Radiology

Ischemic Stroke: Etiologic Work-up with Multidetector CT of Heart and Extra- and Intracranial Arteries[1]

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Purpose: To assess the potential of a single-session multidetector computed tomography (CT) protocol, as compared with established methods, for the etiologic work-up of acute ischemic stroke.

Materials and Methods: Patients found to have recently experienced an ischemic stroke were recruited for this prospective study after institutional review board approval was obtained. Each patient was scheduled for two evaluation strategies: *(a)* a standard approach involving transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), duplex ultrasonography (US) of the neck vessels, and magnetic resonance (MR) angiography of the neck and brain vessels; and *(b)* a protocol involving single-session multidetector CT of the heart, neck, and brain vessels. The authors sought to determine the major etiologic factors of stroke, including cardiac sources of embolism and atheroma of the aortic arch and the extra- and intracranial vessels, by using both strategies.

Results: Multidetector CT, MR imaging, and duplex US were performed in 46 patients, 39 of whom also underwent TEE. The sensitivity and specificity of multidetector CT were 72% (18 of 25 cases) and 95% (20 of 21 cases), respectively, for detection of cardiac sources and 100% (24 of 24 cases) and 91% (20 of 22 cases), respectively, for detection of major arterial atheroma. For the 46 cases of stroke, the final etiologic classifications determined by using the standard combination approach were cardiac sources in 20 (44%) cases, major arterial atheroma in nine (20%), multiple sources in four (9%), and cryptogenic sources in 13 (28%). Multidetector CT facilitated correct etiologic classification for 38 (83%) of the 46 patients.

Conclusion: Multidetector CT is a promising tool for etiologic assessment of ischemic stroke, although the identification of minor cardiac sources with this examination requires the establishment of robust criteria.

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Early determination of the etiologic factors of ischemic stroke is essential for secondary prevention because the risk of recurrence is highly dependent on the underlying cause (1). Major identified causes of ischemic stroke are extra- or intracranial atheroma, cardioembolic sources, microvascular disease, and aortic arch atheroma (2,3). This etiologic work-up is usually based on the findings of a combined imaging protocol that includes duplex ultrasonography (US), magnetic resonance (MR) angiography or computed tomographic (CT) angiography of the neck and brain vessels, transthoracic echocardiography (TTE), and transesophageal echocardiography (TEE). This approach is time-consuming and expensive. In addition, secondary stroke prevention strategies may be delayed.

Multidetector CT has been demonstrated to be an accurate and powerful tool for detecting atheroma in extra- and intracranial vessels (4,5). More recently, electrocardiographically (ECG) gated contrast material–enhanced multidetector CT has been proposed for studying left ventricular wall motion, ejection fraction (6,7), intracardiac thrombus (8), and patent foramen ovale (9,10). A single-session multidetector CT study involving combined examination of the heart, aortic arch, and extra- and intracranial arteries may enable detection of the main sources of ischemic stroke. In this study, we assessed the potential of a single-session multidetector CT protocol, as compared with established imaging methods, for the etiologic work-up of acute ischemic stroke.

Materials and Methods

Study Design

We performed a single-center, prospective open pilot study. A time period of 9 months for evaluation of the multidetector CT protocol was prospectively chosen. The study started August 1, 2007, and ended April 30, 2008. Patients were recruited from the Lyon Stroke Unit, Lyon, France. Inclusion criteria were age between 18 and 90 years and acute ischemic stroke having occurred within less than 1 week of study entry and diagnosed by a stroke neurologist. Exclusion criteria were any contraindications to MR imaging, TEE, or iodine-based contrast material injection and/or the inability to provide informed consent. The National Institutes of Health Stroke Scale score (11) of each patient at admittance was recorded. Local ethics committee and institutional review board approval and informed consent from each patient were obtained. The etiologic work-up of each acute ischemic stroke included a one-time multidetector CT examination of the heart, aorta, and extra- and intracranial vessels and a standard protocol involving combined MR angiography of the extra- and intracranial vessels, duplex US of the extracranial vessels, and TTE and/or TEE of the heart and aorta in all patients.

