Association of high-sensitivity cardiac troponin T with territorial middle cerebral artery brain infarctions and dynamic cerebral autoregulation

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Manuel Bolognese[1], Laura Weichsel[1], Mareike Österreich[1], Martin Müller[1], Grzegorz Marek Karwacki[2] and Lehel-Barna Lakatos[1]

[1]Department of Neurology and Neurorehabilitation, Lucerne Cantonal Hospital, Lucerne, Switzerland.
[2]Department of Radiology and Nuclear Medicine, Section for Diagnostic and Interventional Neuroradiology, Lucerne Cantonal Hospital, Lucerne, Switzerland.

ABSTRACT

BACKGROUND: Cardiac high-sensitivity troponin T (hs-cTnT) is linked to the cardioembolic origin, severity, and outcome of acute ischemic stroke. Furthermore, larger brain infarctions are often accompanied by impaired dynamic cerebral autoregulation (dCA), which is also indicative of a poor prognosis.

OBJECTIVES: This study aimed to investigate whether hs-cTnT levels can serve as a predictor of dCA impairment.

DESIGN: Retrospective cohort study.

METHODS: In 330 consecutive patients with stroke (age 71 years [IQR 59-78]; 100 women; 229 territorial and 111 non-territorial brain infarcts) with successful dCA assessment, hs-cTnT levels were measured within 24 hours of stroke onset. These measurements were analyzed in relation to cerebrovascular risk factors, stroke origin, stroke severity (National Institute of Health Stroke Scale, NIHSS at entry), modified Rankin scale (mRs) at 3 months, and stroke volume determined by cranial computed tomography perfusion (CTP). dCA was assessed using transfer function analysis, which assessed the relationship between middle cerebral artery blood flow velocity and blood pressure. Coherence, gain, and phase were estimated across 3 frequency ranges: very low (0.02-0.07 Hz), low (0.07-0.15 Hz), and high (0.15-0.5 Hz).

RESULTS: In univariate analysis, hs-cTnT was associated with cardioembolism and territorial infarction. In the multinomial logistic regression analysis, independent risk factors for the presence of a territorial infarction included atrial fibrillation, the NIHSS score, the infarct core on CTP, cardioembolism, and large vessel disease, but not hs-cTnT levels. Risk factors for a poor outcome (mRs >2) included age, hs-cTnT, and NIHSS score. Overall, the coherence, gain, and phase were not predicted by hs-cTnT levels.

CONCLUSIONS: Hs-cTnT levels are associated with poor stroke outcomes. However, they do not predict dCA impairment.

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CORRESPONDING AUTHOR: Martin Müller, Department of Neurology and Neurorehabilitation, Lucerne Cantonal Hospital, Spitalstrasse, Lucerne CH-6000, Switzerland.
Email: martin.renatemueller@web.de

Introduction

The most relevant risk factors for acute ischemic stroke include age, sex, race, arterial hypertension, diabetes mellitus, obesity, physical inactivity, atherosclerotic disease of the large brain-supplying arteries, and cardiac diseases.[1] The latter include atrial fibrillation, ischemic coronary heart disease, and cardiomyopathies. High-sensitivity cardiac-specific Troponin T (hs-cTnT) is a biological marker of myocyte damage in cardiac diseases, produced exclusively in cardiac myocytes.[2,3] Levels exceeding the upper limit of 14 ng/L suggest myocardial damage.[2-7] Consequently, cerebral ischemic events accompanied by elevated hs-cTnT levels are often attributed to a cardiac, and thus cardioembolic, origin.[8-10]

Elevated hs-cTnT levels are associated not only with a potential cardioembolic origin of stroke but also with increased stroke severity at the time of the ictus.[9-11] Furthermore, elevated hs-cTnT levels correlate with poorer neurological prognosis,[9,10,12] increased mortality, and a higher incidence of other cardiovascular events.[13,14] The characteristic patterns of brain infarction in cardioembolism include either singular or

multiple territorial infarctions. Territorial strokes are typically more severe than lacunar strokes and are often associated with impaired cerebral autoregulation. When evaluating cerebral autoregulation using the dynamic cerebral autoregulation (dCA) approach, impaired dCA is more frequently observed in larger brain infarctions, particularly territorial infarctions. This impairment suggests a poorer prognosis 3 months after the stroke event.[15,16] This study aimed to investigate whether hs-cTnT levels can serve as a predictor of dCA impairment. We hypothesized that hs-cTnT levels are associated with territorial infarctions, predominantly of cardioembolic origin, and that these levels reflect a greater disturbance in dCA compared to non-territorial infarctions.

Methods

This retrospective cohort study of patients with acute ischemic stroke was approved by the Ethics Committee of Northwest and Central Switzerland (ID 2024-01039). This study was conducted in accordance with the Declaration of Helsinki and adhered to good clinical practice standards. It is part of a larger trial registered at ClinicalTrials.gov (NCT04611672). The corresponding author can provide all data for this study upon request.

