

Emerging role of spectral computed tomography in neurocardiology

Lucia Fontana¹, Juan J. Cirio², Pedro Lylyk³, Gaston A. Rodriguez-Granillo^{1,*}

¹Department of Cardiovascular Imaging, Instituto Medico ENER, Clinica La Sagrada Familia, Buenos Aires, Argentina

²Stroke Unit, Instituto Medico ENER, Clinica La Sagrada Familia, Buenos Aires, Argentina

³Department of Interventional Neuroradiology, Instituto Medico ENER, Clinica La Sagrada Familia, Buenos Aires, Argentina

*Correspondence: grodriguezgranillo@gmail.com (Gaston A. Rodriguez-Granillo)

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The complex and reciprocal relationship between the brain and the heart has gained increasing attention under the concept of neurocardiology. Myocardial injury is common in cerebrovascular disease, and cardiovascular complications are the second leading cause of death after stroke. Cardiac computed tomography (CT) is a fast and reliable non-invasive tool for the assessment of cardioembolic sources. Compared to single energy CT, spectral/dual energy cardiac CT improves tissue characterization and also leads to significant reductions in contrast volume. In this review article, we portray the potential clinical applications of spectral CT in neurocardiology, focusing in the enhanced diagnosis of cardioembolic sources and cardiovascular risk assessment of patients with stroke, including improved detection of thrombus, identification of subtle myocardial disease, and pulmonary complications within the same session.

Keywords

Imaging; Dual-energy; Stroke; Embolic; Tako-Tsubo

1. Introduction

The heart and the brain are deeply interrelated both in health and disease, involving diverse physiological and pathophysiological aspects that can lead to brain injury causing myocardial damage and viceversa [1]. Such complex relationship has recently gained attention under the concept of neurocardiology. Myocardial injury is common in cerebrovascular disease, irrespective of preceding cardiac conditions. Indeed, ischemic heart disease is the second leading cause of death in patients with nonfatal (ischemic or hemorrhagic) stroke, and mortality rates related to all cardiovascular diseases is nearly fourfold higher among these patients compared to the general population [2]. Early investigation of the underlying mechanisms of stroke, and particularly the identification of cardioembolic stroke, is important for proper patient treatment as well as to evaluate the possible cardiovascular complications related to clinical outcome.

Cardiac computed tomography (CT) has gained a prominent role as a frontline strategy in low to intermediate risk patients with suspected coronary artery disease [3–5]. Relevant to the field of neurocardiology, cardiac CT provides a reliable, fast, volumetric, non-invasive tool for the assessment of car-

dioembolic sources (Figs. 1–3). These aspects are critical since most patients with stroke have a number of characteristics including impaired sensory that can lead to gastrointestinal and pulmonary complications, which might potentially be worsened or promoted by transesophageal echocardiogram (TEE) [6, 7].

Moreover, a number of cardioembolic sources less amenable for accurate assessment with TEE such as the left ventricular apex, the distal ascending aorta, and subtle myocardial disease can be evaluated with cardiac CT (Figs. 4, 5). Despite this, conventional single energy CT has some technical limitations related to the polychromatic nature of X-rays, which lead to beam hardening artifacts that can obstruct precise tissue characterization, particularly mimicking myocardial perfusion defects [8].

Spectral or dual energy cardiac CT has the ability to mitigate these limitations and improve tissue characterization since it enables enhanced intravascular signal density levels, therefore also leading to significant reductions in contrast volume (Fig. 6) [9–12].

Accordingly, the aim of this review article was to portray the potential clinical applications of spectral CT in neurocardiology, focusing in the diagnosis of cardioembolic sources and cardiovascular risk assessment of patients with stroke.

2. Technical rationale for spectral cardiac CT in neurocardiology

Tissue characterization using conventional CT is based on single-energy X-ray attenuation levels (Hounsfield units). Therefore, tissues with completely different chemical composition such as calcium and iodine can be difficult to discriminate. Spectral or dual energy CT takes advantage of the energy-dependence of X-ray attenuation to achieve an increased contrast attenuation (Fig. 6) and material decomposition, including quantitative assessment [13–15]. Spectral CT can be obtained using different approaches, briefly broken down into source-based (image acquisition with different tube voltage either by ultrafast kV-switching, dual-source scanner, or by splitting the incident X-ray beam) and

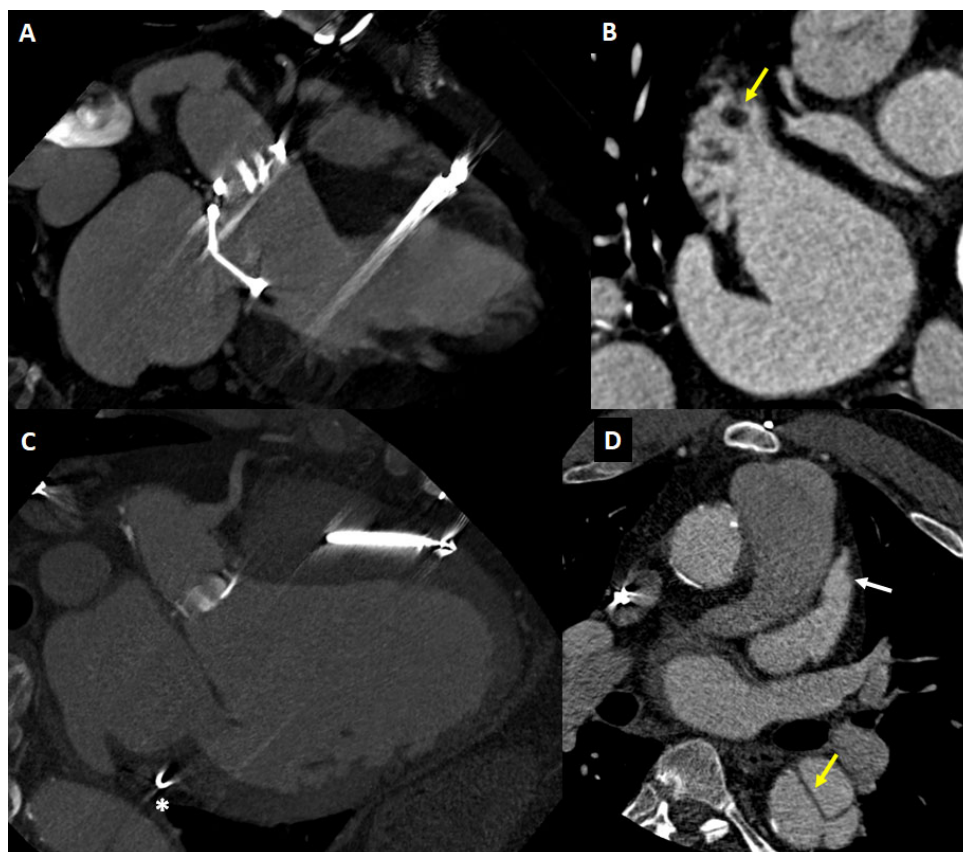


Fig. 1. Complex cases with suspected cardiac embolic causes evaluated with (conventional) cardiac CT. Patient with a cardiac pacemaker and mitral and aortic valve replacements (panels A and B) with identification of a left atrial appendage thrombus (panel B, arrow). Patient (panels C and D) with an aortic replacement and coronary re-implantation due to type-A aortic dissection (yellow arrow in panel D), and a cardiac pacemaker with a resynchronizer (* in panel C). The left atrial appendage in this case is patent (panel D, white arrow).

