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Original Research

Hyperacute Incidental Late Myocardial Enhancement in Ischemic Stroke Using Chest Spectral CT: Relationship with Etiology

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Abstract

Background: Hyperacute cardiac imaging of patients with acute ischemic stroke (AIS), though desirable, is impractical. Using delayed-enhancement, low-dose, non-gated, chest spectral computed tomography scans (DESCT), we explored the prevalence and patterns of incidental myocardial late iodine enhancement (LIE) and embolic sources, and their relationship with stroke etiology. **Methods**: Since July 2020, DESCT was performed after cerebrovascular CT angiography (CTA) among patients with suspected AIS undergoing CT using a dual-layer spectral scanner, without additional contrast administration. Images were analyzed using monoenergetic reconstructions and iodine density maps, and the myocardial extracellular volume fraction (ECV, %) was calculated. **Results**: Eighty patients with AIS were included. DESCT identified a cardiac thrombi in 6 patients (7.5%), and a complex aortic plaque in 4 (5%) cases; reclassifying 5 embolic strokes of uncertain source (28% of ESUS) to cardioembolic (CE, n = 3) and non-CE (n = 2) etiologies. LIE was identified in 38 (48%) patients, most commonly (82%) of ischemic pattern. We did not identify significant relationships between AIS etiology and the presence, pattern, and extent of LIE ($p > 0.05$); ECV ($p = 0.56$), severe aortic ($p = 0.25$) or valvular ($p = 0.26$) disease, or the extent of coronary calcification ($p = 0.39$). Patients with evidence of major cardiovascular DESCT findings had higher rates of all-cause death at 90 days (42% vs. 19%, $p = 0.037$). **Conclusions**: In this study, hyperacute cardiac imaging of AIS with DESCT identified a high prevalence of incidental cardiac disease predominantly involving LIE of ischemic etiology and mostly not related to the stroke etiology.

Keywords: embolic stroke; cardiac disease; cardiovascular computed tomography; myocardial delayed-enhancement; dual energy

1. Introduction

Recently, we reported in a preliminary investigation the potential usefulness of delayed-enhancement, low-dose, non-gated, chest spectral computed tomography scans (DESCT) for the early triage of cardioembolic sources (CES) in acute ischemic stroke (AIS) [1]. Such unsophisticated approach might be useful amid the COVID-19 pandemic context, given the limited healthcare personnel and resources. However, since approximately 40% of patients admitted with AIS usually require advance cardiac imaging to rule out CES, the usefulness of such tool might transcend the pandemic [1,2].

In parallel, aside from the need to establish the presence of CES and determining stroke etiology as early as possible to enable early onset of appropriate treatment strategies such as antithrombotic therapy; the identification of myocardial disease, particularly of myocardial infarcts (MI), is important given the close relationship between AIS and myocardial injury both as a consequence, cause, or as a prognostic marker of stroke [3–6].

Hyperacute advanced cardiac imaging of patients admitted with AIS, though desirable, is impractical. We therefore sought to explore, by means of DESCT performed immediately after cerebrovascular CT angiography (CTA) among patients with AIS, the prevalence and patterns of incidental myocardial late iodine enhancement (LIE) and of CES, and their relationship with stroke etiology.

2. Methods

Since the COVID-19 pandemic onset, patients admitted in our emergency department underwent low-dose chest CT and since July 2020, among patients with suspected AIS, the same scan was performed after CTA with the main attempt to simultaneously rule out cardiovascular thrombotic complications using the same scan. All DESCT scans were performed using a dual-layer spectral CT (IQon Spectral CT, Philips Medical Systems Nederland B.V.). Details regarding DESCT scan acquisition protocol and analysis have been previously reported [1]. Despite some population overlap must be acknowledged with such previous smaller study, there are significant differences between studies including the objectives (former study aimed at evaluating CES and without clinical follow-up) and analyses (current study including detailed analysis of LIE, extracellu-

lar volume, clinical follow-up, and discrimination of embolic stroke of uncertain source after complete diagnostic workup; ESUS).

