Computed tomography perfusion identifies stroke patients with impaired cardiac function.

Carlos Garcia-Esperon, MD[1,2], Neil J Spratt MD, PhD[1,2], Shyam Gangadharan, MD[1], Ferdi Miteff, MD[1,2], Andrew Bivard, PhD[3], Thomas Lillicrap, PhD[2] , Shinya Tomari, MD[2], Christopher R Levi, MD[1,2], Mark W Parsons, MD, PhD[2,3]

[1]Department of Neurology, John Hunter Hospital, University of Newcastle, Newcastle, Australia.

[2]Hunter Medical Research Institute and University of Newcastle, Newcastle, Australia.

[3]Department of Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Australia.

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Corresponding authors

Dr. Carlos Garcia-Esperon

Department of Neurology, John Hunter Hospital, New Lambton, NSW, 2305, Australia

Ph number: +61 2 4922 3352. Email: Carlos.garciaesperon@health.nsw.gov.au

Prof. Mark Parsons

Department of Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital,

Parkville, VIC, 3050, Australia. Ph number: 03 9342 8448 Email: Mark.Parsons@mh.org.au

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Abstract

Background and Purpose

Low left ventricular ejection fraction (LVEF) leads to worse outcomes after stroke. We hypothesized that the arterial input function (AIF) variability on perfusion computed tomography (CTP), especially the time between scan onset and end of AIF (SO-EndAIF), would reflect reduction of cardiac output.

Methods

Retrospective analysis of consecutive stroke patients, who underwent CTP between January 2013 and September 2018, was performed in two parts. (i)To determine the correlation between SO-EndAIF and LVEF, all patients with a transthoracic echocardiogram (TTE) performed +/- 6 months from the time of stroke were included. LVEF was dichotomised as either normal (≥50%) or decreased (<50%). (ii)AIF was compared with hypoperfusion volume, defined as delay time (DT)>3s and with clinical outcome measured using three months modified Rankin Scale (mRS).

Results

A total of 732 ischemic stroke patients underwent CTP, 231 with TTE were included in part(i), 393 with outcome data were included in part(ii). In part(i), 193/231 (83.5%) had normal LVEF (median 61%) and 38/231 (16.5%) decreased LVEF (median 39%). The low-LVEF group had significantly prolonged SO-EndAIF compared to normal-LVEF group (mean of 39.7s vs 26s, $p<0.001$), and larger hypoperfusion lesions (94.9 vs 37.6 mL, $p<0.001$). SO-EndAIF time was strongly associated with EF, with an area under the curve (AUC) of 0.86. 29-seconds was the best threshold to distinguish between normal and impaired EF (AUC 0.77). In part(ii), the SO-EndAIF ≥ 29s group had larger hypoperfusion volumes (21.8 vs 89.7mL; $p<0.001$) and infarct core (12.2 vs 2.3mL; $p<.0001$) and

patients with SO-EndAIF ≥ 29s had fewer excellent or good clinical outcomes (mRS 0-1 40% vs 22%, OR 2.79, p<0.001, mRS 0-2 65% vs 35%, OR 1.41, p=0.033).

Conclusion

AIF width correlates with ejection fraction in acute ischemic stroke. A 29-second threshold from scan onset to end of AIF accurately predicts reduced LVEF and identifies patients more likely to have worse outcomes after stroke.

Introduction

Approximately 20-25 % of ischemic strokes have a cardiac origin (1), most of them secondary to atrial fibrillation (AF) (2-4), however structural cardiac abnormalities can also lead to stroke. Therefore, the standard stroke work-up often includes both assessment of the cardiac rhythm and cardiac structure. The diagnostic yield of transthoracic echocardiogram (TTE) in stroke patients varies widely across different publications, from 7% to 37% (5, 6). TTE also measures left ventricular ejection fraction (LVEF), which may have prognostic relevance in stroke patients (7). Patients with low LVEF have a higher incidence of ischemic stroke (8, 9) and worse outcomes (10, 11).