Lucerne Hospital is a large tertiary teaching hospital equipped with a comprehensive stroke center service. All patients presenting with stroke syndrome receive standardized care, which includes a focused clinical examination followed by multimodal cranial computed tomography (CT) using Siemens Force, Edge, or XCeed CT machines. This process involves native CT imaging, followed by CT perfusion (CTP) analyzed using Syngo via Rapid AI Software (RAPID) to estimate the infarct core and penumbra. A Tmax of >6 seconds indicates hypoperfusion, while a side-to-side difference of 30% indicates infarct core. Additionally, CT angiography is performed to assess vascular status. If indicated, intravenous thrombolysis (IVT) and/or mechanical intra-arterial thrombectomy (MT) are performed promptly. All patients diagnosed with stroke syndrome are subsequently transferred to the stroke unit for intensive clinical monitoring. Monitoring includes the National Institute of Health Stroke Scale (NIHSS)[17] and modified Rankin score (mRs)[18] assessments upon hospital entry, as well as daily assessments while in the stroke unit and 3 months after the ischemic event. Additionally, blood pressure, heart rate, body temperature, blood glucose level, and oxygen saturation are closely monitored. Ultrasound examinations of all brain-supplying arteries are conducted, which include the assessment of dCA and echocardiography. Within 72 hours of hospitalization, brain magnetic resonance imaging (MRI) is performed using diffusion-weighted imaging (DWI), T2-weighted, and susceptibility-weighted imaging sequences on either a Siemens Vida fit (3 Tesla), Siemens Aera (1,5 Tesla), or Philips Achieva (3 Tesla). After all information was collected, stroke etiology was classified based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[19] into the following categories: cardioembolic (CE), large vessel disease (LVD), lacunar (L), other determined causes (Others), and stroke of undetermined origin (SUO), which indicates cases where no source or multiple sources of a stroke were identified. Regardless of their assumed etiology, MRI-visible infarcts per patient were classified by 2 experienced stroke neurologists.[20] The classifications included: territorial infarcts (pure cortical or cortical plus the adjacent subcortical brain tissue in the distribution of a cortical artery; singular or multiple), lacunar infarcts (infarcts with a diameter of 1.5 cm or less, typically located in the subcortical structures such as basal ganglia and white matter),[21] or internal (border zone infarcts associated with severe carotid artery disease).[22] Blood samples were withdrawn as soon as the patients had arrived at the hospital to estimate hs-cTnT levels (Immunoassay Roche Elecsys® on the Roche Cobas 8000 system, Hoffmann-La Roche, Basel, Switzerland). For dCA assessment,[23,24] the target parameters—coherence, phase, and gain—were derived from averaged time series of blood pressure and transcranial Doppler-derived middle cerebral artery blood flow velocity over one-second intervals. These parameters were extracted from their respective power auto-spectra or cross-spectra using Welch's averaged periodogram method, employing a Hanning window length of 100 s, a window overlap of 50%, and a total Fast Fourier transformation data length of 300 seconds. For each participant, the coherence, phase (in radians), and gain (in cm/s/mmHg) were averaged over very low frequency (VLF; 0-0.07 Hz), low frequency (LF, 0.07-0.15 Hz), and high frequency (HF, 0.15-0.5 Hz) ranges.

Patients

For this study, we retrospectively analyzed all patients treated at our stroke unit from January 1, 2020, to April 31, 2022, who underwent a dCA assessment. The inclusion criteria were as follows: age over 18 years, non-pregnant, a characteristic hemispheric syndrome diagnosed as a definitive supratentorial ischemic stroke in the middle cerebral artery territory after initial multimodal imaging, and subsequent confirmation by DWI. Additionally, the dCA assessment had to be of good quality, at least in the stroke-affected hemisphere. Exclusion criteria included a final diagnosis of a stroke mimic, primary intracranial hemorrhage, transient ischemic attack, cerebral sinus or vein thrombosis, or the presence of brain metastasis as the cause of an acute neurological deficit.

Statistics

The MATLAB Statistical Toolbox was used for all data analyses. Categorical variables are reported as absolute numbers and percentages. To compare their distribution between groups, we used either Fisher's exact test or chi-squared test. Continuous data that followed a normal distribution are expressed as mean ± standard deviation (SD), whereas non-normally

distributed data are presented as median with interquartile range (IQR). Most continuous variables were not normally distributed; therefore, we used the non-parametric Kruskal–Wallis test for all between-group comparisons of continuous variables or simple regression analysis for these variables. To evaluate whether hs-cTnT was an independent predictor for the presence of a territorial infarct, we defined the following baseline variables: age, sex, history of arterial hypertension, diabetes mellitus, dyslipidemia, body mass index, metabolic syndrome, atrial fibrillation, ischemic heart disease, left ventricular ejection fraction <50% (indicative of heart failure), hs-cTnT, NIHSS score at entry, CTP infarct core, and stroke origin groups (CE, LVD, L, Others, and SUO). All variables showing a significant difference ($P < 0.05$) or a trend for a difference ($P < 0.1$) between the territorial and non-territorial groups in the univariate analysis were included as independent variables in a multinomial linear logistic regression analysis model, with the presence of a territorial infarct as the dependent variable. For the outcome analysis, we dichotomized the mRs score at 3 months after the stroke event into <= 2 vs >2. For the univariate analysis, we used the baseline variables mentioned above and included the presence of territorial infarct, as well as whether an IVT or MT was performed. All variables showing a significant difference or a trend toward a difference were incorporated into a multinomial linear logistic regression analysis model, with the dichotomized mR outcome as the dependent variable.

Results

A total of 330 patients (median age, 71 [59-78] years, 100 women [30.3%]) were included in this study (Figure 1). Among them, 219 (66.3%) had territorial infarcts, 105 had lacunar infarcts, and 6 border zone infarcts. The latter 2 groups were summarized as non-territorial (n = 111, 33.7%) for comparison with the patients with territorial infarcts. The baseline characteristics are presented in Table 1. The baseline variables used to analyze the outcomes were slightly different and are reported in Table 2. A total of 120 (36.3%) patients received IVT (109 in the territorial group), and 60 patients (18.1%) underwent MT (all in the territorial group).