In brief, the diagnostic algorithm of patients with suspected AIS undergoing CT comprised a non-contrast brain CT (ruling out contraindications for intravenous tPA, if indicated), cerebrovascular CTA with or without brain perfusion at discretion of the attending physician and according to the time since symptoms onset, and a non-contrast, low radiation dose chest CT (64 $\times$ 0.625 mm; voltage 120 kV; current 70–140 mA; gantry speed 270 ms; pitch 1.23; slice thickness 2.0 mm) aimed at 5 minutes after contrast injection (DESCT). In our institution, all patients with suspected AIS undergoing CTA with or without CT perfusion are quantitatively assessed online using an automated software (RAPID, iSchemaView, Menlo Park, CA, USA), that provides automatic detection of intracranial hemorrhage, Alberta Stroke Program Early CT Score (ASPECTS), large vessel occlusion, and perfusion maps in order to discriminate the ischemic core (relative cerebral blood flow $<$30%) from areas of penumbra (Tmax $>$6 s). Such information enables the quantification of the mismatch ratio and volume of penumbra, which is henceforth used to assist the indication of mechanical thrombectomy in patients with large vessel occlusion, mainly in an extended window. Since this process takes between 5 and 10 minutes after contrast administration, DESCT does not delay endovascular therapy. All images were analyzed using dedicated software (IntelliSpace Portal version 11.1; Philips Medical Systems Nederland B.V.) by an observer with experience in dual energy cardiac CT blinded to the clinical history, demographical characteristics, and stroke etiology. Images were specifically analyzed offline for this study, although online information regarding the presence of embolic sources was provided if requested by the Stroke unit treating physician. Images were evaluated using low (40–50 keV) monoenergetic imaging and iodine-based results. Average multiplanar reconstructions (initially using thin-slab reconstructions and gradually increasing up to 8 mm if necessary) were used adjusting width and level at discretion to each specific energy level. Myocardium LIE was defined as areas with focal increase of signal attenuation compared to the normal myocardium or areas with clear interruption of the non-enhanced myocardium (Fig. 1) [7]. Thrombus was defined as an abrupt filling defect with absence or non-significant contrast enhancement, clearly discriminated from surrounding structures involving high or intermediate contrast uptake such as blood and myocardial or vessel walls (Fig. 2) [8,9]. Regions of interest (ROI) were manually traced at the septal wall in a short axis view within an area showing the greatest myocardial thickness and avoiding the myocardium periphery, areas with significant artifacts, or with poor endocardial definition. Blood pool iodine content was calculated by placing a circular ROI at the left ventricular cavity within the same image, avoiding papillary muscles (Fig. 3). Myocardial extracellular volume (ECV), a surrogate marker of diffuse myocardial fibrosis, was calculated at the septal wall using the same-day haematocrit, using the following formula: (1-Ht)* (Iodine$_{myocardium}$/Iodine$_{blood}$). Myocardial iodine ratio was calculated as Iodine$_{myocardium}$/Iodine$_{blood}$ (Fig. 3) [10–14]. Using 5-point Likert scales, the confidence degree for excluding CES and LIE was also evaluated, assigning a score of 1 if non-assessable and a score of 5 if deemed of excellent quality. Left atrial area was manually traced using axial views at the image showing the maximal left atrial area, excluding the pulmonary veins and the left atrial appendage. Left atrial dilatation was defined as an area larger than 26.8 cm^2, as previously reported [15]. We evaluated the presence of major cardiovascular DESCT findings defined as the presence of any of the following: cardiac thrombi or $>$4 mm non-calcified plaque at the ascending aorta or aortic arch, extensive ($>$2 segments) LIE, severe aortic disease ($>$4 mm non-calcified plaque or severe concentric calcification), severe valvular calcification, ventricular dilatation (diameter $>$55 mm), left atrium dilatation (area $>$26.8 cm^2), or extensive ($>$5 segments) coronary artery calcification. Using electronic health records, patients were grouped according to the stroke etiology as follows: non-cardioembolic (non-CE), cardioembolic (CE), and embolic stroke of undetermined etiology (ESUS). Non-CE strokes comprised patients with great vessel atherosclerosis, small-vessel occlusion, unusual causes, or undetermined cause with incomplete diagnostic workup.