Imaging Protocols

Contrast-enhanced multidetector CT was performed by using a Brilliance 40 scanner (Philips Healthcare, Best, the Netherlands), with iomeprol (Iomeron 400; Bracco Diagnostics, Milan, Italy) injected into the right cubital vein with an 18-gauge catheter. The patient was placed in the supine, head-first position. A two-step protocol was performed: First, ECG-gated aortic and heart acquisitions were performed in the head-to-feet direction, encompassing the aortic and heart area from the top of the aortic arch to the diaphragm. The following parameters were used: 40 detectors, individual detector width of 0.625 mm, retrospective ECG gating, tube voltage of 120 kV, tube current of 300 mAs, pitch of 0.2, and half-rotation reconstruction. Seventy milliliters of iomeprol and then 60 mL of saline solution were injected at 4 mL/sec. A bolus-tracking method was used with an attenuation threshold of 200 HU in the ascending aorta. Reconstruction parameters for the axial sections were a 1.5-mm effective section thickness, 1-mm increments, a reconstruction filter CB, and an adapted field of view. Retrospective ECG-gated reconstruction was performed at 40% and 75% of the R-R interval.

Then, 2 minutes later, a non–ECG-gated acquisition from the aortic arch to the intracranial arteries (approximately 50 cm) was performed with the following parameters: feet-to-head direction, section thickness of 1.2 mm, pitch of 1.2, tube voltage of 120 kV, amperage of 300 mAs per section, reconstruction filter B, and the bolus tracker set on the aortic arch with an attenuation threshold at 200 HU. Fifty milliliters of iomeprol and then 60 mL of saline solution were injected at 4 mL/sec, for a total injected contrast material volume of 120 mL. The patient was imaged with the arms over the head during the aortic and heart acquisitions and with the arms at the sides during the second acquisition. General guidelines for

Advances in Knowledge

- One-time multidetector CT is feasible as a first-line examination in the etiologic work-up of acute ischemic stroke.
- Multidetector CT enabled correct classification of the etiologic factors of stroke in more than 80% of patients.

Implication for Patient Care

- Multidetector CT enables rapid work-up of ischemic stroke.

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Abbreviations:
ECG = electrocardiography
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography

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ECG-gated cardiac multidetector CT were followed in terms of the qualifications of the personnel, the radiation dose monitoring, and the safety rules for contrast agent and β-blocker administration (12–14). β-Blockers (esmolol hydrochloride; Brevibloc, Baxter, Deerfield, Ill) (0.5–1.0 mg per kilogram of body weight) were administered intravenously, if necessary, when the heart rate was higher than 80 beats per minute. CT was performed even in cases of atrial fibrillation. The total radiation dose and the heart rate of each patient during the examination were recorded.

Duplex US examinations, including gray-scale, color Doppler, and spectral duplex US at a scanning angle of 60°, were performed by using an Acuson Antares machine (Siemens Healthcare, Erlangen, Germany) according to Society of Radiologists in Ultrasound quality criteria (15). All examinations included peak systolic velocity, end-diastolic velocity, and internal carotid artery velocity–to–common carotid artery velocity ratio measurements and planimetric estimation of the stenosis according to North American Symptomatic Carotid Endarterectomy Trial criteria (16).

MR imaging and contrast-enhanced MR angiography were performed at 1.5 T by using a Philips Intera (Philips Healthcare) or Siemens Avanto (Siemens Healthcare) MR unit. Head MR examinations performed with fast low-angle shot inversion-recovery, diffusion-weighted, and T2*-weighted sequences included brain imaging to confirm and localize the stroke and intracranial vessel angiography performed with a time-of-flight sequence. MR angiography of the extracranial vessels was performed by using a standard, previously described (4) gadolinium-enhanced method based on a three-dimensional gradient-echo acquisition with the following parameters: 3.7/1.3 (repetition time msec/echo time msec), an acquisition time of 56 seconds, a voxel size of 0.5 × 0.5 × 0.6 mm, and intravenous administration of 0.2 mL/kg gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France) with a nonmagnetic power injector and an automatic bolus-detection method.

Echocardiography was performed by using a Hewlett-Packard/Philips Sonos 5500 (Philips Healthcare) or Acuson C512 (Siemens Healthcare) scanner, which included 2.5- and 3.5-MHz transthoracic probes and a 5-MHz transesophageal probe. For TTE, four-, two-, and three-chamber views and short-axis basal, median, and apical views were obtained. For TEE, first cardiac structures were examined at, at least, 0°, 45°, and 120° at the midesophageal and transgastric levels. Then, the transducer was gradually withdrawn so that serial short-axis views of the descending aorta and aortic arch could be obtained. Aortic arch atheroma was evaluated according to previously published criteria (17,18).