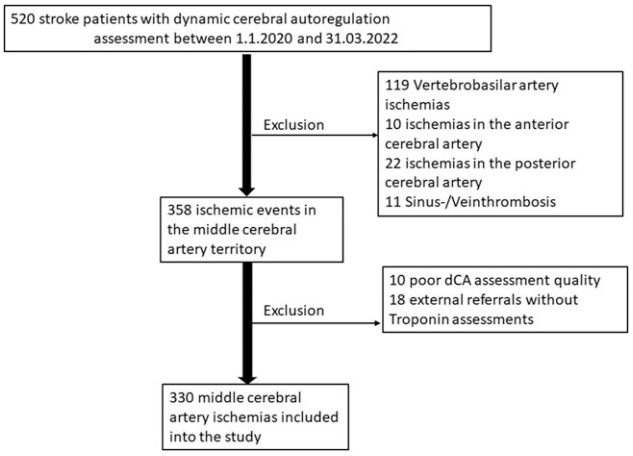

Figure 1. Flow chart of patients to be included in the study.

Territorial vs nonterritorial infarcts

The age and sex distributions were similar in both groups. Among the variables, arterial hypertension, dyslipidemia, L, and SUO were more frequent in the non-territorial group than in the territorial group, while diabetes mellitus and weight (as assessed by the Body Mass index) were evenly distributed across both groups. Conversely, the territorial group demonstrated a higher frequency or greater values of AF, CE, LVD, hs-cTnT, NIHSS score at entry, and CTP core than did the non-territorial group. The incidence of ischemic heart disease was evenly distributed across both groups. Additionally, the territorial infarct group exhibited poorer mRs outcomes than did the non-territorial group after 3 months.

The distribution of territorial and non-territorial infarctions by etiology indicated that territorial infarcts were most prevalent in the CE group and also constituted the majority of strokes in the other etiology groups, with the exception of lacunar strokes.

Regarding hs-cTnT, the CE group (15; IQR 9-44 ng/L) exhibited significantly higher serum concentrations than did all other etiology groups: LVD (10; IQR 6-18), L (11; IQR 6-15), Others (5; IQR 4-9), and SUO (9; IQR 6-18) ($P = .0005$). Neither within each group nor overall was hs-cTnT found to be related to the CTP core. In the regression analysis across all patients, the results showed a beta coefficient of 0.34 (95% Confidence interval: −0.35 to 1.03; $P = .33$). Notably, patients who underwent thrombectomy exhibited a higher hs-cTNT level (14.5, IQR 8-26) than did those who did not undergo thrombectomy (11, IQR 6-18.5; $P = 0.04$).

After categorizing the hs-cTnT levels into normal (<=14 ng/L) and elevated (>14 ng/L), the results showed that the CE group had 56 elevated cases out of 106 (53%). In comparison, the LVD group had 16 out of 53 cases (30%), the L group had 14 out of 57 cases (24.5%), the Others group had 1 out of 9 cases (11%), and the SUO group had 30 out of 105 cases (28.5%). The chi-squared test revealed a significant difference, with a P-value of 0.006.

To evaluate whether hs-cTnT can predict a territorial infarct, we included arterial hypertension, dyslipidemia, atrial fibrillation, hs-cTnT, the NIHSS score at entry, the infarct core on CTP, and the stroke origin groups (CE, LVD, L, and SUO) as the independent variables, and the presence of a territorial infarct as the dependent variable in the multinomial logistic regression model. The likelihood of having a territorial infraction was increased with the presence of atrial fibrillation (adjusted OR 10.2, 95%CI 1.06-115; $P = .04$), the NIHSS score at entry (OR 1.71, 95%CI 1.33-2.2 per score point; $P = .0000$), the infarct core on CTP (OR 85.3, 95%CI 70.6-132 per ml; $P = .0000$), and the stroke origin groups CE (OR 96, 95%CI 64.4-145, $P = .0000$) and LVD (OR 31.8, 95%CI 4.66-208; $P = .0000$). Conversely, the likelihood was decreased in the presence of dyslipidemia (OR 0.23 (95%CI 0.06-0.84; $P = .02$) and in the

Table 1. Baseline characteristics of the patient population, overall and dichotomized according to the presence of territorial vs nonterritorial infarctions. The odds ratios indicate the likelihood of the variable being present in the territorial infarct group.