Patients in whom DESCT identified a cardiac embolic source were reclassified as CE whereas those with a complex (ascending or arch) aortic plaque were reclassified as non-CE. Within our Stroke unit, a minimum 48-hour telemetry including recording and atrial fibrillation alarm is performed in all patients. The data that support the findings of this study are available upon reasonable request.

Continuous data were reported as means $\pm$ standard deviation, or as median (interquartile range, IQR) in case of non-uniform distribution, and categorical variables were reported as frequencies and percentages. Differences between groups were assessed using one-way analysis of variance for continuous variables, and chi-square tests for categorical variables. Differences between groups with non-parametric distribution were evaluated using Kruskal-Wallis tests. A two-sided p value of less than 0.05 indicated statistical significance. Statistical analyses were performed using SPSS software, version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA).

3. Results

3.1 Study Population

Between July 2020 and January 2021, 80 patients (Table 1) with AIS who underwent DESCT after cerebrovascular CTA were included, with a baseline median National Institutes of Health Stroke Scale (NIHSS) of 10 (2–18). Fifty-

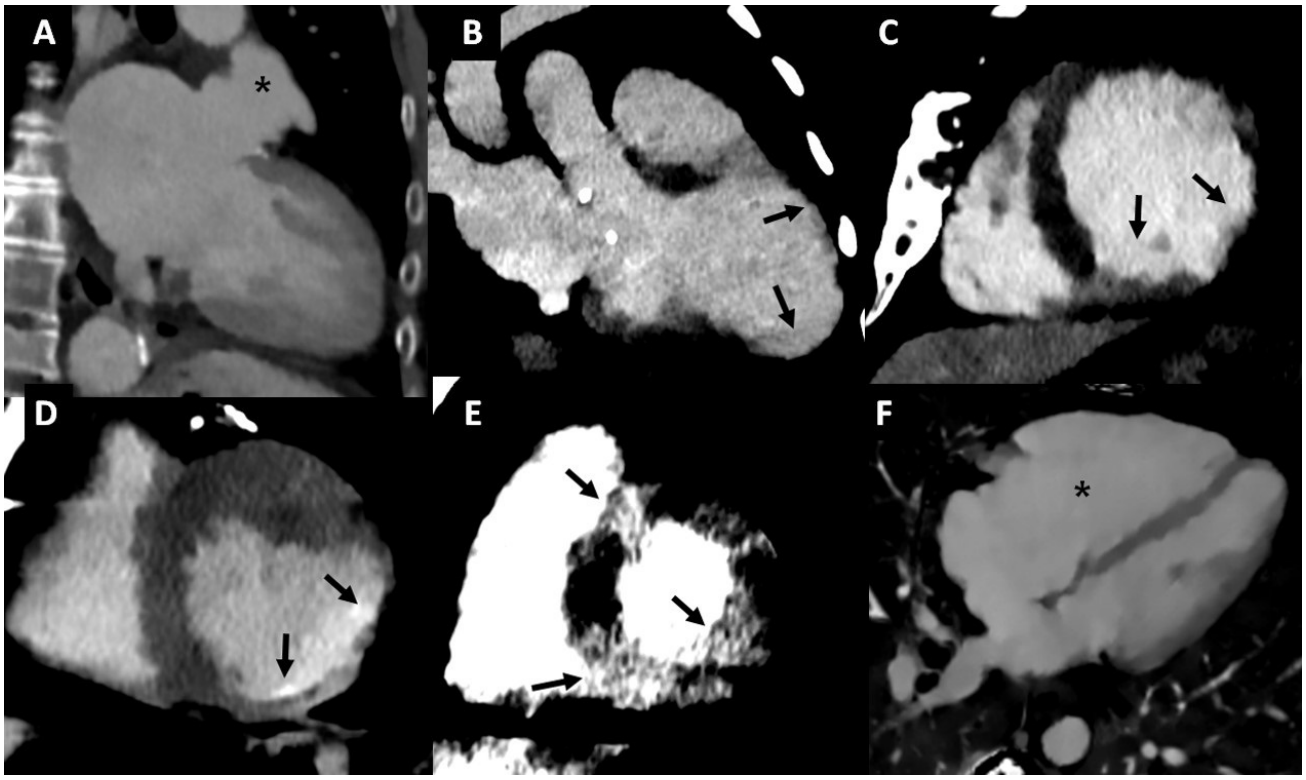

Fig. 1. Late iodine enhancement and ruling out of cardiac thrombi. (A) Left atrial dilatation without left atrial appendage thrombus (*). (B–D) Myocardial infarcts (arrows). (E) Non-ischemic late iodine enhancement (arrows). (F) Marked dilatation of the right cardiac chambers (*), leading to diagnosis of atrial septal defect.