Image Evaluation

Results of duplex US, TEE, TTE, and MR imaging were considered the standards of reference. These images were consensually reviewed independently according to the earlier described criteria by two trained senior radiologists (R.L., P.C.D.). The results of all multidetector CT examinations were consensually analyzed by three independent senior cardiovascular radiologists (L.B., P.C.D., R.L.) who had at least 5 years experience. All reviewers were blinded to the stroke location, clinical findings, and results of the other studies.

For vascular imaging, the diagnostic work-up was focused on the following abnormalities: *(a)* atherosclerotic lesions of the carotid arteries leading to greater than 50% stenosis according to North American Symptomatic Carotid Endarterectomy Trial criteria (16), *(b)* atherosclerotic lesions of the vertebral arteries leading to greater than 70% stenosis (19), *(c)* aortic atheromas larger than 4 mm (18), and *(d)* greater than 50% intracranial arterial stenoses. For cardiac imaging, findings at the 40% and 75% cardiac phases were analyzed. Major sources of cardioembolic stroke—specifically, intracardiac thrombus and akinetic or hypokinetic segmental myocardial wall—were reported. Regarding minor cardiac sources, interatrial septal aneurysm and patent foramen ovale were analyzed by using the following criteria: for patent foramen ovale detection, a distinct flap in the left atrium at the expected location of the septum primum, a continuous column of contrast material between the septum primum and the septum secundum, connecting the left and right atria, or a jet of contrast material from the column into an atrium (9); and for interatrial septal aneurysm, a bulge of the septum secundum that was larger than 10 mm in one of the two atria (10). An additional risk factor for a cardioembolic source, spontaneous echo contrast, which is defined as a pattern of slowly swirling intraatrial echo densities (20,21), was reported when present at TEE or TTE.

Finally, to perform TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification (2), all patients were assigned a classification according to the results of the individual examinations (termed *final classification*) as follows: A classification of cardiac sources or major arterial atheroma was assigned when a unique cardioembolic cause or cause related to atheroma of the major arteries was identified. A classification of multiple sources was assigned when several potential causes were identified in the same patient, and a classification of cryptogenic was assigned when no cause was found. The major arterial atheroma classification was used only for those patients found at presentation to have significant atheroma of the aortic arch or an extra- or intracranial vascular lesion corresponding to the stroke territory.

Statistical Analysis

The sensitivity and specificity of multidetector CT, with corresponding 95% confidence intervals, were calculated for the major arterial atheroma and cardiac sources groups. Concordance between the two methods (multidetector CT and standard approach involving TTE and TEE, duplex US, and MR angiography) was assessed by assigning a κ statistic for cardiac sources, major arterial atheroma, and the final classification. Agreement between the two techniques was rated as good when the κ value was between 0.61 and 0.80 and very good when it was between 0.81 and 1.00. The Mann-Whitney *U* test was used to compare age between the male and female patients. $P \leq .05$ was considered to indicate a statistically significant difference. All statistical analyses were performed by using Intercooled Stata 10.0 software (StataCorp, College Station, Tex).

Results

Between August 2007 and April 2008, 187 patients admitted to our stroke unit were eligible for the study. Forty-seven of them provided informed consent. One patient was excluded from the study because of very poor multidetector CT image quality: This patient, agitated and unable to collaborate, could not achieve apnea for the multidetector CT examination. Thus, the data of 46 patients were interpreted. The demographic data and risk factors for these patients are summarized in Table 1. The mean patient age was 63 years ± 11.4 (standard deviation) (range, 36–84 years). There was no significant difference ($P = .5$) in age between the male (63.6 years ± 11.1; range, 38–84 years) and female (60 years ± 13.1; range, 36–76 years) patients. The mean National Institutes of Health stroke score at admission was 8.4 ± 3.8 (range, 3–17). All patients had a sufficient level of consciousness and understanding to provide informed consent and to follow the apnea commands during the CT examination. Ischemic infarcts were detected at brain MR imaging in the internal carotid territory in 40 (87%) patients and in the vertebrobasilar territory in six (13%). One patient was found at presentation to have had a pure lacunar stroke of the basis pontis, which was proved with MR imaging. The mean radiation dose to the patients was 20.8 mSv ± 3.2 (range, 15.6–33.1 mSv). During the multidetector CT examination, the mean heart rate was 67 beats per minute ± 15 (range, 57–95 beats per minute). β-Blockers were administered in 17 patients. Three patients had atrial fibrillation at presentation.