VARIABLE	ALL PATIENTS (N = 330)	TERRITORIAL (N = 219)	NONTERRITORIAL (N = 111)	DEGREE OF FREEDOM (DF), CHI2 - STATISTICS, *P* (LEVEL OF SIGNIFICANCE) = OR, UNADJUSTED ODDS RATIO
Age (years)	71 (59-78)	71.5 (59-78)	71 (59-78)	df 1, chi2 0.08, = .79
Sex; male/female	230 (70)/100 (30)	153 (70)/67 (30)	76 (68.5)/35 (31.5)	df 1, chi2 0.61, = .73
Arterial hypertension	199 (60.3)	116 (52.9)	83 (74)	df 1, chi2 14.6, = .0001
				OR 0.37 (0.22-0.62)
Diabetes mellitus	77 (23.3)	51 (17.5)	26 (23.4)	df 1, chi2 0.003, = .98
Dyslipidemia	258 (78.1)	164 (74.8)	94 (84.6)	df 1, chi2 3.05, = .06
				OR 0.54 (0.30-1.00)
Body mass index (kg/m^2)	25.7 (23.2-28.7)	25.5 (23.3-28.3)	25.8 (22.9-29.4)	df 1, chi2 0.37, = .54
Metabolic syndrome	42 (12.7)	25 (11.4)	17 (15.3)	df 1, chi2 1.00, = .31
Atrial fibrillation	57 (17.2)	44 (20.0)	13 (11.7)	df 1, chi2 3.56, = .06
				OR 1.89 (0.96-3.67)
Ischemic heart disease	70 (21.2)	43 (19.6)	27 (24.3)	df 1, chi2 0.72, = .32
Left ventricular ejection fraction <50%	59 (17.8)	41 (18.7)	18 (16.2)	df 1, chi2 0.17, = .64
Hs-cTnT (ng/l)	11 (7-20.5)	12 (7-26)	11 (6-16)	df 1, chi2 4.64, = .03
NIHSS at entry	3 (1-7.5)	5 (2-11)	2 (0-3)	df 1, chi247.9, = .0000
CTP-core (ml)	0 (0-0)	0 (0-9) [Mean ± SD 8.61 ± 18.4]	0 (0-0) [Mean ± SD 4.46 ± 16.8]	df 1, chi2 37.8, = .0000
Stroke etiology	106 (32.1)	106 (48.4)	6 (5.4)	df 4, chi2 147.02, = .0000
-Cardioembolic	53 (16.0)	47 (21.4)	57 (51.3)	= .0001 (OR 4.78 [1.97-11.57])
-Large vessel disease	57 (17.2)	0 (0)	1 (0.9)	= .01 (OR 3.02 [1.27-7.28])
-Lacunar	9 (2.7)	8 (3.6)	47 (42.3)	= .17
-Others	105 (31.8)	58 (26.4)		= .004
-Undetermined source				OR 0.49 (0.30-0.79)
mRs3month	1 (0-2)	1 (0-3)	0 (0-1)	df 1, chi2 21.2, = .00002
mRs3month (1-5), n = 320	0 (0-2)	1 (0-2)	0 (0-0)	df 1, chi216.71, = .0001
mRs3month (1-6), n = 336 mRs3month ≤2/>2	270/64	169/57	103/7	OR for mRs >2
				Including death
				4.9 (2.18-11.29)
				= .0001
				Excluding death
				OR 4.4 (1.84-10.85)
				= .0001

Values are presented as absolute numbers and percentages (%), or as medians (interquartile range). The infarct size measured on CTP was significantly different; thus, we also provide the mean ± standard deviation (SD) of the infarct volumes to illustrate these differences. Chi2, chi-squared statistic; Hs-cTnT, high-sensitivity cardiac Troponin T; NIHSS, National Institute of Health Stroke Scale; CTP, cranial computed tomography perfusion; mRs3month, modified Rankin score at 3 months after the stroke; Large vessel disease, extracranial atherosclerotic obstructive carotid artery disease (>50% occlusion).

Table 2. Baseline variables and outcome dichotomized into modified Rankin scale score ≤2 vs > 2. The odds ratios (OR) are given for categorical variables and indicate the likelihood for mRs >2.

	MRS ≤2 (N = 270)	MRS >2 (N = 60)	P (LEVEL OF SIGNIFICANCE) = DEGREE OF FREEDOM (DF), CHI2-STATISTIC, OR, UNADJUSTED ODDS RATIO (95% CI)
Age	70 (58-77)	76 (66-83)	.0001 (df 1, chi2 12.68)
Sex (male/female)	192 (71.1)/78 (28.9)	38 (63.3)/22 (36.7)	.35
Arterial hypertension	159 (58.8)	44 (73.3)	.12
Diabetes mellitus	59 (21.8)	19 (31.6)	.19
Dyslipidemia	211 (78.1)	47 (78.3)	.84
Body mass index (kg/m^2)	25.7 (15.6-36.7)	25.0 (18.6-32.3)	.56
Metabolic syndrom	32 (11.8)	10 (16.6)	.31
Atrial fibrillation	43 (15.9)	14 (23.3)	.10
Ischemic heart disease	51 (18.8)	19 (31.6)	.03 (df 1, chi2 4.79) OR 1.99 (1.06-3.71)
Left ventricular ejection fraction <50%	26 (9.6)	11 (18.3)	.06 OR (2.10 [0.97-4.54])
Territorial infarct	170 (62.9)	49 (81.6)	= .006 (df 1, chi2 14.42) OR 2.62 (1.30-5.27)
Intravenous thrombolysis	88 (32.5)	32 (53.3)	.002 (df 1, chi2 9.12) OR 2.36 (1.34-4.16)
Mechanical thrombectomy	29 (10.7)	32 (53.3)	.0000 (df 1, chi2 59.10) OR 9.49 (5.02-17.9)
Hs-cTnT (ng/l)	11 (6-18)	18 (10-32)	.0004 (df 1, chi2 12.22)
NIHSS at entry	2 (1-11)	14 (3-27)	.0000 (df 1, chi2 101.54)
CTP-core (ml)	0 (0-0)	7 (0-26)	.0000 (df 1, chi2 259.34)
Stroke etiology -Cardioembolic -Large vessel disease -Lacunar -Others -Undetermined source	79 (29.2) 43 (15.9) 52 (19.2) 7 (2.5) 90 (33.3)	27 (45) 10 (16.6) 5 (8.3) 2 (3.3) 15 (25)	.004 (df 4, chi2 15.11) .02 (OR 1.97 [1.11-3.50]) .84 .05 (OR 0.39 [0.14-1.02]) .66 .22

Values are presented as absolute numbers and percentages (%), or as medians (interquartile range). Chi2, chi-squared statistic; Hs-cTnT, high-sensitivity cardiac Troponin T; NIHSS, National Institute of Health Stroke Scale; CTP, cranial computed tomography perfusion; mRs3month, modified Rankin scale score at 3 months after the stroke event; Large vessel disease, extracranial atherosclerotic obstructive carotid artery disease (>50% occlusion).

stroke origin group L (OR 0.006, 95%CI 0.0006-0.05; P = .0001). However, hs-cTnT levels were not significantly different between the 2 groups.