nine (74%) patients also underwent brain CT perfusion. The mean age was 70.9±15.2 years, with no significant differences between etiological groups (non-CE 68.9 ± 16.0 years, CE 73.9 ± 13.3 years, ESUS 65.5 ± 16.2 years, p = 0.18). Eleven (14%) patients had a previous history of MI and 17 (22%) atrial fibrillation. Five patients (6%) had increased cardiac enzyme levels (troponin T >40 U/L) upon admission. Thirty-seven (46%) patients underwent reperfusion treatment, of which only one received intravenous tPA, 10 intravenous tPA plus mechanical thrombectomy, and the rest direct mechanical thrombectomy. Metrics comprised a median onset of symptoms at admission of 118 minutes (IQR 77–363 minutes), median onset of symptoms at imaging of 132 minutes (IQR 98–415 minutes), median onset of symptoms at intravenous tPA of 173 minutes (IQR 135–191 minutes), and a median onset of symptoms to groin of 205 minutes (IQR 132–470 minutes).

3.2 DESCT Cardiovascular Findings

DESCT involved a low radiation dose protocol comprising a mean radiation dose-length product of 200.0 ± 67.6 mGy*cm and scans were performed at a mean heart rate of 82.0 ± 12.7 bpm. All cases were deemed assessable (Likert ≥2) for ruling out cardiac thrombi, whereas for the identification of LIE DESCT was considered non assessable in 5 cases (6%) and of regular quality in 23 (20%) cases. The mean confidence degree for the identification of cardiac thrombi was significantly higher than for LIE (Likert 4.6 ± 0.7 vs. 3.2 ± 1.3, $p < 0.0001$).

DESCT identified a cardiac thrombi in 6 patients (7.5%), located at the left atrial appendage (LAA) in 3 cases and at the left ventricle in 3 cases (Table 2 and Fig. 2). Three of these were confirmed with transesophageal echocardiogram (TEE) or cardiac CT and in 3 other cases the Stroke unit decided not to undergo further advanced imaging given the clarity of the DESCT images (Fig. 2, panels A–C). Two LAA thrombi undetected by DECST comprised patients who developed atrial fibrillation later during the same hospitalization and underwent TEE 3 and 4 weeks, respectively, after DESCT. The presence of a complex plaque (Fig. 2) at the ascending aorta/aortic arch was identified in 4 (5%) patients. One patient with ESUS had marked dilatation of the right cardiac chambers (Fig. 1) motivating the search and identification of an atrial septal defect. Based on DESCT findings, 5 (28%) patients with ESUS were reclassified to CE (n = 3) and non-CE (n = 2) etiologies. Overall, patients with CE stroke had a higher prevalence of major DESCT findings (non-CE 42%, CE 80%, ESUS 29%, p = 0.0001).

Table 1. Demographics.

	Total population
Age (years)	70.2 ± 15.3
Male sex (%)	50 (63%)
Systolic blood pressure (mmHg)	160.4 ± 31.7
Diastolic blood pressure (mmHg)	89.2 ± 16.8
Creatinine levels (mg/dL)	1.05 ± 0.4
Glucose levels (mg/dL)	131.4 ± 65.2
NIHSS	10.0 (2.0; 18.0)
NIHSS-24 hours	9.0 (1.0; 19.3)
Diabetes (n, %)	15 (19%)
Hypertension (n, %)	66 (84%)
Hypercholesterolemia (n, %)	25 (32%)
Smoking (n, %)	16 (13%)
Obesity (n, %)	12 (15%)
Atrial fibrillation (n, %)	17 (22%)
Previous myocardial infarction (n, %)	11 (14%)
Previous stroke (n, %)	14 (18%)

NIHSS, National Institutes of Health Stroke Scale.