Multimodal brain imaging with CT, includes non-contrast CT, CT angiography (CTA) and CT perfusion (CTP). CTP is now performed widely in acute stroke as it provides important pathophysiologic information about extent of reversible ischemia (penumbra), as well as tissue likely to be irreversibly injured (infarct core) (12-16). To generate CTP maps, a bolus of radio-opaque contrast is administered rapidly (5-6 mL/s) into an antecubital vein, and imaging is performed to track the bolus passage through the brain vasculature and parenchyma. Arterial input function (AIF), venous outflow function (VOF) and tissue contrast concentration versus time curves are generated, and these are used to produce maps of tissue perfusion (Figure 1)(17). We have observed that in some patients there are considerable delays in the contrast bolus reaching and transiting the brain vessels. This can be seen as a delay from contrast injection to commencement and peak of the arterial input function curve, and/or slower transit or widening of the contrast concentration versus time curves. We hypothesized that these delays, in particular the time between the scan is triggered, to the end of AIF (ScanOnset-EndAIF - SO-EndAIF), may be a marker of reduced cardiac output.

Collateral blood flow is the main determinant of penumbral survival and rate of infarct core growth after ischaemic stroke (18-20). The collateral system bypasses the occlusion via the Circle of Willis proximally and leptomeningeal anastomoses distally, supplying retrograde perfusion to the ischemic region (18, 20). We also therefore hypothesised that delays in contrast travelling via the leptomeningeal collaterals (measured by Delay Time in seconds) in patients with poor cardiac output would be larger, being represented as larger hypoperfusion lesion volumes, and consequently worse outcomes after stroke. Lastly, we also hypothesised that SO-EndAIF, as a surrogate marker of poor LVEF, could identify this patient population.

Methods

Study design and study population

We retrospectively analysed consecutively recruited acute ischemic stroke patients from a single comprehensive stroke centre between January 2013 and September 2018. They were prospectively enrolled as part of the International Stroke Perfusion Imaging Registry (INSPIRE), approved by the Hunter New England Local Health District Human Research Ethics Committee in accordance with Australian National Health and Medical Research Council guidelines (Reference No: 11/08/17/4.01). Opt out consent approach used. Deidentified data from this study will be shared at the request of other researchers on reasonable timeframe from the first author.

All patients underwent CTP acutely. Ischemic stroke was defined as an acute neurological deficit and evidence of acute infarction on diffusion weighted imaging (DWI) MRI, or as new hypodensity on repeat non-contrast CT. CTP hypoperfused lesion was not required to be included in the analysis. To determine the correlation between SO-EndAIF and LVEF, all patients included in the study who had a TTE or TEE (transesophageal echocardiogram) performed +/- 6 months from the time of the stroke were analysed. LVEF was initially

classified according to the American Heart Association (21) three categories; normal LVEF if EF ≥ 50%, decreased if ≤ 40% and borderline between 41 and 49%. However, for analysis purposes, we dichotomised the EF variable as either normal (LVEF ≥ 50%) or decreased ejection fraction (if LVEF < 50%). To determine the correlation between poor cardiac output as determined by SO-EndAIF, hypoperfusion lesion volumes, and 3-month clinical outcome, a larger sample (consisting of all consecutive stroke patients undergoing CTP with full clinical data) was used. Blood pressure was described as the first blood pressure / heart rate record found in notes of the patients at arrival of hospital or performed en route by paramedics. Clinical outcome after stroke was defined using the three months modified Rankin Scale (mRS), with mRS 0-1 defined as excellent, mRS 0-2 defined as good and 3-6 as poor outcome.

AIF was calculated automatically by the MIStar CTP software (Apollo Medical Imaging Technology, Melbourne, Australia), which detects pixels within an intracranial artery with the highest and earliest take-off (typically proximal anterior or middle cerebral artery). If the automated AIF curve selection did not select a proximal artery (usually due to motion artefact), the site for AIF was selected manually, choosing an unaffected proximal anterior or the middle cerebral artery. SO-EndAIF was defined as the time between onset of CT scanning and the end of the AIF. “Onset of AIF curve To Peak” was defined as the time between the contrast arrival to the brain (detected as an increase in HU) to the HU peak. “Peak To End” was defined as the time between the peak and the return to baseline. Width of the curve was defined as the total duration of the curve (Onset to Peak + Peak to End). Some patients also have an obvious second, smaller and delayed peak (due to recirculation of the contrast bolus). This was defined as present if there was a second peak curve appearing after the first AIF with an arbitrary amplitude of at least 30 HU (Figure 1). All these values were calculated from each patient’s AIF in MIStar by a stroke neurologist (CG-E). Patients with

CTP perfusion acquisition with significant artefact, which did not create reliable curves after attempts with manual processing, were excluded from the analysis.

