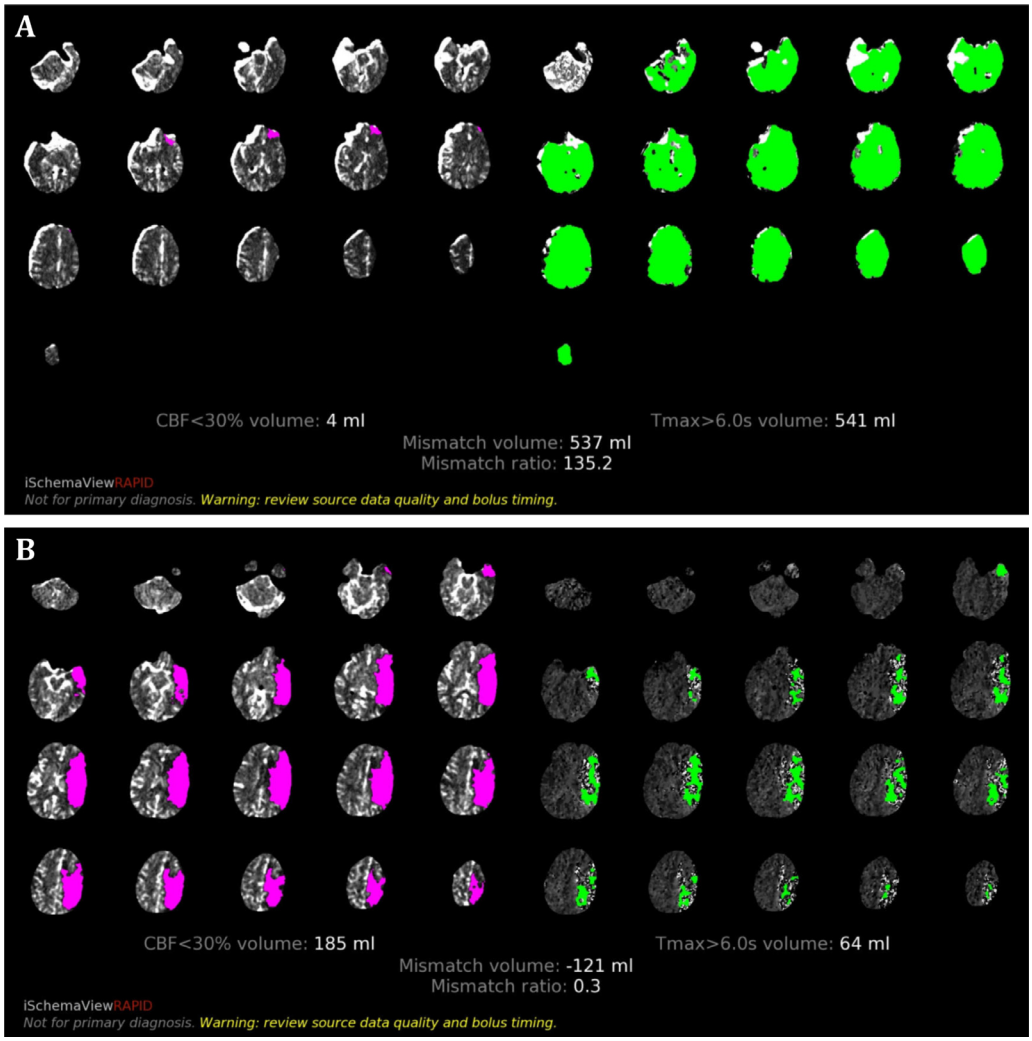

Figure 1. *Examples of unreliable RAPID-generated CTP maps. (A) Overestimated penumbra volume due to delayed perfusion in a patient with heart failure with reduced ejection fraction. (B) Estimated infarct core volume appears larger than ischemic penumbral volume, likely related to adaptive cerebral autoregulatory hemodynamic mechanisms. Abbreviation: CTP, computed tomography perfusion.*

Table 1. *Comparison of patients with large vessel occlusion who underwent CTP imaging with reliable and unreliable automated maps*