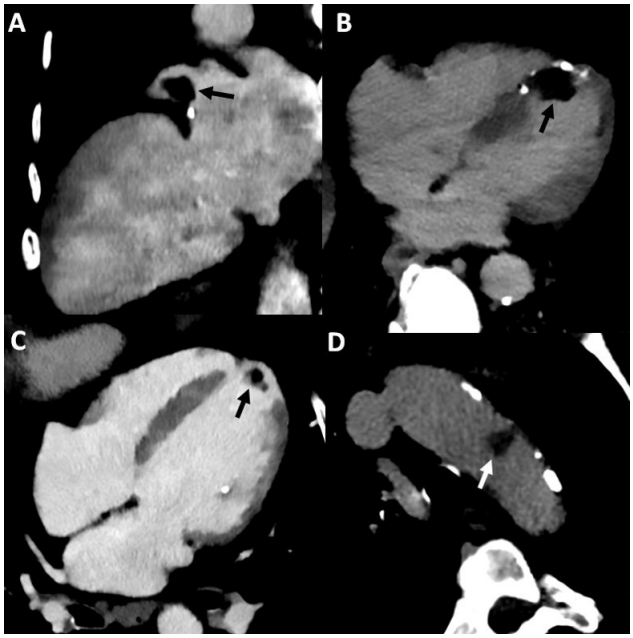

Fig. 2. Identification of embolic sources. (A) Large left atrial appendage thrombus (arrow). (B,C) Left ventricular thrombus (arrows). (D) Aortic arch thrombi (arrow).

3.3 Myocardial Late Iodine Enhancement Patterns

Myocardial LIE (Fig. 1) was identified in 38 (48%) patients, involving a significant (more than 2 ventricular segments) burden in 19 (24%) cases. The most common (82%) pattern of LIE was ischemic (subendocardial or transmural). We did not identify a relationship between AIS etiology and the presence, pattern, or extent of LIE. The mean myocardial ECV was 33.5 ± 6.7%, with no significant differences between etiologies (non-CE 32.7 ± 6.0%, CE 33.9 ± 8.2%, ESUS 34.9 ± 4.5%, $p = 0.56$).

3.4 Additional Cardiac Findings

Twenty-nine (36%) patients had extensive coronary artery calcification (more than 5 coronary segments). Left atrial dilatation was identified in 24 (30%) cases using DESCT, and was significantly more prevalent in CE stroke (non-CE 17%, CE 57%, ESUS 7%, $p < 0.0001$). Patients with left atrial dilatation did not show evidence of incremented myocardial fibrosis compared to those without left atrial dilatation (iodine ratio 0.58 ± 0.2 vs. 0.54 ± 0.1, $p = 0.13$; ECV 34.6 ± 9.4% vs. 33.1 ± 5.3%, $p = 0.39$).

We did not identify significant differences between stroke etiologies regarding the presence of severe aortic ($p = 0.10$) or valvular ($p = 0.23$) disease, or with respect to the presence and extent of coronary calcification (Table 2). Sixty-six (83%) patients underwent transthoracic echocardiogram (TTE), with a mean left ventricular ejection fraction of 58.7 ± 7.7% and the identification of wall motion abnormalities in only 9 (11%) patients.

3.5 Clinical Outcome

Clinical follow-up data was available in 77 (96%) cases. Among these, 24 (31%) patients died and 40 (52%) had functional independence (modified Rankin scale ≤2) after 90 days. Age and NIHSS scale were the only clinical variables associated with functional dependence and death, whereas the stroke etiology was not related to such adverse outcomes (Table 3). Patients with evidence of major cardiovascular DESCT findings had higher rates of all-cause death at 90 days compared to patients without major findings (42% vs. 19%, $p = 0.037$), and left atrial area evaluated with DESCT was significantly larger among patients with death (26.4 ± 10.3 cm^2 vs. 21.6 ± 6.4 cm^2, $p = 0.04$).