Imaging protocol

CTP for all cases was performed on a 320-Slice Toshiba Aquilion One (Toshiba Medical Systems, Otawara, Japan). A 50 ml bolus of contrast agent (Ultravist 370; Bayer HealthCare, Berlin, Germany) injected in the cubital fossa using a 18 Gauge cannula at a rate of 6 ml/s was used to acquire CTP images. The first CTP acquisition was acquired 7 seconds after the start of contrast injection, followed by another 18 time points over 72 seconds. MIStar (Apollo medical imaging, Melbourne Australia) was used to generate the CTP maps, using semi-automatic processing of infarct core and penumbra volumes. A model-free singular value decomposition is used to deconvolve the tissue enhancement curve and the AIF with automated delay and dispersion correction (22, 23). Brain MRIs were performed on either a 1.5 or 3 Tesla MRI (Siemens Aera / Siemens Verio, Siemens AG, Healthcare Sector, Erlangen, Germany). Previously validated thresholds were applied in order to measure the volume of the acute perfusion lesion (relative Delay Time ≥3 seconds) and acute ischemic core (relative cerebral blood flow ≤30% within the perfusion lesion) (13). MIStar uses DT maps for penumbra definition whereas some other software uses Tmax.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. A priori, $p<0.05$ was used to indicate statistical significance. According to pretesting with Kolmogorov-Smirnov and Shapiro-Wilk tests, the study data did not follow a normal distribution. Therefore Chi-squared and Mann-Whitney tests were used to compare the means of the different parameters (baseline, AIF characteristics) between groups. Receiver-operator curves (ROC curves) were created for the association between AIF

width and the optimal cut-off point. Next, logistic regression was used to identify predictors of SO-EndAIF≥ cut-off point, and if the cut-off point was associated with patient clinical outcomes dichotomised as mRS 0-1 versus 2-6 and mRS 0-2 versus 3-6. Covariates included in the logistic regression model included patient age, gender, baseline National Institutes of Health Stroke Scale (NIHSS) and volumes of ischemic core and penumbra. A separate logistic regression model was created to determine whether other cardiac measures were related to extended AIF. These variables included AF, heart rate, presence of a large vessel occlusion, medication taken, and blood pressure (systolic and diastolic). Results are presented as mean ± standard deviation (SD) or median [Interquartile range –IQR], as indicated.

RESULTS

(i) AIF dispersion and LVEF.

From January 2013 to September 2018, 732 confirmed acute ischemic strokes underwent multimodal CT scanning and were selected for this study. Of these, 301 (41.1%) had a cardiac echocardiogram (TTE and/or TEE), however seventy were excluded from the final analysis, as follows: 54 had TTE performed >6 months from stroke, 7 did not have ventricular ejection fraction quantified in the report, 6 had severe motion artefact in their CTP, and 3 had incomplete clinical data. Finally, a total of 231 patients were included in the ejection fraction analysis.

The median age was 66 [57-75] years, 127 (55%) were male, the median baseline NIHSS was 9 [4-16], and the median time from CTP to cardiac echocardiogram was 6 days [2-21], with a range from -180 to +169 days. 193 patients (83.5%) had normal LVEF and 38 (16.5%) decreased LVEF. LVEF ranged from 50 to 80%, with a median of 61% [56-65%] in the group with preserved LVEF, compared to a median of 39% [31-45%], and a range from 15% to 49% in the 38 patients with decreased LVEF.

There were no differences in age, gender or baseline heart rate or blood pressure between decreased and normal LVEF groups, however patients with decreased LVEF had higher rates of hypertension, atrial fibrillation (past or current) and previous cerebrovascular events. Patients with decreased LVEF also suffered more clinically severe strokes, with a significantly higher baseline NIHSS (Table 1). Notably, patients with low LVEF had significantly larger perfusion lesions (94.9 mL vs 37.6 mL, p=0.001), ischemic cores (15.2 mL vs 4 mL, p=0.015), penumbras (72.7 mL vs 25.5 mL, p=0.001) and DT>4, 6 and 8 s volumes (Table 2).