Outcome

Compared to the patients with a good clinical outcome (mRs ≤2), those with a poorer outcome (mRs >2) were significantly older, had a higher rate of ischemic heart disease, were more likely to receive either IVT or MT, had a higher hs-cTnT, a higher NIHSS core at entry, and a larger infarct core on CTPI. Overall, stroke etiology was significantly related to outcome, with CE being significantly linked to poor prognosis, while L was associated with a favorable outcome (by trend).

To evaluate whether hs-cTnT can predict outcome, we included age, ischemic heart disease, frequency of left ventricular ejection fraction <50%, IVT, MT, hs-cTnT, the presence of a territorial infarction at the stroke event, the NIHSS score at entry, the CTP infarct core, and the stroke origin groups CE and L as the independent variables, and the dichotomized mRs score at 3 months as the dependent variable in the multinomial logistic regression model. The likelihood of a poorer mRs score increased with age (adjusted OR 1.04, 95%CI 1.02-1.06 per year, P = .02), the hs-cTnT serum level (OR 1.003, 95%CI 1.001-1.005, per ng/l; P = .03), and the NIHSS score at entry (OR 1.34, 95%CI 1.23-1.47 per scale point; P = .0000). A trend toward poorer outcome was observed for MT (OR 1.53, 95%CI 0.94-2.48,

P = .08) and for the stroke origin group CE (OR 2.74, 95% CI 0.96-7.92, P = .06).

dCA assessment

Apart from the coherence observed in the VLF range, no significant differences were observed between patients with and without hs-cTnT elevation (Table 3). In the regression analysis, hs-cTnT levels did not predict any dCA parameters (Table 4).

Discussion

Regarding common stroke risk factors, the group with territorial infarctions did not differ from the non-territorial infarction group. The number of AF was higher in the territorial stroke group; however, this difference was not statistically significant. The larger infarct size, higher number of clinically classified cardioembolic stroke origins, and elevated hs-cTNT levels in the territorial group suggest that the number of detected AF cases may have been underestimated and could be higher if recent electrocardiographic advancements had been incorporated into the initial cardiac evaluations.[25,26] In the univariate analysis, hs-cTnT levels were significantly increased in the territorial infarct group, indicating that cardiac diseases are involved in the etiology of territorial strokes. It is well established that stroke outcomes are influenced by factors such as age and initial stroke severity, and our results further confirm this. Our findings also confirm that hs-cTnT serves as an independent risk marker for outcome prediction. However, it is worth considering whether this result holds in the multivariate model, given the presence of various cardiac conditions and the strong statistical influence of age and NIHSS score at entry.

The first hypothesis of our study was that elevated hs-cTnT levels are associated with territorial brain infarctions. We found an association between hs-cTnT level and territorial infarctions, primarily driven by its link to cardioembolism. This is consistent with previous studies.[9,10] Nevertheless, nearly half of our stroke cases, classified clinically as cardioembolic in origin, did not exhibit elevated serum hs-cTnT levels. The high number of embolic infarct patterns in the SUO group suggests a cardiac origin, yet only about 30% of the patients in this group had elevated troponin levels. A similar observation of a high number of embolic strokes of undetermined source (ESUS) patients without hs-cTnT elevation was reported by Yaghi et al.[9] This indicates that other proximal embolic sources, such as

Table 3. Dynamic cerebral autoregulation (dCA) parameter coherence, phase, and gain in patients with and without elevated high-sensitivity cardiac Troponin T (hs-cTnT) levels.

DCA PARAMETER	HS-CTNT ≤14 NG/L	HS-CTNT >14 NG/L	KRUSKAL–WALLIS TEST
AHCohVLF	0.58 (0.50-0.69)	0.55 (0.48-0.66)	df 1, chi2 4.32, = .03
AHCohLF	0.65 (0.54-0.78)	0.64 (0.50-0.74)	df 1, chi2 2.13, = .14
AHCohHF	0.68 (0.58-0.76)	0.66 (0.54-0.76)	df 1, chi2 0.28, = .59
AHPhaseVLF	0.82 (0.54-1.06)	0.76 (0.55-0.96)	df 1, chi2 1.98, = .15
AHPhaseLF	0.65 (0.44-0.82)	0.57 (0.43-0.80)	df 1, chi2 1.68, = .19
AHPhaseHF	0.23 (0.05-0.42)	0.17 (0.03-0.37)	df 1, chi2 3.40, = .06
AHGainVLF	0.24 (0.14-0.42)	0.26 (0.16-0.38)	df 1, chi2 0.08, = .77
AHGainLF	0.39 (0.27-0.53)	0.42 (0.28-0.57)	df 1, chi2 1.00, = .31
AHGainHF	0.48 (0.36-0.64)	0.52 (0.37-0.69)	df 1, chi2 1.38, = .23
UHCohVLF	0.56 (0.48-0.67)	0.55 (0.50-0.65)	df 1, chi2, 0.01, = .91
UHCohLF	0.66 (0.54-0.76)	0.66 (0.52-0.77)	df 1, chi2, 0.03, = .86
UHCohHF	0.66 (0.56-0.77)	0.66 (0.55-0.77)	df 1, chi2, 0.02, = .89
UHPhaseVLF	0.84 (0.57-1.11)	0.82 (0.59-1.03)	df1, chi2, 0.73, = .39
UHPhaseLF	0.64 (0.49-0.85)	0.58 (0.43-0.77)	df 1, chi2, 1.36, = .24
UHPhaseHF	0.24 (0.07-0.44)	0.18 (0.03-0.35)	df 1, chi2, 2.61, = .10
UHGainVLF	0.25 (0.14-0.45)	0.24 (0.13-0.37)	df 1, chi2, 0.26, = .62
UHGainLF	0.43 (0.30-0.58)	0.42 (0.26-0.60)	df 1, chi2, 0.05, = .81
UHGainHF	0.50 (0.40-0.66)	0.53 (0.38-0.72)	df 1, chi2, 0.54, = .56