4. Discussion

The main findings of the present observational study can be summarized as follows. Firstly, DESCT identified a high prevalence of cardiac disease among patients with AIS, mostly involving LIE of ischemic etiology. Secondly, DESCT findings reclassified 28% of patients with ESUS. And thirdly, LIE was not related to the stroke etiology. In a pilot investigation, we recently reported a good performance of DESCT for ruling out CES upon admission in patients with AIS undergoing CTA, without the need of additional bolus or incremented iodine contrast administration [1]. This tool, provided that a dual-layer spectral CT scanner is available, comprises a low-dose, non-gated chest CT scan that does not require any modification of the acquisition protocol. Besides, since non-contrast brain CT is performed before contrast injection, the decision to administrate intravenous fibrinolysis, if indicated, is not delayed.

Previous investigations have shown the ability of extending the CTA to cover the ascending aorta and cardiac chambers to rule out cardiac and aortic sources of embolism [16–18]. Though useful, such strategies lead to higher radiation dose and might be prone to significant motion artifacts

Table 2. Hyperacute identification and characterization of comprehensive cardiovascular findings identified by delayed-enhancement, low-dose, non-gated, chest spectral CT scans (DESCT); discriminated by stroke etiology.

	Overall	Non-CE	CE	ESUS	*p* value
	(n = 80)	(n = 36)	(n = 30)	(n = 14)	
DESCT findings					
Embolic sources (n, %)					
LAA thrombi	3 (4%)	0	3 (10%)	0	0.048
Ventricular thrombi	3 (4%)	0	3 (10%)	0	0.048
Complex aortic plaque	4 (5%)	3 (8%)	1 (3%)	0	0.31
Myocardium					
LIE presence	38 (48%)	17 (47%)	15 (50%)	6 (43%)	0.91
Ischemic LIE	31 (82%)	15 (88%)	12 (80%)	4 (67%)	0.49
Non-ischemic/mixed LIE	7 (17%)	2 (12%)	3 (20%)	2 (33%)	
Myocardial iodine ratio	0.55 ± 0.1	0.55 ± 0.1	0.55 ± 0.1	0.59 ± 0.1	0.47
ECV (%)	33.5 ± 6.7	32.7 ± 6.0	33.9 ± 8.2	34.9 ± 4.5	0.56
LA area (cm^2)	23.1 ± 8.0	21.0 ± 6.9	27.1 ± 8.8	19.8 ± 5.4	0.001
LA dilatation (n, %)*	24 (30%)	6 (17%)	17 (57%)	1 (7%)	<0.0001
CAC presence (n, %)	67 (84%)	30 (83%)	27 (90%)	10 (71%)	0.30
CAC n segments	4.3 ± 3.6	3.9 ± 3.6	5.0 ± 3.5	3.7 ± 3.7	0.39
CAC >5 segments	29 (36%)	10 (28%)	13 (43%)	6 (43%)	0.36
Severe aortic disease	6 (8%)	4 (11%)	2 (7%)	0	0.25
Severe valve calcium	6 (8%)	1 (3%)	4 (13%)	1 (7%)	0.26
Transthoracic echocardiography					
LVEF (%)	58.7 ± 7.7	58.6 ± 8.0	58.2 ±9.1	60.2 ± 2.3	0.77
WMA (n, %)	9 (14%)	4 (13%)	5 (21%)	0	0.11
LA area (cm^2)	19.8 ± 5.4	19.7 ± 4.6	21.9 ± 6.2	16.3 ± 4.1	0.013

LAA, left atrial appendage; CE, cardioembolic; ESUS, embolic stroke of uncertain source; LIE, late iodine enhancement; ECV, extracellular volume; LVEF, left ventricular ejection fraction; WMA, wall motion abnormalities. *LA dilatation (>26.8 cm^2).