All measures of AIF dispersion and delay except presence of second AIF curve, were significantly associated with low EF (all p<0.001) (Supplementary table I). The association between scan onset and the end of the AIF (SO-EndAIF) as a continuous variable and EF was good, with an area under the curve (AUC) of 0.86 (95% CI 0.8-0.92). The threshold of 29 seconds performed best for prediction of poor EF on ROC calculation, with an AUC of 0.77, sensitivity of 0.82 and specificity of 0.73 (Supplementary table II).

In the subgroup of patients with severely decreased ejection fraction (≤35%), the threshold of 35 seconds was found to be the best for prediction of poor EF on ROC calculation, with an AUC of 0.80, sensitivity of 0.78, specificity of 0.83, positive predictive value of 0.27 and negative predictive value of 0.98 (Supplementary table III).

Using logistic regression, only age was significantly associated with a SO-EndAIF ≥ 29 s (p=0.019), while ischemic core, penumbra, severe delay volume or sex and baseline NIHSS were not (all p>0.05). Lastly, the presence of AF (p<0.001), heart rate (p=0.026) and systolic blood pressure (p=0.046), were all significant predictors of extended SO-EndAIF, but large vessel occlusion or diastolic blood pressure were not.

(ii) AIF, hypoperfusion volumes and clinical outcome

From January 2013 to September 2018, 393 confirmed stroke patients had acute CTP with full clinical data including 3-month follow-up. The median age was 70 years [60-79] and 226 (57.5%) were male. The median NIHSS was 9 [4-18], and 36% had a large vessel occlusion. Using the 29-second threshold to classify the patients between good and poor LVEF, 156 patients (39.7%) had a SO-EndAIF≥29, and 237 (60.3%) had a SO-EndAIF < 29 seconds. Notably, SO-EndAIF≥29 seconds patients were older, had worse premorbid function (mRS), higher prevalence of hypertension and atrial fibrillation, were more likely to have a proximal vessel occlusion, and had much higher baseline NIHSS ($p<0.05$, Table 3).

Patients with SO-EndAIF≥29 seconds had substantially larger perfusion lesions across all the different Delay Time thresholds and baseline infarct core volumes (core 12.2 mL, penumbra 67.9 mL, DT>3 89.7 mL vs 2.3 mL, 14.8mL and 21.8mL respectively ,$p<0.001$) (Table 4). Lastly, a backwards logistic regression model containing SO-EndAIF>29, ischemic core volume, penumbra volume, age, medications, gender and NIHSS was used to predict mRS outcomes. Ischemic core volume, SO-EndAIF>29 and age remained in the model as significant predictors of excellent clinical outcomes (mRS 0-1 40% vs 22%, OR 2.79, CI 1.63-5.41, $p<0.001$) and also of good clinical outcomes (mRS 0-2 65% vs 35%, 1.41, CI 1.14-6.52, $p=0.033$).

Discussion

The arterial input function obtained from CTP provides an excellent indicator of cardiac ejection fraction. We found a strong association between SO-EndAIF width and LVEF (AUC of 0.86). The 29-second width was the best threshold to differentiate between normal and decreased LVEF, with an AUC of 0.77. Increased AIF width accurately captures a subpopulation who are likely to have decreased ejection fraction, which could be used to

prioritise more urgent need for echocardiography. Although the 29-second threshold proposed has a specificity of 0.27 and positive predictive value of 0.37, the negative predictive value is 0.95, thus in our population it was an excellent triage tool as the vast majority of patients with an AIF<29 seconds had a normal EF. Notably, we have shown for the first time, not only a correlation with echocardiography, but clinical consequences of this - patients with impaired LV function had worse baseline stroke severity, and larger baseline core and hypoperfusion lesion volumes. Moreover, the 35-second width was the best threshold to identify patients with severely decreased LVEF, with an AUC of 0.80. This group represents stroke patients in whom anticoagulation has proven to offer a greater reduction of ischemic stroke recurrence compared to antiplatelet therapy(24), hence a group in which formal echocardiography would be strongly indicated.