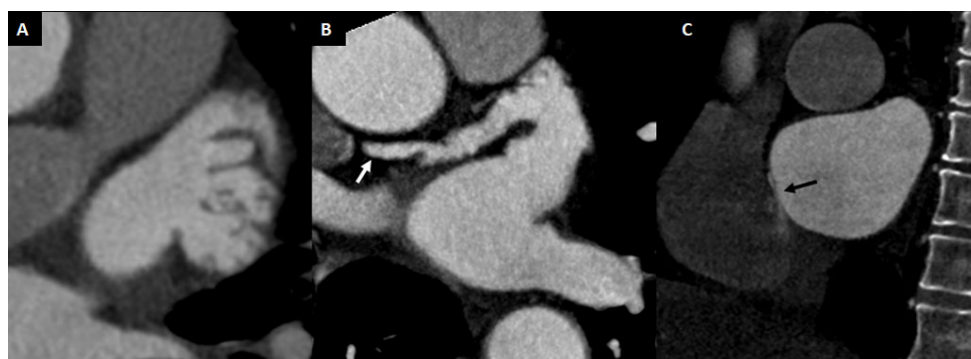


Fig. 2. Examples of the various morphology and complexity of left atrial appendage, including multilobed secondary appendages and prominent pectinate muscles (panel A), and elongated lobes with a distal tip (panel B, arrow). Patent foramen ovale (panel C, arrow) demonstrated with cardiac CT.

detector-based (dual-layer). One of the main differences between these approaches is that detector-based scanners do not require a pre-decision to acquire images in the spectral mode. Regardless of the approach, this technique enables the discrimination between the two mechanisms by which X-rays interact with matter (Compton scatter and photoelectric effect), thereby offering improved tissue characterization. Dual-layer spectral CT uses two layers (*sandwich*) of detec-

tors with different photon-absorption capacity; the top layer detecting low-energy photons and the bottom layer detecting high-energy photons. Accordingly, in addition to conventional (polychromatic) images, two distinct energy data sets are provided thus generating multiparametric data that include virtual monoenergetic imaging (VMI), iodine maps, and virtual non-contrast images among other, aimed at diverse clinical applications [16].

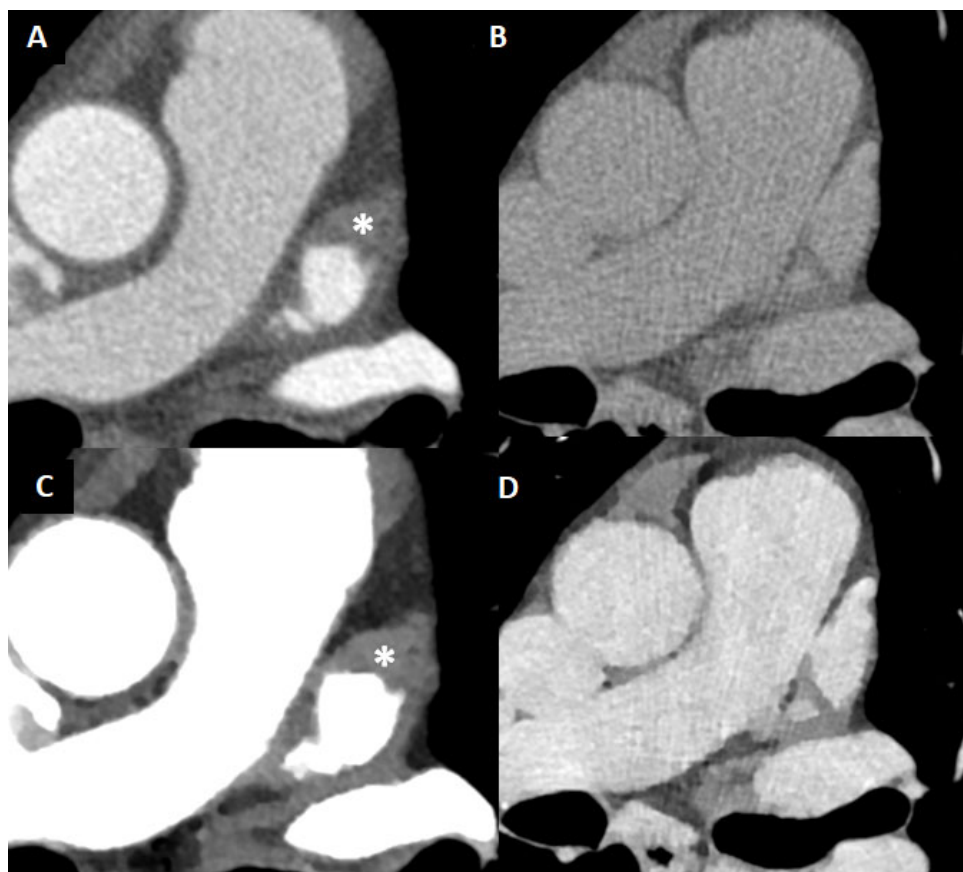


Fig. 3. Usefulness of dual-phase cardiac CT and spectral imaging for the identification of left atrial appendage stasis. Cardiac CT shows an early filling defect at the arterial phase (panel A, conventional CT; panel C, virtual monoenergetic imaging at 40 keV) that resolves at delayed imaging (panel B, conventional CT; panel D, virtual monoenergetic imaging at 40 keV).

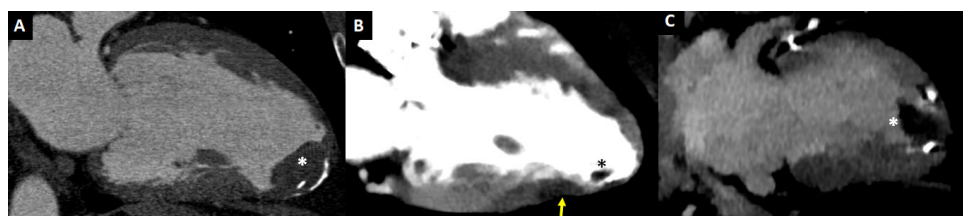


Fig. 4. Examples of left ventricular thrombus (*) in three patients using conventional cardiac CT (panel A); spectral cardiac CT at low monoenergetic imaging [panel B; note the adjacent myocardial perfusion defect (arrow)]; and low-dose, delayed-phase, non-gated, chest spectral CT performed five minutes after cerebrovascular CT angiography in a patient with acute ischemic stroke (panel C).

VMI at low energy levels (40-55 keV) provides great increase in contrast attenuation levels (Fig. 7), thus allowing increased sensitivity for late iodine detection and major reductions in iodinated contrast dose [10, 15]. The latter is clinically relevant in the context of neurocardiology imaging since this population usually involves patients with multiple cardiovascular risk factors at risk of contrast-induced nephropathy [17]. Indeed, state-the-art acute ischemic stroke care generally involves CT angiography and if indicated, invasive angiography; leading to an increased likelihood of acute kidney injury [18]. Besides, low VMI can salvage suboptimal vascular studies resulting from technical errors or contrast ex-

travasation.

In parallel, low-energy VMI enables improved discrimination between tissues, being this an advantage among these patients. On one hand, enabling a better identification of thrombus (Figs. 4-9) including improved discrimination between left atrial appendage (LAA) thrombus and stasis (Figs. 8-10), and the detection of subtle myocardial disease (Figs. 7, 11) [19]. And on the other hand, improving carotid plaque characterization and thus potentially enhancing risk stratification of patients with intermediate carotid stenosis; although this remains to be explored (Fig. 12) [20, 21].