	Unreliable CTP		Reliable CTP		*P* value
	n = 10		n = 68		
Age (y; IQR)	57	47-70	68	55-79	*P*= .12
Female (%)	4	40%	30	44%	*P*= 1
PMHx (%)					
Hypertension	7	70%	44	65%	*P*= 1
Hyperlipidemia	5	50%	50	74%	*P*= .15
Diabetes mellitus	3	30%	20	29%	*P*= 1
HFrEF	3	30%	6	9%	*P*= .09
Atrial fibrillation	3	30%	20	29%	*P*= 1
Tobacco use	3	30%	20	29%	*P*= 1
NIHSS (IQR)	18	16-21	19	13-23	*P*= .85
ASPECTS (IQR)	8	7-9	8	6-9	*P*= .97
Occlusion site (%)					
ICA	3	30%	23	34%	*P*= .68
MCA M1	6	60%	30	44%	
MCA M2	1	10%	15	22%	
Stroke etiology (%)					
Large artery atherosclerosis	2	20%	15	22%	*P*= 1
Cardioembolism	5	50%	35	51%	
Other (hypercoagulable state)	1	10%	5	7%	
Cryptogenic	2	20%	13	19%	

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CTP, computed tomography perfusion; HFrEF, heart failure with reduced ejection fraction (left ventricular ejection fraction <40%); ICA, internal carotid artery; IQR, interquartile range; M1, M1 segment; M2, M2 segment beyond the inferior and superior division; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PMHx, past medical history.

Forty-one of 49 patients had a final self-adjudicated modified thrombolysis in cerebral infarction greater than or equal to 2b (84%). Eighty-six percent of patients who underwent thrombectomy were determined to have a favorable clinical outcome by discharge disposition.

Forty one of 49 patients who underwent thrombectomy had reliable automated CTP studies. Eight patients with unreliable automated CTP maps had NIHSS greater than or equal to 7 and ASPECTS greater than or equal to 7 and all 8 of these patients underwent thrombectomy. Median NIHSS in these 8 patients was 18 (IQR 16-21) and median ASPECTS was 8 (IQR 7-9). The other 2 patients with unreliable automated CTP maps did not undergo thrombectomy due to low ASPECTS (2 and 5). Compared to patients with reliable automated CTP maps who underwent thrombectomy, age, NIHSS, ASPECTS, proportion who received bridging IV-tPA, and technical success of the intervention did not differ. Favorable clinical outcomes were similar between the 2 groups (75% versus 88%; $P = .58$) (Table 2).

Discussion

In the present study, 13% of patients with LVO who underwent CTP for thrombectomy patient selection in the extended time window had unreliable automated CTP maps. Unreliable automated CTP maps were largely due to contrast bolus flow issues, whereas a smaller percentage were due to motion artifact.

Even before the efficacy of thrombectomy was demonstrated in the early time window, patient selection using preintervention perfusion imaging was associated with improved outcomes after thrombectomy.[12-14] However, there remains controversy in selecting thresholds for determining infarct core and ischemic penumbra. A universally accepted, automated postprocessing software may allow for generalization. Automated postprocessing of CTP imaging minimizes the time to interpretation by eliminating the time needed for manual reconstruction and immediate neuroradiology expertise. This may be especially beneficial in remote health care settings where rapid decision making with automated diagnostic aids can contribute to more rapid transfer to comprehensive stroke centers. Contemporary trials have employed perfusion imaging to select candidates using a central core laboratory to verify CTP imaging and correct for artifact, a benefit that is not widely available.[1-2] It is essential for the vascular neurologist, neuroradiologist, and neurointerventionalist to be aware of the incidence of unreliable automated CTP maps in the evaluation and management of acute ischemic stroke particularly when considering widespread adoption and incorporation into guidelines.

Automated CTP imaging processing software, eg, RAPID (iSchemaView, Menlo Park, CA), has been

Table 2. *Comparison of patients who underwent thrombectomy in the extended time window*

	Unreliable CTP		Reliable CTP		*P* value
	n = 8		n = 41		
Age (y; IQR)	57	47-70	68	57-76	*P* = .23
NIHSS (IQR)	18	16-21	18	11-21	*P* = .91
ASPECTS (IQR)	8	7-9	9	7-10	*P* = .23
CTP core (mL; IQR)	-	-	0	0-21	-
CTP penumbra (mL; IQR)	-	-	151	81-203	-
IV-tPA prior to thrombectomy (%)	0	0%	13	32%	*P* = .09
Time from groin puncture to recanalization (min, IQR)*	36	24-48	35	22-54	*P* = .95
Passes (IQR)	2	2-3	1	1-2	*P* = .16
Final mTICI ≥ 2b (%)	5	63%	36	88%	*P* = .11
Discharge disposition (%)					
Favorable outcome	6	75%	36	88%	*P* = .58
Home	2	25%	6	15%	
Acute rehabilitation facility	4	50%	30	73%	
Unfavorable outcome	2	25%	5	12%	
Skilled nursing facility	0	0%	2	5%	
Hospice	2	25%	1	2%	
Death	0	0%	2	5%	

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CTP, computed tomography perfusion; IQR, interquartile range; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale.