A novel finding of this study was that AIF width was a strong marker of low LVEF and the 29-second threshold identified patients with worse 3-month outcomes after stroke. This could support our hypothesis that patients with poor cardiac output have poorer collateral flow, with recent data indicating a strong link between Delay Time, poor collaterals and poor stroke outcome(25). The pathophysiology behind this phenomenon is uncertain, but it seems plausible that poor cardiac output could lower perfusion pressure via collaterals, much the same as we have recently shown that lower blood pressure is associated with poorer collateral flow (25).

A strength of this study is that we have quantified a previously noted clinical observation, using a relatively large and very well characterised clinical data, including comprehensive CT perfusion volumetrics. There are also limitations to this study. Firstly, the echocardiography data was collected retrospectively and we used a wide time window (6 months before or after the stroke). Nonetheless, the median time of TTE was 6 days after stroke onset. Secondly, our echo-confirmed reduced LVEF group was limited to a small sample of 38 patients. This

group were younger than the overall SO-EndAIF>29 seconds group, likely representing a selection bias for echocardiography to be performed more commonly in younger patients with cryptogenic stroke. Nonetheless, we were able to find an excellent correlation between SO-EndAIF and EF. Thirdly, the population groups created using the SO-EndAIF 29-cut-off were imbalanced, patients with a SO-EndAIF of 29 seconds or greater having more comorbidities, worse baseline mRS and more severe baseline stroke severity. However, this is consistent with known data that cardioembolic strokes typically are more severe, and obviously low EF would be associated with poorer pre-stroke functioning. Lastly, our results have been confirmed in a particular CT Perfusion protocol and using a specific automated perfusion software. Therefore, results may vary with different CT Perfusion protocols or software employed.

In conclusion, the time between the onset of scan to end of AIF has a strong association with cardiac ejection fraction in patients with acute ischemic stroke. The 29-seconds cut-off identified patients with normal and poor ejection fraction with good sensitivity. Moreover, this cut-off identifies a population with worse clinical outcome three months after stroke.

Table 1

	Normal LVEF (n=193)	Decreased LVEF (n=38)	p-value
Median age - yr [IQR]	66 [55-75]	67 [62-79]	0.122
Median NIHSS score [IQR]	8 [3-16] n=187	14 [6-20] n=37	0.014
Male sex — no. (%)	102 (52.8)	25 (65.8)	0.143
Median heart rate – bpm [IQR]	80 [67-89] n=187	80 [69-90]	0.074
Median systolic blood pressure – mmHg [IQR]	145 [130-160] n=187	135 [125-160]	0.207
Median diastolic blood pressure – mmHg [IQR]	81 [71-90] n=187	82 [70-90]	0.902
Median mean blood pressure– mmHg [IQR]	102 [93-112] n=187	99 [89-110]	0.562
Clinical history — no. (%)			
Atrial Fibrillation	34 (17.6)	20 (52.6)	<0.001
Hypertension	115 (59.6)	33 (86.8)	0.001
Diabetes mellitus	29 (15.1)	10 (26.3)	0.092
Hypercholesterolemia	53 (27.5)	9 (23.7)	0.631
Previous stroke/transient ischemic attack	27 (14)	11 (28.9)	0.023
Beta blocker therapy	35 (18.1)	18 (47.4)	<0.001
Digoxin therapy	4 (2.1)	5 (13.2)	<0.001
Proximal occlusion - no. (%) (M1/T-ICA/Tandem/Basilar)	59 (30.6)	18 (47.4)	0.045
Acute treatment— no. (%)			
Intravenous thrombolysis	85 (44) n=191	19 (50)	0.534
Endovascular clot retrieval	21 (10.9)	7 (18.4)	0.193
Three months mRS 0-1 — no. (%)	79 (40.9) n=190	9 (23.7) n=37	0.039
Three months mRS 0-2 — no. (%)	124 (64.2) n=190	18 (47.4) n=37	0.044