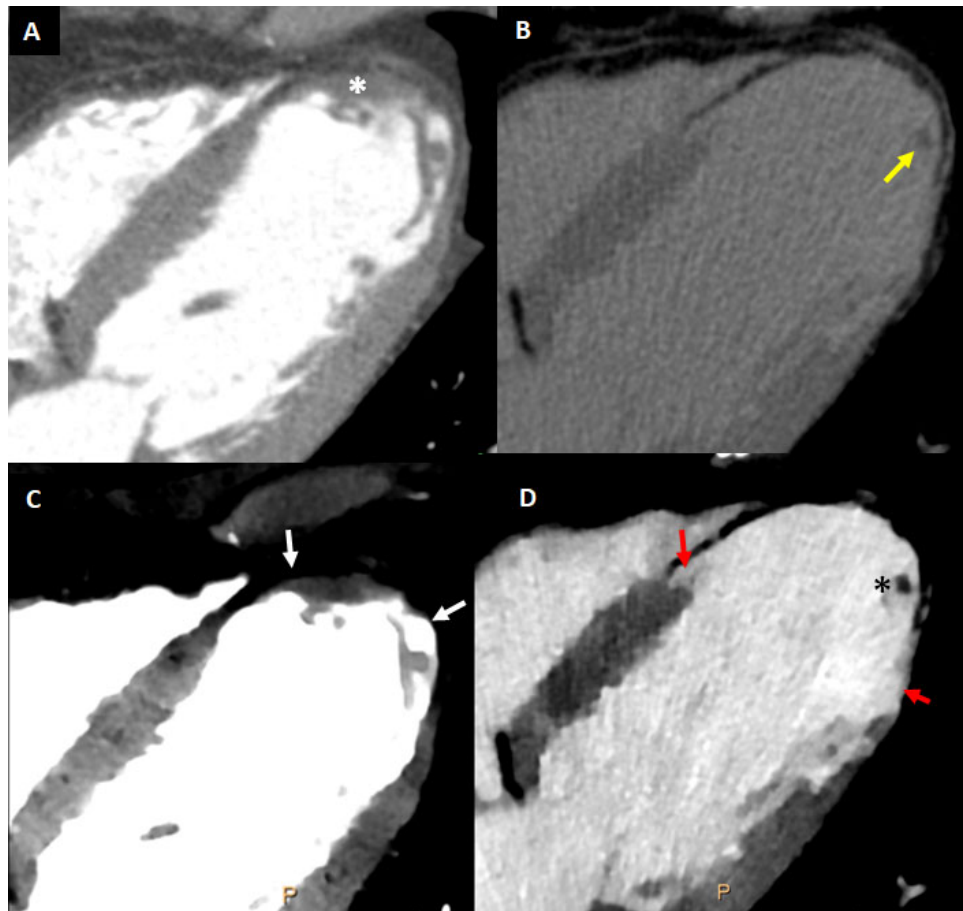


Fig. 5. Fifty-seven year-old female with multiple coronary risk factors, admitted with an ischemic stroke for which she underwent thrombectomy. She had a previous history of myocardial infarction six years before without obstructive coronary lesions, and an ischemic stroke three years ago. Echocardiography showed apical wall motion abnormalities. Dual-phase (arterial, panels A and C; and delayed imaging, panels B and D) cardiac CT was performed to rule out cardioembolic sources. At conventional cardiac CT (panels A and B), myocardial thinning of the apical wall was identified, with a relatively large underlying filling defect (* in panel A) that resolved at delayed imaging (panel B). However, a very small and vague filling defect persisted (arrow in B). Spectral analysis provided a much clearer discrimination of these findings, including the apical perfusion defect related to lipomatous metaplasia (white arrows in C), late iodine enhancement (red arrows in D), and the small apical thrombi (* in D).

At the other end of the VMI spectrum, mid to high energy levels (> 80 keV) attenuate or cancel artifacts that usually affect single energy CT such as beam hardening, thus further aiding tissue characterization and avoiding potential misdiagnosis [9, 14]. Moreover, calcium blooming is an important artifact in vascular imaging that causes overestimation of stenosis and inappropriate classification of lesion severity. Both VMI at high energy levels and virtual non-contrast images can decrease the blooming effect and therefore achieve a more precise assessment of the lumen [15].

The rationale supporting material decomposition relies on the fact that tissues have different attenuation coefficients that depend on the energy levels of the X-ray beam. As a result, one of the multiparametric features derived from spectral CT allows choosing specific components such as iodine or calcium. In the case of iodine, the generation of iodine density maps enables the quantification of iodine concentration of any specific cardiac structure (Fig. 10) [14]. This ap-

proach has numerous applications such as quantitative evaluation of myocardial perfusion, and detection and characterization of cardiac masses and thrombus. Conversely, calcium suppression can be achieved thereby aiding tissue characterization and discrimination between total and subtotal carotid occlusions [15].

Regarding radiation exposure, it is noteworthy that spectral CT does not imply a significant increase in radiation dose compared to conventional CT. Indeed, dual-layer spectral CT is acquired using the standard procedure thus using the same radiation dose as in conventional CT. Furthermore, by enabling virtual non-contrast images, the non-contrast phase commonly used for the evaluation of acute aortic syndromes or for the surveillance of endovascular or valve prosthesis among other, might be avoided [22].

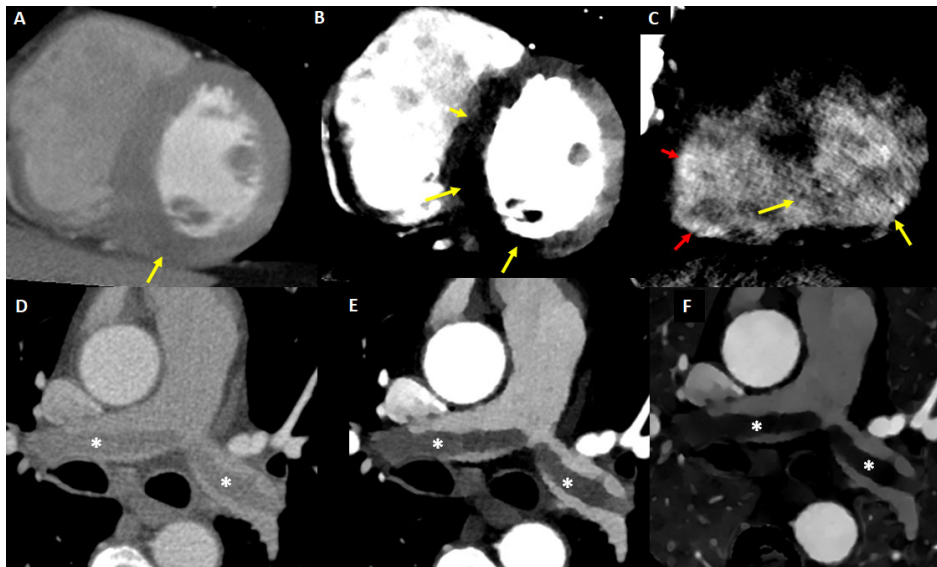


Fig. 6. Patient evolving with shortness of breath after primary percutaneous coronary intervention. Cardiac CT was requested, with a patent stent. A very subtle myocardial perfusion defect was visible using conventional cardiac CT (panel A, arrow), whereas a severe perfusion defect of the septal and inferior wall was clearly detected using virtual monoenergetic imaging (VMI) at 40 keV (panel B, arrows). At delayed imaging (5 minutes after contrast, performed using prospective ECG gating), transmurals late iodine enhancement was detected at the inferior and septal segments (panel C, yellow arrows). In addition, involvement of the right ventricle was also identified (red arrows). Notably, bilateral pulmonary thromboembolism (*) was detected at conventional CT (panel D), much clearer using VMI at 40 keV (panel E) and iodine maps (panel F).

3. Imaging strategies in cardioembolic stroke

Despite the etiology of ischemic stroke is heterogeneous, approximately up to 30% of strokes result from cardiac or aortic origin. This figure* will possibly increase in the upcoming years given the continuing improvements in medical treatment for hypertension and hypercholesterolemia, which are risk factors more related to non-cardioembolic ischemic strokes [23]. The identification of a cardioembolic source is essential for selecting the appropriate therapeutic management, particularly related to the indication and/or strategy of anticoagulation [24]. The main risk factors for cardioembolic stroke comprise atrial fibrillation (AF), systolic dysfunction, (recent) myocardial infarction, paradoxical emboli through a patent foramen ovale (PFO, Fig. 2), complex aortic arch atherosclerotic plaques, mechanical prosthetic heart valves, infective endocarditis and other causes such as cardiac tumors (myxoma and papillary fibroelastoma) and mitral calcification [23]. Among these, LAA thrombus (Figs. 1, 8, 9, 10) secondary to AF or flutter represent the underlying cause in roughly half of all cardioembolic strokes [25].

With regard to specific cardiac imaging in patients with stroke, transthoracic echocardiography (TTE) is the most frequent test for detecting cardiac abnormalities. Despite obvious advantages related to its portability and low cost, TTE is limited for the purpose of ruling out cardioembolic sources. Aside from acoustic window limitations, enhanced among these patients given the restricted possibility to modify the supine position, TTE is a suboptimal technique for the detection of LAA thrombus and aortic plaque.