* One patient in the "Unreliable CTP" group (n = 7) and 3 patients in the "Reliable CTP" group did not achieve recanalization (n = 38). Forty-five patients with reliable automated CTP maps were taken for thrombectomy. Four patients had distal migration of the occlusive clot from the time of computed tomography angiography to conventional digital subtraction angiography and no longer required thrombectomy.

designed to enhance standardization and reproducibility.[10] Multiple prior studies have reported on the practicability and limitations of RAPID software. However, no studies to our knowledge have described the incidence of unreliable automated CTP maps due delayed perfusion states or adaptive cerebral autoregulatory hemodynamics in the setting of cerebral ischemia.

The majority of unreliable automated CTP maps had irregular Tmax calculations. Tmax is the time to the maximum of the deconvoluted residue function representing the arrival delay between the arterial input function and the concentration of contrast in the cerebral parenchymal tissue.[14] Tmax is dependent on bolus delay and dispersion through the cerebral vasculature. Cardiac insufficiency, hemodynamic instability, and most notably arterial stenosis can lead to bolus delay altering Tmax measurement.[15] Additionally, collateral flow may variably affect Tmax by various deconvolution methods. In our data, there were several instances of widespread prolongation of Tmax illustrated by either hemispheric or bihemispheric "penumbra". (Fig 1, A) This has been interpreted as a result of either cardiac insufficiency, hemodynamic instability, and hemodynamically significant carotid stenosis. If known prior to the onset of perfusion imaging, patients with cardiac insufficiency, hemodynamic instability, or hemodynamically significant carotid stenosis may benefit from longer scan durations (>60-70 seconds) in order to fully capture contrast passage through tissue.

There were also several examples of estimated penumbral volume (Tmax > 6 seconds) smaller than estimated infarcted core volume (CBF < 30%). (Fig 1, B) This likely reflects adaptive cerebral autoregulatory hemodynamics in the setting of cerebral ischemia, sometimes referred to as luxury perfusion. Alternatively, an estimated penumbra smaller than infarct core can be misclassified in cases of extensive collateral blood flow, partial occlusion or after recanalization, however LVO was evident at the time of the CTP study in our patients. The influence of such dynamic cerebrovascular pathophysiology on the reliability of automated CTP software and methods to correct for it has yet to be reported.

In the largest study to evaluate the feasibility of automated CTP software, RAPID software failed to form perfusion maps in only 26 of 776 cases (3.4%).[10] An additional 9% of patients required correction for artifactual mismatch by a neurologist.[10] In the CRISP trial 6 of 197 patients in the endovascular cohort (3.0%) had CTP failures.[16] In the DEFUSE 3 trial 2 of 182 randomized patients (1.1%) reported technically inadequate perfusion studies.[2] A higher percentage was reported in a retrospective study by Dehkharghani et al where 8.1% of patients had uninterpretable automated CTP maps strictly due to motion artifact.[17] However, none of these studies addressed the group of patients who underwent thrombectomy despite unreliable RAPID-generated maps.

We compared a contemporary cohort of patients presenting in the extended time window with unreliable CTP

maps who underwent thrombectomy to a group of patients selected for thrombectomy guided by reliable automated CTP maps. Clinical, radiographic, and intervention variables were similar amongst the groups and clinical outcomes did not differ in our sample. While no specific protocol was in place for patients presenting in the extended time window with unreliable CTP imaging, all patients who underwent thrombectomy had evidence of LVO, NIHSS greater than or equal to 7 and ASPECTS greater than or equal to 7 and would have been considered good candidates in the early time window.[3] This data adds to the growing evidence that in carefully selected patients thrombectomy may be beneficial in the extended time window guided solely by a plain head CT.[18-19]

This study has several limitations. The retrospective nature of our analysis limited our ability to more thoroughly evaluate for specific causes for unreliable studies. Our medical center did not make use of the live technical assistance provided by iSchemaView for unreliable studies. This study did not include RAPID-generated maps obtained from magnetic resonance imaging sources. These results represent the experience of a single center that sees the large majority of thrombectomy candidates as transfers, which may limit the generalizability. Lastly, the sample size of those treated with unreliable studies is small, limiting any generalization on whether CTP imaging is necessary. However, this study sample does report on a relatively large, contemporary sample from a medical center that has been familiar with the use of automated CTP maps for thrombectomy patient selection for several years prior to this study.