Table 2

	Core	Penumbra	DT>3s	DT>4s	DT>6s	DT>8s	Mismatch Ratio (DT>3/core)
Normal LVEF	4 [0.4-12.9] n=190	25.5 [3-71.7] n=190	37.6 [4.3-90.5] n=190	19 [1.2-57.2] n=189	4 [0.3-26.8] n=189	1.8 [0-10.4] n=189	3.8 [1.9-8.2] n=162
Decreased LVEF	15.2 [1.7-37] n= 35	72.7 [19.6-116.7] n=35	94.9 [35.3-140.3] n=35	70.9 [12.3-105.1] n=32	26 [5.4-60.6] n=32	12 [0.7-31.7] n=32	4.3 [1.9-8.5] n=30
p-value	0.015	0.001	0.001	0.002	0.002	0.002	0.95

Table 3

	SO-EndAIF<29 (n=237)	SO-EndAIF≥29 (n=156)	p-value
Median age - yr [IQR]	65 [55-74]	78 [68-83]	<0.001
Median NIHSS score [IQR]	6 [3-14] n=234	15 [7-21] n=152	<0.001
Male sex — no. (%)	118 (49.8)	107 (68.6)	<0.001
mRS 0-2 — no. (%)	219 (92.4)	134 (85.9)	0.054
mRS on ordinal analysis [IQR]	0 [0-0] n=235	0 [0-2] n=153	<0.001
Median heart rate – bpm [IQR]	80 [70-90] n=231	72 [60-85] n=150	0.146
Median systolic blood pressure – mmHg [IQR]	150 [130-162] n=231	140 [129-161] n=150	0.522
Median diastolic blood pressure – mmHg [IQR]	82 [73-91] n=231	80 [70-90] n=150	0.340
Median mean blood pressure– mmHg [IQR]	105 [97-113] n=231	102 [90-113] n=150	0.496
Clinical history — no. (%) Atrial Fibrillation Hypertension Diabetes mellitus Hypercholesterolemia Previous stroke/transient ischemic attack Beta blocker therapy Digoxin therapy	 39 (16.5) 137 (57.8) 43 (18.1) 69 (29.1) 40 (16.9) 43 (18.1) 4 (1.7)	 80 (51.3) 127 (81.4) 30 (19.2) 55 (35.3) 29 (18.6) 78 (50) 12 (7.7)	 <0.001 <0.001 0.79 0.22 0.68 <0.001 0.003
Proximal vessel occlusion - no. (%) (M1/T-ICA/Tandem/Basilar) Any intracranial occlusion – no. (%)	61 (25.7) 103 (43.5)	80 (51.3) 104 (66.7)	<0.001 <0.001
Median Last time seen well to CT – minutes [IQR]	227 [100-305] n=227	135 [95-218] n=153	0.136
Acute treatment— no. (%) Intravenous thrombolysis Endovascular clot retrieval	 87 (36.7) n=236 29 (12.2)	 61 (39.1) n=155 22 (14.1)	 0.67 0.65
Three months mRS 0-1 — no. (%)	95 (40.1)	35 (22.4)	<0.001
Three months mRS 0-2 — no. (%)	154 (65)	55 (35.2)	<0.001
Median three months mRS on ordinal analysis [IQR]	2 [1-3]	3 [2-5]	<0.001

Table 4

	Core	Penumbra	DT>3s	DT>4s	DT>6s	DT>8s	Mismatch ratio (DT>3/core)
SO-EndAIF<29	2.3 [0.2-14] n=235	14.8 [1.9-61.2] n=235	21.8 [2.7-80.3] n=235	11.8 [0.8-46.9] n=219	4 [0.2-28.3] n=234	1.5 [0-8.5] n=220	3.4 [1.6-6.7] n=189
SO-EndAIF≥29	12.2 [1.8-42] n=152	67.9 [19.2-106.1] n=152	89.7 [26.4-154.4] n=152	62.2 [11.3-113.4] n=140	29 [3.5-66.8] n=149	10.8 [0.9-37.3] n=141	4.3 [2.1-9] n=139
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.57

Legends

Table 1 – Baseline characteristics and treatment of patients with normal and decreased left ventricular ejection fraction (LVEF).

IQR: Interquartile range. NIHSS: National Institutes of Health Stroke Scale

Table 2 – Baseline imaging characteristics of patients with normal and decreased left ventricular ejection fraction (LVEF).

Median volumes are in mL [Interquartile Range]. DT: Delay Time (in seconds)

Table 3 – Baseline characteristics and acute treatment distribution according the symptom onset- end arterial input function (SO-EndAIF) width.