Conversely, TEE offers improved imaging of LAA and the aorta and is, to date, the reference standard imaging modality for ruling out cardioembolic sources.

Nonetheless, although rare, TEE can be associated to complications including esophageal perforation, infection, oropharyngeal and dental trauma, nonfatal arrhythmias, and adverse reactions related to sedation [7, 26]. The potential risks associated with TEE, and particularly the risk of esophageal lesions, might be incremented among patients with stroke who can be affected by impaired sensory. In this regard, the recent randomized Transesophageal Echocardiography - Dysphagia Risk in Acute Stroke (TEDRAS) trial comprising stroke patients showed a significant increase in dysphagia after TEE [6].

In parallel, cardiac CT has been positioned in the past decade as a validated and less invasive alternative diagnostic tool for ruling out cardioembolic sources.

Overall, about 40% of acute ischemic strokes are evaluated with either TEE or cardiac CT for this purpose, and in approximately 20-30% of cases a major source of embolism is detected, being AF or LAA or left ventricular thrombi the most frequent underlying etiology [27, 28].

4. Cardiac CT for ruling out cardiac thrombi

As aforementioned, TEE is the most widely validated diagnostic tool for the detection of LAA thrombus. Notwithstanding, TEE might offer a deficient or inconclusive assessment in certain specific anatomic scenarios such as multi-lobed appendages, prominent pectinate muscles, or in case of thrombus at the tip of the LAA (Fig. 2) [29].

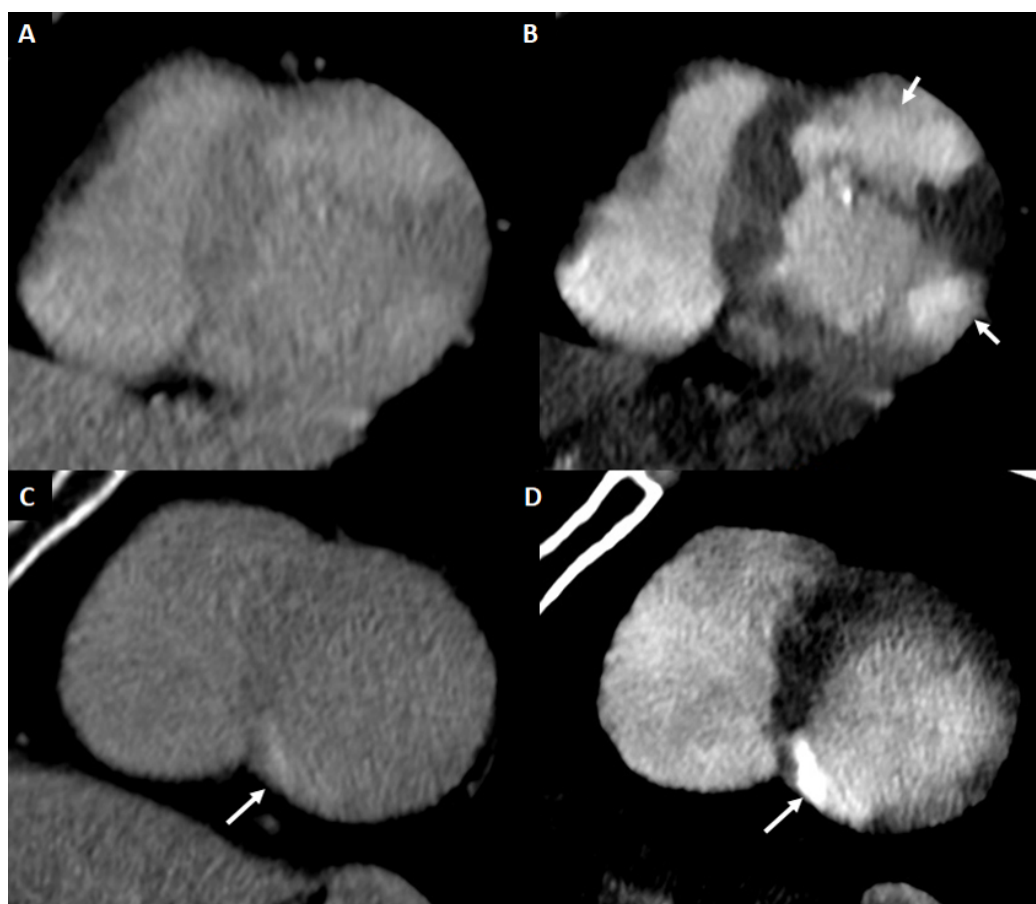


Fig. 7. Low-dose, delayed-phase, non-gated, chest spectral CT for the detection of myocardial disease and/or injury. Panels A and B show a patient with subarachnoid hemorrhage treated with coils who underwent a chest CT 5 minutes after cerebrovascular CT without additional contrast administration. Using virtual monoenergetic imaging (VMI) at 40 keV (panel B), extensive late iodine enhancement is noted at the anterior wall and at the inferior lateral segment, sparing the endocardium. These findings were vague using conventional CT (panel A). Panels C and D depict a patient who underwent non-contrast low-dose chest CT immediately after primary percutaneous intervention for an ST-segment elevation acute myocardial infarction. Inferior-septal late iodine enhancement reflecting irreversible myocardial damage is clearly detected using VMI at 40 keV (arrow, panel D), whereas these findings were inconclusive using conventional CT images (panel C).

Cardiac CT is a less invasive tool that has a good diagnostic capability for detecting intracardiac thrombus and evaluating the aorta. In a meta-analysis including 19 studies and 2,955 patients who underwent TEE and cardiac CT prior to pulmonary vein isolation or cardioversion for AF, or after an ischemic stroke, the sensitivity, specificity, and accuracy for detection of thrombus by TEE were 96%, 92%, and 99%, respectively, with positive predictive value of 41% and negative predictive value of 94% [30]. Among the subset of patients ($n = 753$) undergoing delayed-phase acquisition (Fig. 3), the sensitivity, specificity, and accuracy were almost 100%, and the positive predictive value increased to 92%.

The reason for such difference is attributed to the fact that using single-phase (arterial) CT a non-negligible number of cases have incomplete opacification of the LAA, related partly to the supine position of the patient and thereby the anterior position of the LAA (Figs. 3, 8). Also for this reason, cerebrovascular CT angiography extended to include the LAA might lead to equivocal findings.

Such filling defects, unless a thrombus is present, resolve with delayed-phase acquisitions (Figs. 3, 8A) and represent slow-flow phenomena/stasis, also referred as spontaneous echo contrast in TEE. In a recent study including 260 patients with AF referred to pulmonary vein ablation, TEE demonstrated LAA spontaneous echo contrast in 20% of cases and cardiac CT showed an early filling defect in 24% of patients. Remarkably, LAA thrombus was identified in only 4%, with 100% agreement between techniques. Furthermore, the authors tested different timing of delayed acquisitions at 1-, 3-, and 6-min after contrast administration, and demonstrated the best agreement using images acquired 6 min after contrast [31].

The discrimination between slow-flow from LAA thrombus can be intricate and, as aforementioned, require multiple acquisitions or specific protocols [32]. In this regard, the spectral CT technology has emerged as a means to measure specific iodine concentrations (Fig. 10) and thereby potentially aiding such distinction.