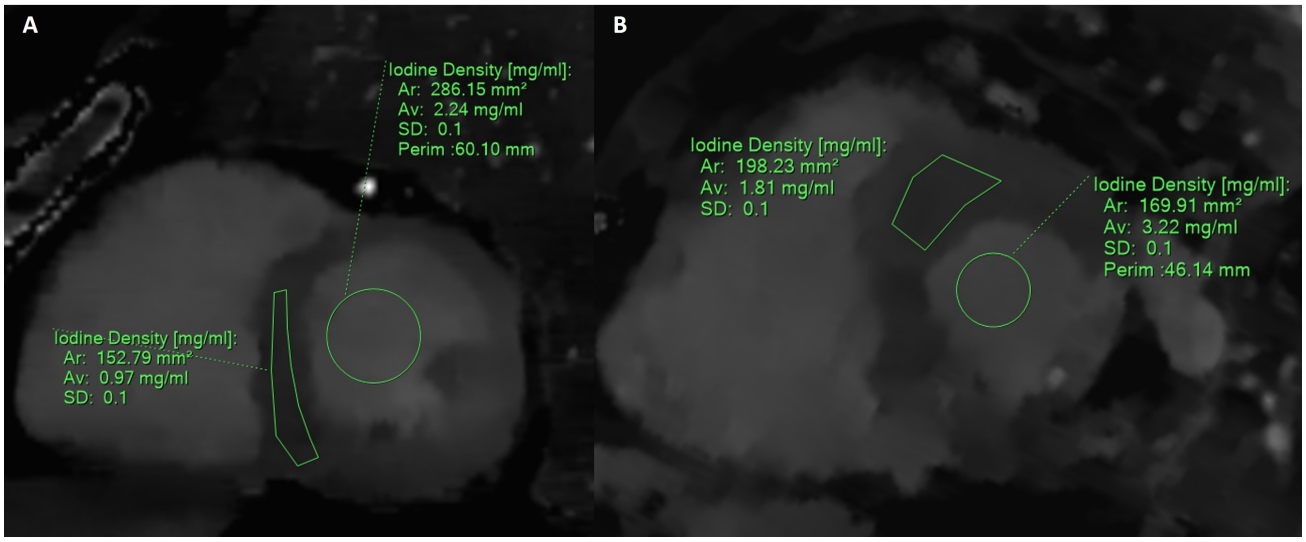

Fig. 3. Regions of interest traced at the septal wall and at the left ventricular cavity in order to measure iodine content (mg/mL). (A) Patient with a myocardial extracellular volume of 24% (based on a haematocrit of 45.5%). (B) Patient with myocardial disease and incremented extracellular volume of 35% (based on a haematocrit of 38.6%).

Table 3. Cardiovascular findings identified by delayed-enhancement, low-dose, non-gated, chest spectral CT scans (DESCT); discriminated by the occurrence of death or functional dependence, among patients with 90-day clinical follow-up.

	Death		*p*	Functional dependence		*p*
	No (n = 53)	Yes (n = 24)		No (n = 40)	Yes (n = 37)	
Age (years)	66.6 ± 15.9	78.4 ± 11.1	0.002	65.7 ± 15.8	75.2 ± 13.8	0.007
NIHSS	7.5 ± 8.0	17.7 ± 9.4	<0.0001	5.3 ± 6.6	16.5 ± 8.9	<0.0001
NIHSS-24 h	6.5 ± 8.2	23.4 ± 12.2	<0.0001	3.4 ± 5.0	20.6 ± 11.7	<0.0001
Etiology:			0.21			0.45
Non-CE	28 (79%)	8 (22%)		21 (58%)	15 (42%)	
CE	16 (57%)	12 (43%)		14 (50%)	14 (50%)	
ESUS	9 (69%)	4 (31%)		5 (39%)	8 (62%)	
DESCT major*	7 (19%)	17 (42%)	0.037	18 (62%)	11 (37%)	0.17
LIE n segments	1.6 ± 2.0	1.1 ± 1.6	0.31	1.6 ± 2.2	1.2 ± 1.6	0.38
CAC n seg	4.2 ± 3.6	4.8 ± 3.6	0.45	4.2 ± 3.8	4.6 ± 3.5	0.64
LA $area_{DESCT}$	21.6 ± 6.4	26.4 ± 10.3	0.04	21.9 ± 5.5	24.5 ± 10.1	0.16
ECV (%)	34.2 ± 0.1	32.6 ± 0.1	0.35	34.0 ± 0.1	33.3 ± 0.1	0.63
$LVEF_{echo}$ (%)	58.5 ± 7.5	58.5 ± 9.4	0.94	58.4 ± 8.4	58.6 ± 6.9	0.91
LA $area_{echo}$	20.1 ± 4.9	20.9 ± 6.2	0.65	20.5 ± 5.2	19.9 ± 4.9	0.64