CT: Computed tomography, IQR: Interquartile range, M1: Middle cerebral artery, proximal segment, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, T-ICA: Terminal internal carotid artery.

Table 4- CT Perfusion characteristics in patients with SO-EndAIF<29 and SO-EndAIF≥29.

Median volumes are in mL [Interquartile Range]. DT: Delay time (in seconds), SO-EndAIF: Scan Onset- End of arterial input function.

Figure 1 – Arterial input function (red) and venous outflow function (blue) curves: a) patient with normal cardiac output b) patient with low ejection fraction.
Note the delay to onset of AIF, AIF peak, and wider curve in the patient with poor ejection fraction. x-axis: Time in seconds. y-axis: Contrast concentration (tissue density) in Hounsfield units. Second 0 of the graphic matches with the start of CT scanning. Contrast injection commenced 7 seconds prior to this timepoint.
OTP: Onset to Peak. PTE: Peak to End. So-EndAIF: Scan onset to end of arterial input function.

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SUPPLEMENTAL MATERIAL

Table I. Arterial Input function (AIF) characteristics. LVEF: Left ventricular ejection fraction, SD: Standard deviation.

Arterial input function characteristics (in seconds)	Normal LVEF (n=193)	Decreased LVEF (n=38)	p-value
Mean Onset Scan –Take Off AIF (SD)	5.5 (3.3)	10.3 (4.1)	<0.001
Mean Onset AIF - Peak (SD)	8.9 (2)	11.4 (2.9)	<0.001
Mean Peak AIF - End (SD)	11.6 (3)	18 (7.4)	<0.001
Mean AIF width (SD)	20.4 (3.9)	29.4 (9.3)	<0.001
Mean Scan Onset– End of AIF (SD)	26 (6.1)	39.7 (12.2)	<0.001
Second arterial curve - no. (%)	40 (20.7%)	4 (10.5%)	0.216
Scan Onset-EndAIF equal or greater than 29 seconds – no. (%)	52 (26.7%)	31 (81.6%)	<0.001

Table II. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) for different scan onset-end of arterial input function (SO-EndAIF) width thresholds. CI: Confidence interval.

SO-EndAIF (seconds)	Decreased Ejection Fraction				
	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
≥27	0.89	0.59	0.3	0.96	0.74 (0.67-0.82)
≥28	0.84	0.67	0.34	0.96	0.76 (0.68-0.84)
≥29	0.82	0.73	0.37	0.95	0.77 (0.7-0.85)
≥30	0.71	0.81	0.43	0.93	0.76 (0.67-0.85)
≥31	0.68	0.83	0.45	0.93	0.76 (0.67-0.85)
≥32	0.68	0.84	0.46	0.93	0.76 (0.67-0.86)
≥33	0.68	0.85	0.48	0.93	0.77 (0.68-0.86)
≥34	0.68	0.85	0.48	0.93	0.77 (0.68-0.86)
≥35	0.66	0.86	0.49	0.93	0.76 (0.67-0.84)
≥36	0.58	0.90	0.52	0.91	0.74 (0.64-0.84)

Table III. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) for different scan onset-end of arterial input function (SO-EndAIF) width thresholds. CI: Confidence interval.

SO-EndAIF (seconds)	Decreased Ejection Fraction (≤35%)				
	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
≥27	0.94	0.55	0.15	0.99	0.75 (0.66-0.84)
≥28	0.89	0.63	0.17	0.99	0.76 (0.66-0.86)
≥29	0.89	0.69	0.19	0.99	0.79 (0.69-0.88)
≥30	0.83	0.78	0.24	0.98	0.79 (0.7-0.91)
≥31	0.78	0.79	0.24	0.98	0.79 (0.67-0.91)
≥32	0.78	0.80	0.25	0.98	0.79 (0.67-0.91)
≥33	0.78	0.81	0.26	0.98	0.80 (0.68-0.91)
≥34	0.78	0.81	0.26	0.98	0.80 (0.68-0.91)
≥35	0.78	0.83	0.27	0.98	0.80 (0.69-0.92)
≥36	0.72	0.86	0.31	0.97	0.79 (0.67-0.92)