Values are presented as median (interquartile range). Chi2, chi-squared-test; AH, affected hemisphere; UH, unaffected hemisphere; Coh, coherence; Phase, phase; Gain, gain; VLF, very low frequency; LF, low frequency; HF, high frequency.

Table 4. Regression analysis between high-sensitivity cardiac Troponin T (hs cTnT) and dynamic cerebral autoregulation (dCA) parameter coherence, phase, and gain in the affected and unaffected hemispheres.

HS CTNT VS DCA PARAMETER	REGRESSION ANALYSIS	P (LEVEL OF SIGNIFICANCE) =
AHCohVLF	b = 0.000, r2 = 0.003	.28
AHCohLF	b = 0.000, r2 = 0.002	.32
AHCohHF	b = −0.003, r2 = 0.000	.83
AHPhaseVLF	b = 0.000, r2 = .0004	.71
AHPhaseLF	b = 0.000, r2 = .0003	.62
AHPhaseHF	b = 0.000, r2 = .0001	.52
AHGainVLF	b = 0.000, r2 = .0002	.80
AHGainLF	b = 0.000, r2 = .0001	.87
AHGainHF	b = 0.000, r2 = .0001	.85
UHCohVLF	b = 0.000, r2 = .0001	.86
UHCohLF	b = 0.000, r2 = .0007	.66
UHCohHF	b = 0.003, r2 = .0003	.36
UHPhaseVLF	b = −0.001, r2 = .0008	.13
UHPhaseLF	b = −0.002, r2 = .0004	.30
UHPhaseHF	b = 0.000, r2 = .0000	.94
UHGainVLF	b = −0.001, r2 = .0000	.69
UHGainLF	b = 0.000, r2 = .0004	.76
UHGainHF	B = 0.002, r2 = .005	.23

AH, affected hemisphere; UH, unaffected hemisphere; Coh, coherence; Phase, phase; Gain, gain; VLF, very low frequency; LF, low frequency; HF, high frequency.

atheroembolic stroke from nonobstructive atherosclerotic lesions, might be etiologically relevant in this group. Such assumptions might be supported by recent randomized clinical trials[27,28] that compared anticoagulation with standard care in patients with ESUS, which failed to show a benefit of anticoagulation after patients were stratified according to whether they had elevated hs-cTnT levels.[13] In the LVD and L subgroups, the hs-cTnT levels also increased in a significant number of patients. Elevated hs-cTnT levels have been reported in occlusive carotid artery disease, with only some cases attributed to concomitant heart disease.[29-31] In lacunar stroke, involvement of the temporal insular cortex is very unlikely. Therefore, a cortical autonomic pathway origin, as suggested by the Brain-Heart-Syndrome,[8] is unlikely to explain heart involvement. In the NAVIGATE ESUS trial, a post hoc infarct pattern analysis revealed that approximately 11% of patients with ESUS exhibited subcortical or lacunar strokes,[32] indicating that some lacunar strokes could be of cardioembolic origin.[33] Von Renneberg et al.[34] found a correlation between elevated hs-cTnT levels and more extensive signs of small vessel disease on MRI. The authors suggested that the degree of microcirculatory diseases in the brain, heart, and other atherosclerotic vessels (such as the carotid arteries) may reflect a similar level of microvascular cell damage across these organs. Thus, the role of hs-cTnT in the clinically diagnosed stroke subtypes remains unresolved, including our result that the patients with large vessel occlusion and those without large vessel occlusion did not exhibit significantly different hs-cTnT level (median 11 ng/L in both groups).

dCA

Our second hypothesis was that hs-cTnT levels could predict dCA impairment as brain infarction size increased. dCA reflects the degree of compromised cerebral blood flow regulation.[15] If dCA, assessed within 72 hours post-stroke, remains undisturbed or only slightly impaired, it is considered indicative of smaller infarcts and a better prognosis.[16] However, as dCA impairment worsens, infarct size tends to increase as well, leading to a poorer outcome.[16] We failed to support this hypothesis, likely because of small infarct cores on CTP, a limited number of larger infarcts, or because cardiac damage indicated by hs-cTnT was unrelated to the brain infarct size.