Conclusion

CTP maps generated by RAPID software were unreliable in 13% of cases within our cohort, a higher rate than prior publications. Unreliable automated maps more commonly occurred in patients with heart failure with reduced ejection fraction. Given the rate of unreliable automated CTP maps, further studies are warranted to not only establish the true necessity of currently available CTP software, but also more reliable methods to select patients for thrombectomy presenting in the extended time window.

Competing Interests

No author has any competing interests or disclosures.

References

1. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11-21.
2. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018;378:708-718.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49:e46-e110.
4. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke 2013;44:2650-2663.
5. Zhang Q, Yang Y, Saver JL. Discharge destination after acute hospitalization strongly predicts three month disability outcome in ischemic stroke. Restor Neurol Neurosci 2015;33:771-775.
6. Qureshi AI, Chaudhry SA, Sapkota BL, et al. Discharge destination as a surrogate for modified rankin scale defined outcomes at 3-and 12-months poststroke among stroke survivors. Arch Phys Med Rehabil 2012;93:1408-1413.
7. Belagaje SR, Zander K, Thackeray L, et al. Disposition to home or acute rehabilitation is associated with a favorable clinical outcome in the SENTIS trial. J NeuroInterv Surg 2015;7:322-325.
8. Belagaje SR, Sun C-HJ, Nogueira RG, et al. Discharge disposition to skilled nursing facility after endovascular reperfusion therapy predicts a poor prognosis. J NeuroInterv Surg 2015;7:99-103.
9. Rai AT, Raghuram K, Domico J, et al. Pre-intervention triage incorporating perfusion imaging improves outcomes in patients undergoing endovascular stroke therapy: a comparison with the device trials. J NeuroInterv Surg 2013;5:121-127.
10. Campbell BC, Yassi N, Ma H, et al. Imaging selection in ischemic stroke: feasibility of automated CT-perfusion analysis. Int J Stroke 2015;10:51-54.
11. Yancy CW, Jessup M, Bozkurt B, et al. ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:1810. 2013.
12. Rai AT, Raghuram K, Domico J, et al. Pre-intervention triage incorporating perfusion imaging improves outcomes in patients undergoing endovascular stroke therapy: a comparison with the device trials. J NeuroInterv Surg 2013;5:121-127.
13. Ryu WHA, Avery MB, Dharampal N, et al. Utility of perfusion imaging in acute stroke treatment: a systematic review and meta-analysis. J NeuroInterv Surg 2017;9:1012-1016.
14. Calamante F, Christensen S, Desmond P, et al. The phsyiological significance of the time-to-maximum (Tmax) parameter in perfusion MRI. Stroke 2010;41:1169-1174.
15. Heit JJ, Wintermark M. Perfusion computed tomography for the evaluation of acute ischemic stroke: strengths and pitfalls. Stroke 2016;47:1153-1158.
16. Lansberg MG, Christensen S, Kemp S, et al. Computed tomographic perfusion to predict response to recanalization in ischemic stroke. Ann Neurol 2017;81:849-856.
17. Dehkharghani S, Bammer R, Straka M, et al. Performance and predictive value of a user-independent platform for CT perfusion analysis: threshold-derived automated systems outperform examiner-driver approaches in outcome prediction of acute ischemic stroke. AJNR Am J Neuroradiol 2015;36:1419-1425.
18. Santos T, Carvalho A, Cunha AA, et al. NCCT and CTA-based imaging protocol for endovascular treatment selection in late presenting or wake-up strokes. J NeuroInterv Surg 2019;11:200-203.
19. Tsurukiri J, Ota T, Jimbo H, et al. Thrombectomy for stroke at 6-24 hours without perfusion CT software for patient selection. J Stroke Cerebrovasc Dis 2019;28:774-781.