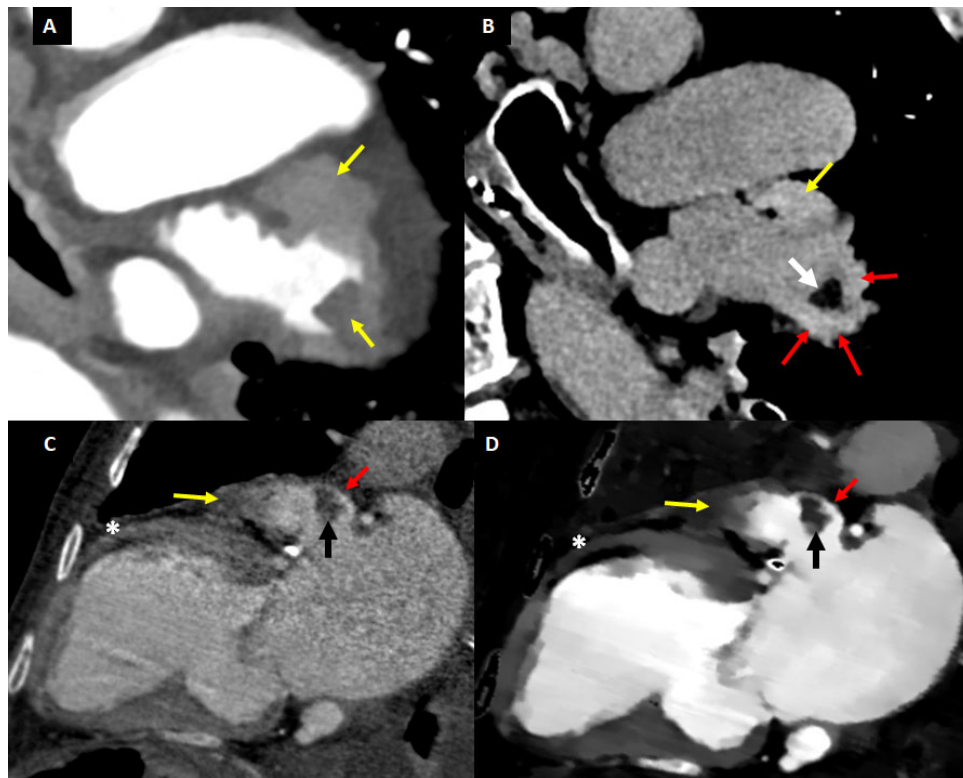


Fig. 8. Coexistence and discrimination between left atrial appendage (LAA) thrombus and blood stasis using spectral cardiac CT in patients with ischemic stroke. Dual-phase (arterial, panel A; delayed-phase, panel B) cardiac CT shows an early filling defect of the LAA (arrows, panel A). Five minutes after contrast, virtual monoenergetic imaging at 40 keV (panel B) demonstrated a small LAA thrombus (white arrow), whereas most of the early filling defect corresponded to blood stasis (yellow arrow). The panels below (panel C, conventional CT; panel D, iodine maps) show a patient with a well-defined LAA thrombus (black arrows), that did not require delayed imaging for accurate diagnosis. Note that one of the distinctive aspects for the discrimination between LAA slow-flow and thrombus is that the former involves a gradual and complete defect of the distal portion of the LAA whereas thrombi are abrupt and well-defined defects, generally with contrast separating the atrial wall from the mass (red arrows in B, C, and D). This patient also had a myocardial perfusion defect (* in panels C and D).

Iodine concentration differs significantly between normal blood flow (i.e. aortic), slow-flow, and thrombus. Spectral CT has the ability to perform specific measurement of local iodine concentrations at any region of interest, both during arterial and delayed-phase images. This enables a clearer discrimination between thrombus and stasis.

In one of the first studies exploring this, Hur *et al.* demonstrated a mean iodine concentration of 1.23 ± 0.34 mg/mL for thrombus and of 3.61 ± 1.01 mg/mL for spontaneous echo contrast ($P = 0.001$) [19]. In a more recent study, Li *et al.* reported an improved diagnostic accuracy using iodine concentration compared to conventional attenuation measurements for detecting LAA thrombus [33]. Nonetheless, the optimal cutoff values for discrimination between blood, slow-flow, and thrombus remain uncertain. In this regard, the LAA-ascending aorta Hounsfield unit ratio threshold for differentiating thrombus from stasis, though variable, is generally below around 0.20 [19].

5. Late iodine enhancement and left ventricular thrombus

Acute myocardial infarction is a long established risk factor of ischemic stroke, usually related to a left ventricular thrombus overlying areas of wall motion abnormalities. Left ventricular thrombus (Figs. 4, 5) are relatively common among patients with anterior-wall myocardial infarction, with an estimated prevalence of 15-20% [34, 35]. Transthoracic and particularly transesophageal echocardiography have lower sensitivity for the detection of left ventricular thrombus compared to other tools with improved tissue characterization and devoid from acoustic window limitations such as cardiac magnetic resonance (MR) or CT [36, 37]. Single-phase imaging using conventional cardiac CT enables accurate identification of LV thrombus (Fig. 4), and a threshold below 65 Hounsfield units has been reported to convey a sensitivity of 94% and a specificity of 97%. Moreover, as in cardiac MR, late enhancement images provide a much better discrimination between thrombus and the myocardium (Fig. 5) [38].

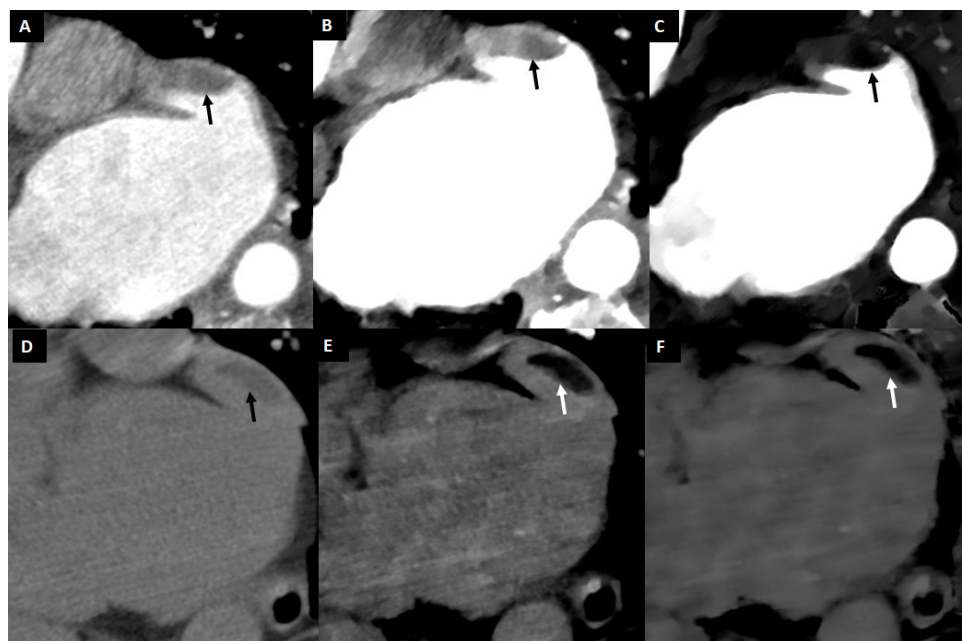


Fig. 9. Left atrial appendage thrombus detected using dual-phase cardiac CT (arterial phase: panels A to C; delayed-phase: panels D to F) in a patient with acute ischemic stroke. Conventional cardiac CT (panels A and D) show a filling defect persisting at delayed imaging. This finding is much more clearly detected using spectral images (panels B and E: VMI at 40 keV; panels C and F: iodine maps), particularly using delayed-phase spectral imaging (panels E and F).

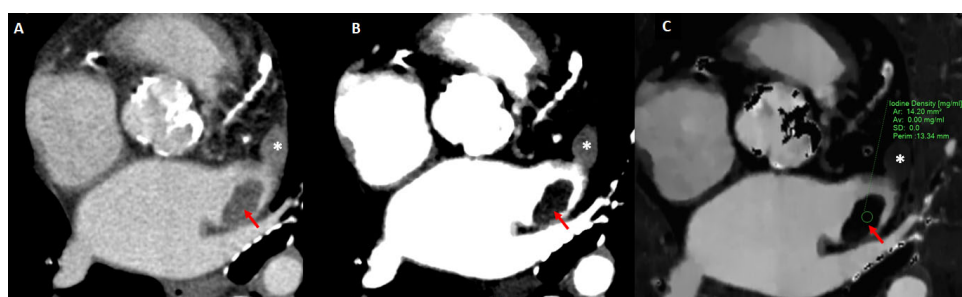


Fig. 10. Left atrial appendage thrombus detected using cardiac CT in a patient with acute ischemic stroke and congestive heart failure. Conventional CT (panel A), virtual monoenergetic imaging at 40 keV (panel B), and iodine maps (panel C) are portrayed. Using iodine density maps, lack of iodine uptake (0 mg/mL), ruled out a cardiac tumor (panel C). Also note that the more gradual filling defect of the distal LAA (*) might represent blood stasis. Delayed imaging was not performed in this case due to the clear diagnosis.