Study limitations

This was a retrospective observational study of a cohort of patients with stroke over a specified time period. An a priori power calculation for group size was not performed. However, using a type I error of 5% and a power of 80%, the estimated sample sizes needed to compare significant differences, such as the frequency of SUO between the 2 outcome groups, would be 39 patients in the mRs >2 group and 118 patients in the mRs ≤2 group. Therefore, we considered our group size to be sufficiently large to obtain reliable results. In our SUO group, we did not find an association between hs-cTnT levels and the cardioembolic stroke pattern. In contrast, Yaghi et al.[4] described such an association in a larger ESUS group. One conclusion could be that, in our SUO group, other stroke causes were predominant rather than cardioembolic ones. Nevertheless, in the cohorts studied by Yaghi et al.[4] and Ahn et al.,[5] which were similar to ours, a substantial number of patients with territorial infarct were hs-cTnT-negative. Thus, diagnosing strokes in this population remains a significant challenge.[35] Another limitation of our study is that we did not consider the insular cortex separately. The concept of "Brain-Heart Syndrome" hypothesizes that brain injury, particularly from events like ischemic stroke, can lead to myocyte damage, potentially through autonomic nervous system pathways. Specifically, lesions in the temporal insular cortex may disrupt these pathways, leading to heart-related issues following a stroke.[3] While the "Brain-Heart Syndrome" remains a topic of discussion, 2 studies failed to identify insular cortex infarcts as independent risk factors for elevated hs-cTnT.[9,10] Hs-cTnT was not trended during hospitalization in about 2/3 of the patients. Thus, we can't provide valid data and decided, therefore, not to report them further. In those patients who had a second hs-cTnT assessment the values were not much different to the first assessment. Future research should explore the pathophysiological mechanisms linking hs-cTnT to stroke outcomes and identify alternative biomarkers that may more effectively predict dCA impairment and subsequent patient prognosis.

Conclusion

In this cohort of patients with mild to moderate acute ischemic stroke in the middle cerebral artery territory, hs-cTnT was associated with territorial infarctions in the univariate analysis but not in the multinomial analysis. Hs-cTnT levels were associated with poor outcomes in the univariate and multinomial analyses. Hs-cTnT levels did not predict dCA impairment. These insights imply that clinicians should exercise caution when interpreting hs-cTnT levels in the context of acute ischemic stroke, recognizing that its predictive value may be limited by the complexity of underlying conditions.

Author contributions

Manuel Bolognese: Investigation, Visualization, Laura Weichsel: Data curation, Validation, Grzegorz Marek Karwacki: Investigation, Resources, Lehel-Barna Lakatos: Formal analysis, Writing - original draft, Mareike Oesterreich: Investigation, Validation, Martin Mueller: Conceptualization, Writing - review & editing.

Ethical statement

Ethical approval

This retrospective cohort study of patients with acute ischemic stroke was approved by the Ethics Committee of Northwest and Central Switzerland (ID 2024-01039), adhered to the Declaration of Helsinki, used good standards of clinical practice, and was part of a larger trial registered at ClinicalTrials.gov (NCT04611672). The patient provided verbal consent.

Consent for publication

All patients or their representatives gave their verbal consent for publication.

ORCID iD

Martin Muller https://orcid.org/0000-0001-5763-5400

REFERENCES

1. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American heart association/American stroke association. *Stroke*. 2021;52:e364-e467. doi:10.1161/STR.0000000000000375
2. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. *Circulation*. 2011;124:2350-2354. doi:10.1161/CIRCULATIONAHA.111.023697
3. McCarthy CP, Yousuf O, Alonso A, Selvin E, Calkins H, McEvoy JW. High-sensitivity troponin as a biomarker in heart rhythm disease. *Am J Cardiol*. 2017;119:1407-1413. doi:10.1016/j.amjcard.2017.01.032
4. Lopez-Ayala P, Nestelberger T, Boeddinghaus J, et al. Novel criteria for the observe-zone of the ESC 0/1h-hs-cTnT algorithm. *Circulation*. 2021;144:773-787. doi:10.1161/CIRCULATIONAHA.120.052982
5. Emdin M, Aimo A, Vergaro G, et al. sST2 predicts outcome in chronic heart failure beyond NT-proBNP and high-sensitivity troponin T. *J Am Coll Cardiol*. 2018;72:2309-2320. doi:10.1016/j.jacc.2018.08.2165
6. Vergaro G, Gentile F, Aimo A, et al. Circulating levels and prognostic cut-offs of sST2, hs-cTnT, and NT-proBNP in women vs. men with chronic heart failure. *ESC Heart Fail*. 2022;9:2084-2095. doi:10.1002/ehf2.13883
7. Gommans DHF, Cramer GE, Fouraux MA, et al. Usefulness of high-sensitivity cardiac troponin T to predict long-term outcome in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2021;152:120-124. doi:10.1016/j.amjcard.2021.04.040
8. Scheitz JF, Erdur H, Haeusler KG, et al. Insular cortex lesions, cardiac troponin, and detection of previously unknown atrial fibrillation in acute ischemic stroke: insights from the troponin elevation in acute ischemic stroke study. *Stroke*. 2015;46:1196-1201. doi:10.1161/STROKEAHA.115.008681
9. Yaghi S, Chang AD, Ricci BA, et al. Early elevated troponin levels after ischemic stroke suggests a cardioembolic source. *Stroke*. 2018;49:121-126. doi:10.1161/STROKEAHA.117.019395
10. Ahn SH, Lee JS, Yun MS, et al. Explanatory power and prognostic implications of factors associated with troponin elevation in acute ischemic stroke. *J Stroke*. 2023;25:141-150. doi:10.5853/jos.2022.02012
11. Kuczynski AM, Rzyczniak G, Cheong GHL, Famiyeh P, Vyas MV. Association between stroke severity and serum troponin in acute stroke. *Can J Neurol Sci*. 2023;Dec 6:1-3. doi:10.1017/cjn.2023.323
12. Broersen LHA, Stengl H, Nolte CH, et al. Association between high-sensitivity cardiac troponin and risk of stroke in 96 702 individuals: a meta-analysis. *Stroke*. 2020;51:1085-1093. doi:10.1161/STROKEAHA.119.028323
13. Scheitz JF, Pare G, Pearce LA, et al. High-sensitivity cardiac troponin T for risk stratification in patients with embolic stroke of undetermined source. *Stroke*. 2020;51:2386-2394. doi:10.1161/STROKEAHA.120.029628
14. Hellwig S, Ihl T, Ganeshan R, et al. Cardiac troponin and recurrent major vascular events after minor stroke or transient ischemic attack. *Ann Neurol*. 2021;90:901-912. doi:10.1002/ana.26225