CE, cardioembolic; ESUS, embolic stroke of uncertain source; *DESCT major refers to major finding; LIE, late iodine enhancement; CAC, coronary artery calcification; LA, left atrium; ECV, extracellular volume; LVEF, left ventricular ejection fraction; NIHSS, National Institutes of Health Stroke Scale.

given that they involve acquisitions with slower gantry rotation and lower pitch compared to DESCT [1]. Moreover, such studies included arterial-phase acquisitions, whereas delayed-phase CTA images improve LAA thrombi given that LAA stasis can be relatively common in these patients [19]. One of the most interesting findings was the documentation of LIE in approximately half of the patients, unrelated to the stroke etiology and mostly of ischemic pattern, including 14% of ESUS with extensive LIE. Whether these patients should be reclassified to CE, as well as those with left atrium dilatation (7%), remains uncertain. Despite only 13 patients underwent cardiac CT to validate such findings, the identification of ischemic LIE particularly when involving more than 2 myocardial segments was feasible and well defined. The ability of such unsophisticated tool for the simultaneous assessment of both CES and myocardial LIE, aside from the improved tissue characterization enabled by spectral imaging, is also partly related to a low exposure time of DESCT, thus decreasing the likelihood of significant cardiac motion artifacts [20].

MI has been unequivocally recognized as a major cause of AIS, related not only to left ventricular thrombus, but also to other diverse mechanisms usually not identified by TTE [3,6]. In this regard, two very large registries have reported an enduring incremented risk of stroke among patients with previous MI [4,6]. In addition, patients with AIS have an increased risk of MI [5,21]. In keeping with this, 39% of the patients included in our study had evidence of ischemic LIE, being extensive in 24%. Although this might seem a high figure, previous studies have shown that silent infarcts are significantly more common than expected [22]. As a counterpart, only 11% of TTE showed wall motion abnormalities. Furthermore, left atrial area evaluated with DESCT but not with TTE was related to mortality, as it was the evidence of major cardiovascular DESCT findings. In parallel, though very rare, during the COVID-19 pandemic a number or reports of concurrent AIS and MI have been published, which might underscore the potential usefulness of our findings in certain clinical scenarios [23].

A number of limitations should be acknowledged. Since DESCT images were analyzed by a specialist with experience in dual energy imaging within a comprehensive stroke center, extrapolation of our results should be cautious. Moreover, since DESCT was not compared to an established standard, findings must be interpreted as exploratory. For the same reason, the 3 cases among whom further testing was not performed given the assuring DESCT findings (Fig. 2) cannot be confirmed. Besides, as an observational study where downstream testing and cardiac diagnostic workup was left at the discretion of the treating physicians, the ability of DESCT to accurately reclassify the stroke etiology and to address whether LIE was cause or consequence of the cerebrovascular insult were not specifically tested and thus cannot be concluded from our findings. Notwithstanding, it is noteworthy that the initial symptom in all patients was a neurologic deficit. In this regard, since the rate of further advanced cardiac imaging (34%) was average, incidental findings such as LIE did not seem to trigger additional testing. Future prospective studies powered for clinical outcomes and cost-effectiveness are warranted.

5. Conclusions

In this study, hyperacute cardiac imaging of AIS by means of DESCT identified a high prevalence of incidental predominantly ischemic cardiac disease, and most findings were not related to the stroke etiology. This tool might potentially aid reclassification of ESUS, although this should be demonstrated in prospective studies.

Author Contributions

GARG, JJC, CC, PL—Conception or design of the study; MLC, LAF, MDB, PD—Data collection; GARG, JJC, CC, PD—Data analysis and interpretation. Critical revision and final approval—All authors.

Ethics Approval and Consent to Participate

All patients or tutors involved provided a written informed consent (habeas data). The study was conducted in accordance with the Declaration of Helsinki and later amendments, and the institutional review board approved this observational registry (TCAT-ACVi-v14oct).

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Conflict of Interest

The authors declare no conflict of interest. Gaston A. Rodriguez-Granillo is serving as one of the Editorial Board members of this journal. We declare that Gaston A. Rodriguez-Granillo had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Peter A. McCullough.

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