In this regard, CT delayed-enhancement (CTDE) imaging shares the same principle than late gadolinium enhancement (LGE) with cardiac MR, with similar contrast kinetics [39]. Therefore, as in LGE, the presence of myocardial late iodine enhancement (LIE) (Figs. 5-7, 11) is a predictor of systolic dysfunction, arrhythmia, major adverse cardiac events, and death; having this been demonstrated in diverse populations including ischemic and non-ischemic cardiomyopathy [40-44]. From a pathophysiological basis, LIE represents an expansion of the extracellular volume (ECV) associated to irreversible myocardial damage or fibrosis [45].

CTDE can be performed after coronary CT angiography generally using prospective ECG-gating thus involving a low radiation dose, in many cases without additional contrast administration, and has a very high agreement with LGE-MRI

(sensitivity and specificity over 90%) [40-42, 46].

Spectral CT offers improved tissue characterization compared to conventional CT, both in terms of myocardial perfusion and delayed-enhancement imaging [41, 42, 46-49]. At first-pass (arterial phase), spectral CT both using iodine density maps and VMI allows more accurate discrimination between normally perfused structures and myocardial perfusion defects (Figs. 4-6, 11, 12). Furthermore, using delayed-phase acquisition, particularly 5-7 minutes after contrast administration, improved discrimination between areas of normal myocardium (mildly enhanced, with intermediate iodine concentration), myocardial injury/late iodine enhancement (highly enhanced, similar than intravascular or ventricular cavity), and thrombus (non-enhanced, with minimal or absence of iodine) can be achieved (Figs. 5-7, 11-12).

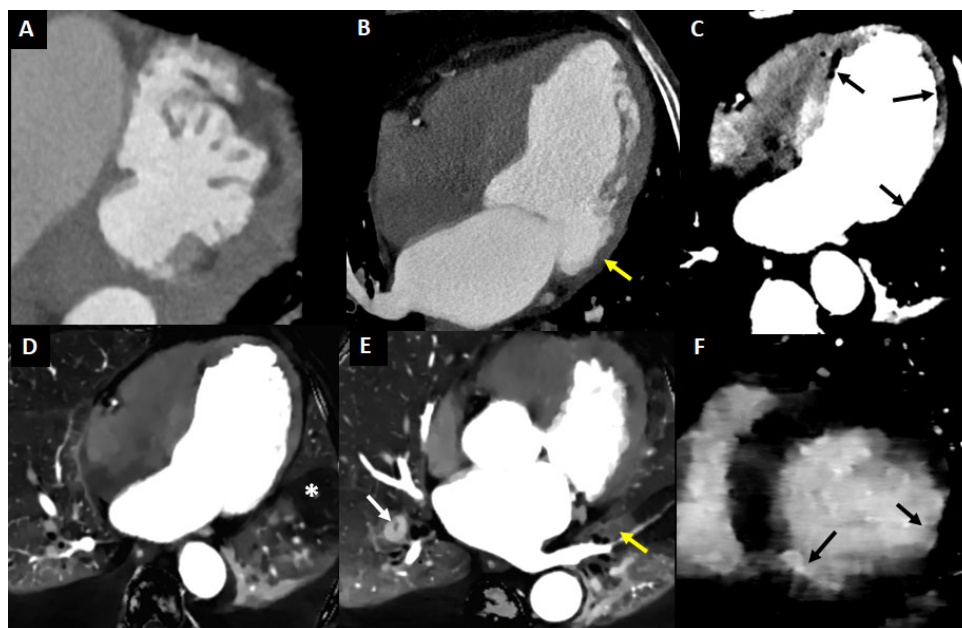


Fig. 11. Seventy-five year-old male, with hypertension. He was admitted with an acute ischemic stroke, for which he underwent mechanical thrombectomy of the left middle cerebral artery. Five days before admission he was isolated due to cough and dysgeusia. RT-PCR swab test for COVID-19 was not obtained at that moment. Upon admission, the patient had cardiac enzyme elevation and atypical peripheral lung infiltrates. The ECG showed sinus rhythm, frequent premature ventricular beats, and abnormal Q waves in the inferior-lateral wall (DII, DIII, aVF, V4, V5 and V6), without ST-segment abnormalities. Cardiac CT ruled out left atrial appendage thrombus (panel A) and revealed dilated left chambers, with severe systolic dysfunction (panel B, systolic four-chamber view using conventional CT) including akinetic inferior lateral wall (arrow). Spectral analysis (panel C, virtual monoenergetic imaging, VMI, at 40 keV, and panels D and E, iodine maps) showed multiple perfusion defects (arrows in panel C) not identified using conventional CT. Iodine maps also showed a lung perfusion defect (*, in panel D), with occlusive (yellow arrow in panel E) and non-occlusive (white arrow in panel E) pulmonary emboli. Spectral images acquired five minutes after contrast demonstrated inferior and lateral late iodine enhancement of the myocardial wall (arrows in panel F).

Accordingly, subtle myocardial disease including small infarcts can be detected more easily using spectral compared to conventional CT (Fig. 7).

6. Aortic thrombi

Almost half of subjects older than 45 years have atherosclerotic plaques in the aorta [50]. Complex (≥ 4 mm) aortic atheromatous plaques are a source of acute ischemic stroke, particularly if ulcerated or mobile. However, ulcerated plaques are a relatively common finding in patients with cerebrovascular disease [51]. Aside from the aforementioned limitations of TEE involving the LV apex, the right ventricle, and subtle myocardial infarcts, the thoracic aorta has blind spots for the assessment with TEE surrounding the distal ascending aorta and the aortic arch. In this regard, Chatzikonstantinou *et al.* reported a significantly better identification of plaques in the aortic arch using CT angiography [52].

The potential usefulness of spectral over conventional CT for the identification of aortic plaques seems limited to the discrimination between thrombus/plaques and aortic masses, an exceedingly rare finding [53].

7. Atrial cardiopathy and pulmonary complications

Atrial cardiopathy is a functional or structural disorder of the left atrium that has been associated with LAA stasis or thrombus, even in absence of AF. This condition has an increasingly relevant role in the pathogenesis of embolic stroke of undetermined source (ESUS), a concept that will be addressed in the following section [54]. Atrial cardiopathy may be defined using biomarkers, electrocardiographic indexes and the detection of cardiac fibrosis [54, 55].

LGE using MRI has shown to provide a pre-procedural estimation of the extent of atrial fibrosis and therefore to predict outcomes in patients undergoing AF ablation [56]. Nonetheless, atrial fibrosis imaging is challenging due a number of issues. Among these, the atrial wall is substantially thinner than the ventricular wall, and the spatial resolution of LGE-MRI is approximately 1.5 mm. Accordingly, spectral CTDE might potentially provide a good alternative for this purpose given a better (sub-millimetric) spatial resolution.