15. Nogueira RC, Aries M, Minhas JS, et al. Review of studies on dynamic cerebral autoregulation in the acute phase of stroke and the relationship with clinical outcome. *J Cerebr Blood Flow Metabol*. 2022;42:430-453. doi:10.1177/0271678X211045222
16. Beishon L, Vasilopoulos T, Salinet ASM, et al. Individual patient data meta-analysis of dynamic cerebral autoregulation and functional outcome after ischemic Stroke. *Stroke*. 2024;55(5):1235-1244. doi:10.1161/STROKEAHA.123.045700
17. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH stroke scale using video training. NINDS TPA stroke study group. *Stroke*. 1994;25:2220-2226. doi:10.1161/01.str.25.11.2220
18. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-607. doi:10.1161/01.str.19.5.604
19. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35-41. doi:10.1161/01.str.24.1.35
20. Lakatos L, Bolognese M, Müller M, Österreich M, von Hessling A. Automated supra- and in-fratentorial brain infarct volume estimation on diffusion weighted imaging using the RAPID software. *Front Neurol*. 2022;13:907151. doi:10.3389/fneur.2022.907151
21. Fazekas F, Barkhof F, Wahlund LO, et al. CT and MRI rating of white matter lesions. *Cerebrovasc Dis*. 2002;13(Suppl 2):31-36. doi:10.1159/000049147
22. Del Sette M, Eliasziw M, Streifler JY, Hachinski VC, Fox AJ, Barnett HJ. Internal borderzone infarction: a marker for severe stenosis in patients with symptomatic internal carotid artery disease. For the North American Symptomatic Carotid Endarterectomy (NASCET) Group. *Stroke*. 2000;31:631-636. doi:10.1161/01.str.31.3.631
23. Müller M, Österreich M, von Hessling A, Smith RS. Incomplete recovery of cerebral blood flow dynamics in sufficiently treated high blood pressure. *J Hypertens*. 2019;37:372-379. doi:10.1097/HJH.0000000000001854
24. Panerai RB, Brassard P, Burma JS, et al. Transfer function analysis of dynamic cerebral autoregulation: a CARNet white paper 2022 update. *J Cerebr Blood Flow Metabol*. 2023;43:3-25. doi:10.1177/0271678X221119760
25. Hayıroğlu Mİ, Çınar T, Selçuk M, et al. The significance of the morphology-voltage-P-wave duration (MVP) ECG score for prediction of in-hospital and long-term atrial fibrillation in ischemic stroke. *J Electrocardiol*. 2021;69:44-50. doi:10.1016/j.jelectrocard.2021.09.006
26. Korkmaz Y, Hayıroğlu Mİ, Selçuk M, et al. Evaluation of cardiac-electrophysiological balance according to National Institutes of Health Stroke Scale score at admission and discharge in acute ischemic stroke patients: a pilot study. *Rev Assoc Med Bras*. 2022;68:1441-1446. doi:10.1590/1806-9282.20220574
27. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med*. 2018;378(23):2191-2201. doi:10.1056/NEJMoa1802686
28. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med*. 2019;380:1906-1917. doi:10.1056/NEJMoa1813959
29. Pereira-Macedo J, Rocha-Neves JP, Dias-Neto MF, Andrade JPV. Prognostic effect of troponin elevation in patients undergoing carotid endarterectomy with regional anesthesia - a prospective study. *Int J Surg*. 2019;71:66-71. doi:10.1016/j.ijsu.2019.09.015
30. Nagy B, Engblom E, Matas M, et al. Increased serum level of high sensitivity troponin T even prior to surgery can predict adverse events during carotid endarterectomy. *Vascular*. 2021;29:938-944. doi:10.1177/1708538120986297
31. Kotsis T, Christoforou P, Tsekoura D, Nastos K. Eversion carotid endarterectomy: cardiac troponin assessment. *Int J Angiol*. 2022;32:100-105. doi:10.1055/s-0042-1743254
32. Sharma M, Smith EE, Pearce LA, et al. Frequency and patterns of brain infarction in patients with embolic stroke of undetermined source: NAVIGATE ESUS trial. *Stroke*. 2022;53:45-52. doi:10.1161/STROKEAHA.120.032976
33. Zito M, Muscari A, Marini E, Di Iorio A, Puddu GM, Abate G. Silent lacunar infarcts in elderly patients with chronic non valvular atrial fibrillation. *Aging*. 1996;8:341-346. doi:10.1007/BF03339591
34. von Rennenberg R, Siegerink B, Ganeshan R, et al. High-sensitivity cardiac troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke. *J Neurol*. 2019;266:37-45. doi:10.1007/s00415-018-9085-3
35. Albers GW, Bernstein R, Brachmann J, et al. Reexamination of the embolic stroke of undetermined source concept. *Stroke*. 2021;52:2715-2722. doi:10.1161/STROKEAHA.121.035208