Pulmonary embolism (PE) is a serious complication of stroke (Fig. 11), associated with higher rates of death. A Canadian registry that included 11,287 patients with acute ischemic stroke (AIS), reported a rate of PE of almost 1%, and associated with a higher risk of death at 30 days (26.8% vs. 13.6%; $P < 0.001$), at 1 year (47.2% vs. 24.6%; $P < 0.001$),

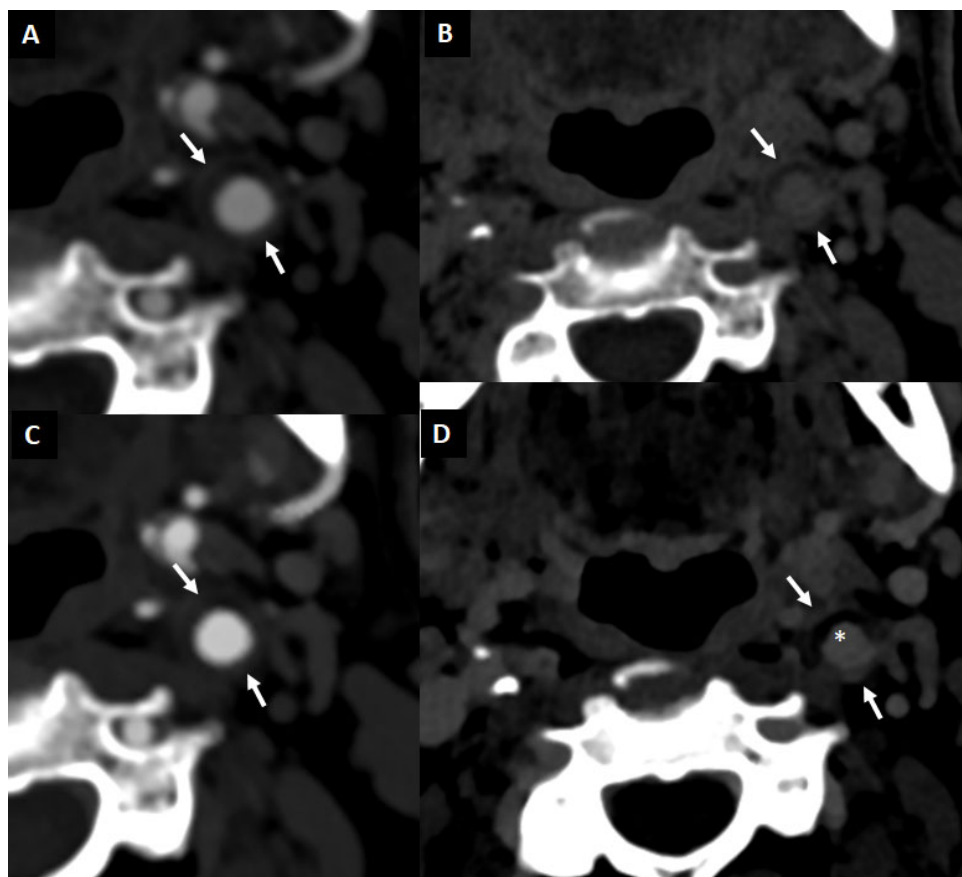


Fig. 12. Mild, non-calcified carotid plaque evaluated with CT angiography using conventional CT images (panels A and B) and virtual monoenergetic imaging at 45 keV (panels C and D) at arterial phase (A and C) and delayed-phase (B and D). Improved discrimination between tissues with spectral imaging including carotid wall-enhancement (white arrows) and mural thrombus (asterisk).

and disability (85.4% vs. 63.6%; $P < 0.001$) compared to AIS patients without PE [57]. Indeed, subtle signs of PE or deep vein thrombosis are generally overlooked (or misinterpreted as pneumonia or hemiplegic edema for instance) in these patients. Notably, the first clinical manifestation of PE after stroke in approximately half of the cases is sudden death, underscoring the underestimation and relevance of such condition [58].

Spectral CT using iodine maps offers incremental benefit for the detection of PE (Figs. 6, 11) [59]. Such added value, though modest in patients with suspected PE undergoing CT pulmonary angiography, might be enhanced in patients with stroke in whom the level of suspicion of PE is lower and its diagnosis can be delayed or even neglected. Moreover, the increased intravascular enhancement associated with spectral CT (particularly using VMI at low energy levels) enables the detection of PE during cardiac CT not specifically targeted to evaluate the pulmonary tree (Figs. 6, 11).

8. Embolic stroke of undetermined source

Approximately one third of strokes have no identifiable etiology after extensive evaluation, and are therefore classified as cryptogenic [60]. Nonetheless, it is currently per-

ceived that a share of these cryptogenic strokes might actually have undetectable cardioembolic sources, missed by conventional imaging techniques [26].

ESUS represents a large patient group that involves approximately 17% of all ischemic stroke patients. In addition, these patients have a rate of stroke recurrence of 4% to 5% a year [54]. Diagnosis of ESUS requires exclusion of major cardioembolic sources, as well as proximal occlusive atherosclerosis and lacunar stroke due to cerebral small artery disease [61]. The main pathologies that could be etiologically associated with ESUS are mainly categorized in 7 embolic sources, some of which were previously addressed: 1) atrial cardiopathy, 2) covert atrial fibrillation, 3) left ventricular disease, 4) atherosclerotic plaques, 5) PFO, 6) cardiac valvular disease, and 7) cancer [54].

Cardiac spectral CT might be a useful noninvasive modality for the etiologic assessment of ESUS, particularly for detecting unrecognized or subtle myocardial disease, or embolic sources that might have been overlooked by other imaging techniques. On top of this, it has been recently suggested that low-dose, non-gated, chest spectral CT performed upon admission after cerebrovascular CT (without additional contrast administration) might represent an unsophisticated tool

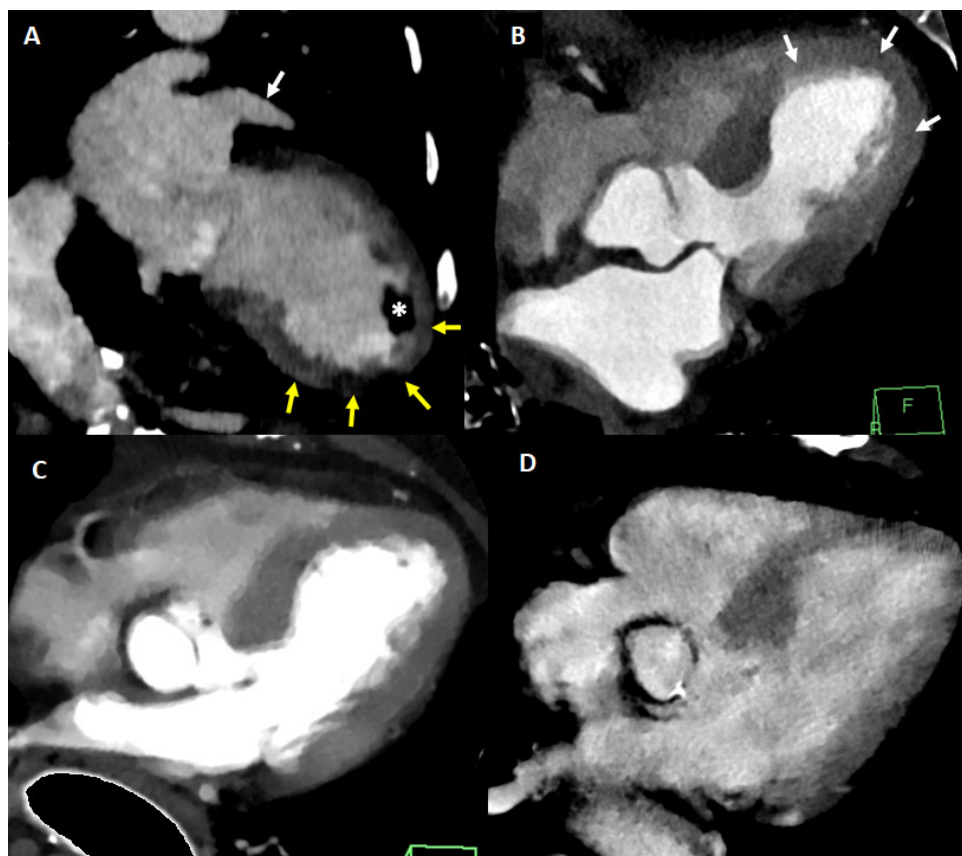


Fig. 13. Neurogenic stress cardiomyopathy. Ninety-one year-old female without coronary risk factors other than age. She underwent endovascular treatment (coils) for a subarachnoid hemorrhage related to rupture of an anterior communicating aneurysm, evolving with episodes of supraventricular tachycardia that resolved spontaneously, without chest pain or anginal equivalents. The ECG showed anterior-wall T-wave inversion, and cardiac enzyme level elevation was noted. Low-dose, non-gated, chest spectral CT was performed upon admission immediately after cerebrovascular CT and without additional contrast administration (panel A), showing complete opacification of the left atrial appendage (white arrow), and a dilated apical left ventricular wall (yellow arrows), with underlying thrombus (*). Notably, the absence of late myocardial enhancement suggested a non-ischemic etiology. Echocardiography confirmed these findings. Cardiac CT performed four days later identified akinetic apical segments (arrows in panel B, systolic view). Spectral analysis (virtual monoenergetic imaging at 40 keV) demonstrated normal myocardial perfusion (panel C) and absence of late iodine enhancement (panel D). The left ventricular thrombus was not identified. Echocardiogram performed 5 days later demonstrated complete normalization of wall motion abnormalities.

for the early triage of cardioembolic sources as well as simultaneously ruling out myocardial disease and pulmonary complications (Figs. 4, 7, 13) [53].

In parallel, spectral CT might be useful for carotid plaque imaging (Fig. 12). Conventional carotid CT angiography has a higher spatial resolution than MRI angiography, lower cost, is more widely available, and comprises much shorter acquisition time. Notwithstanding, evaluation of diffusely calcified plaques is challenging with conventional CT, overestimating the degree of stenosis and even leading to inaccurate discrimination between occlusive and sub-occlusive lesions. As aforementioned, spectral CT might overcome some of these artifacts thereby portraying a more fair assessment of the lumen. Moreover, spectral CT has shown to improve the discrimination between carotid plaque tissue components, thus potentially aiding risk prediction; albeit this remains to be established [20, 21]. In this regard, non-significant (< 50% stenosis) carotid lesions have been recognized as an impor-

tant source of ESUS, with significantly larger non-stenotic carotid plaques ipsilateral compared to contralateral to ischemic stroke (Fig. 12).

9. Neurogenic stress cardiomyopathy and Tako-Tsubo

The clinical features of cardiac injury in the context of acute brain damage (neurogenic stress cardiomyopathy or neurogenic stunning, NS) and Tako-Tsubo syndrome (TS) are quite similar, although some differences have been described between these conditions. Among other, TS has been reported to involve older patients, a higher rate of ST-segment elevation (with NS more frequently showing T-wave inversion), lower left ventricular ejection fraction, and apical type (while NS showing more frequently a mid-ventricular or basal type) [62].

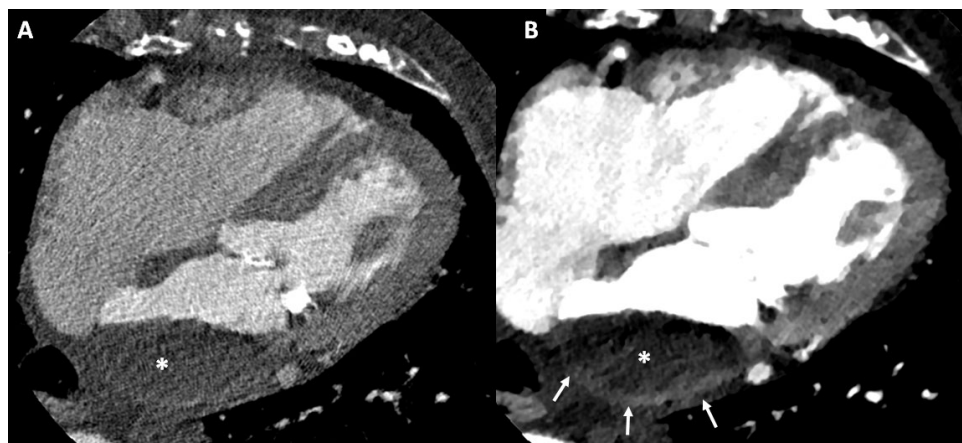


Fig. 14. Patient with an acute ischemic stroke and atrial fibrillation, with multiple coronary risk factors and a history of previous myocardial infarction treated with stents. Echocardiogram demonstrated akinetic apical segments without thrombus, whereas the left atrium was unremarkable. Cardiac CT using conventional imaging (panel A) showed diffuse mitral calcification, and a cardiac mass (well delineated, with smooth contours) occupying the posterior atrial wall with unclear differentiation between the atrial wall and mediastinum. Virtual monoenergetic imaging at 55 keV (panel B), demonstrated a clear discrimination between structures, portraying the atrial wall (arrows).

Both involve a sudden, transient, and reversible myocardial dysfunction (regional, beyond a coronary territory distribution; very rarely global and in some cases biventricular). Cardiac enzyme elevation is present in both conditions, predominantly brain natriuretic peptide and mild troponin rise. Importantly, triggers are clearly different. While TS is caused by psychological stress in the absence of physical damage to the brain, leading to a catecholamine storm, NS results from acute brain injury (generally related to subarachnoid hemorrhage) leading to a catecholamine storm and profound endocrine derangements (Fig. 13) [1, 63].

The autonomic nervous system; acutely affected during brain hemorrhage, has a significant influence on the cardiovascular system due to its ability to modulate heart rate, conduction velocity and cardiac contractility; rapidly increasing systemic vascular resistance and leading to increased left ventricular afterload that can cause, among other, coronary ischemia. It is therefore not surprising that cardiovascular complications represent the second leading cause of death after stroke [2]. Besides, stroke induced cardiac damage may lead to potentially lifelong cardiac problems related to complications of the aforementioned conditions as well as to the incremented likelihood of acute coronary syndromes given the sharing cardiovascular risk factors.

Imaging plays a crucial role in the screening, detection, and characterization of cardiomyopathies. Cardiac CT enables the simultaneous evaluation of coronary arteries, characterization of cardiomyopathy phenotype and quantification of cardiac volumes and function, particularly in patients who are not able to undergo other non-invasive imaging tests such as MRI due to the presence of incompatible pacemakers-defibrillators, particularly in the acute setting [64].

Spectral CT offers an integral evaluation for TS and NS, improving the characterization of myocardial disease. This

technique offers a combination between the features provided by conventional cardiac CT (coronary tree and functional assessment) and some of those best provided by cardiac MRI (functional assessment and late enhancement) (Fig. 13). Furthermore, myocardial extracellular volume (ECV) fraction, an emerging surrogate marker of subclinical myocardial disease, has been validated with CT with similar results compared with cardiac MRI [65, 66]. In this regard, unlike conventional CT, spectral CT allows calculation of the ECV without the need of non-contrast acquisition [45].

10. Future perspectives

Cardiac CT is a useful modality for detection of embolic sources, comparable to TEE. In addition, it offers additional risk assessment features in patients with stroke within a single session, such as simultaneous diagnosis of CAD, myocardial perfusion, and LIE; all with incremental prognostic value. Spectral CT might represent a valuable asset in the field of neurocardiology, not only in terms of its ability to reduce iodinated contrast load, but also aided by a significant improvement in tissue characterization. Accordingly, spectral CT shows promise to enable a better thrombus detection and the identification of subtle myocardial disease and/or cardioembolic sources that might be neglected by other imaging techniques (Fig. 14), thus potentially redefining patients with ESUS.

In parallel, since spectral imaging provides some benefit in terms of improved characterization of carotid plaques (Fig. 12), it might aid risk stratification of intermediate lesions, although the prognostic value of this technique remains uncertain.

Last but not least, the great improvement in tissue characterization provided by spectral imaging combined with the improved temporal resolution of newer generation scanners,

might allow the early triage of cardioembolic sources in patients with acute ischemic stroke upon admission immediately after cerebrovascular CT angiography using a low-dose, non-gated, non-contrast chest spectral CT scan (Figs. 4, 7, 13) [53]. Since stroke-related pneumonia is a major cause of increased morbidity and mortality in these patients, using this approach might also be of worth by comprehensively ruling out pulmonary complications within the same session [67].

Overall, spectral CT might enable a more comprehensive cardiovascular evaluation among neurological patients with suspected cardiac injury or cardioembolic sources. Specific prospective studies are warranted to explore whether this technique might promote an accurate reclassification of stroke etiologies or improve risk assessment, as well as its potential prognostic role in hemorrhagic stroke.

Author contributions

LF conceived and drafted the review article; JJC reviewed the article for critical content; PL reviewed the article for critical content; GRG reviewed the article for critical content.

Ethics approval and consent to participate

All patients or tutors provided informed consent for the anonymous use of their clinical data.

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Conflict of interest

None of the authors has conflicts of interest related to this work.

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