All patients underwent MR imaging, duplex US, and TTE. Thirty-nine patients underwent TEE, which was not possible in seven patients because of swallowing abnormalities. MR imaging was performed a mean of 2.8 days ± 3.1 before multidetector CT (range, 7 days before to 6 days after CT). Duplex US and TTE were performed on the same day a mean of 0.8 day ± 2.4 before multidetector CT (range, 6 days before to 4 days after CT), and TEE was performed a mean of 2.5 days ± 2.8 after multidetector CT (range, 5 days before to 10 days after CT).

The results of the cardiac explorations are provided in Table 2. Regarding the major sources of cardioembolic stroke, one case of intracardiac thrombus, which was localized at the apex of the left ventricle, was observed with multidetector CT but missed with TEE performed on the same day (Fig 1). Multidetector CT failed to depict one left ventricular wall hypokinesia out of nine that were diagnosed with TEE. Regarding minor sources, 10 of the 13 cases of septal abnormalities (patent foramen ovale and/or interatrial septal aneurysm) were diagnosed with multidetector CT (Figs 2, 3). Finally, spontaneous echo contrast was detected with TEE in three cases. These results led to multidetector CT having sensitivity and specificity for the detection of cardiac sources of 72% (18 of 25 cases; 95% CI: 50.6%, 87.9%) and 95% (20 of 21 cases; 95% CI: 76.1%, 99.8%), respectively, and a κ value of 0.79, corresponding to good agreement

Table 1

Demographic Data and Vascular Risk Factors for 46 Patients

Demographic or Risk Factor	Value
Mean age (y)*	63 ± 11.4
Male patients	38 (83)
Hypertension	22 (48)
Diabetes	7 (15)
Hyperlipemia	12 (26)
Active or previous smoker	15 (33)

Note.—Unless otherwise noted, data are numbers of patients ($n = 46$), with percentages in parentheses.

* Mean patient age ± standard deviation.

Figure 1

Figure 1: On multidetector CT image (two-chamber long-axis reconstruction) in 77-year-old man, thrombus (arrow) of left ventricular apex appears as nonenhanced lesion in left ventricular cavity.

Table 2

Cardiac Sources of Emboli Detected with Multidetector CT and Either TTE or TEE

	Multidetector CT							
	Intracardiac Thrombus		Left Ventricular Hypokinetic Wall		Patent Foramen Ovale and/or IASA*		Spontaneous Echo Contrast	
TTE or TEE	Detected	Not Detected	Detected	Not Detected	Detected	Not Detected	Detected	Not Detected
Detected	0	0	8	1	10	3	0	3
Not detected	1	45	0	37	0	33	0	43

* IASA = interatrial septal aneurysm.

between the two techniques. Regarding examination of the aortic arch, four patients with an atheroma greater than 4 mm in thickness were identified by using TEE. Multidetector CT confirmed these four cases and depicted two additional atheromas that were missed with TEE (Fig 4).

At analysis of the extra- and intracranial arteries, 14 carotid arterial stenoses of greater than 50%, including 10 cases of complete obstruction, and four extracranial vertebral artery lesions were detected with multidetector CT. These lesions were confirmed at duplex US and/or MR angiography in all cases. Regarding stroke of the internal carotid territory, a homolateral carotid arterial stenosis of greater than 50% was the only detected source in six patients. One case of stroke of the vertebrobasilar territory was related to atheroma. Finally, MR angiography facilitated the detection of two cases of asymptomatic (ie, contralateral to the actual stroke) intracranial arterial stenosis (middle cerebral artery), which was confirmed with multidetector CT. These results led to multidetector CT having sensitivity and specificity for the detection of major arterial atheroma of 100% (all 24 cases; 95% CI: 85.7%, 100%) and 91% (20 of 22 cases; 95% CI: 70.8%, 98.9%), respectively, and a κ value of 0.92, corresponding to very good agreement between the two techniques.

Figure 2

Figure 2: Multidetector CT image (four-chamber long-axis reconstruction) in 63-year-old man shows bulging (arrow) of septum secundum in right atrium. The bulging is considered an interatrial septal aneurysm.

The final classification of stroke cause assigned by using the combined strategy was cardiac sources in 20 (44%) of the 46 cases, major arterial atheroma in nine (20%), multiple sources in four (9%), and cryptogenic in 13 (28%). With use of multidetector CT, the final classification of stroke cause was cardiac sources in 15 (33%) of the 46 cases, major arterial atheroma in 12 (26%), multiple sources in three (6%), and cryptogenic in 16 (35%). These results led to a correct multidetector CT–based classification for 38 (83%) of the 46 patients and a κ value of 0.78, corresponding to good agreement between the two techniques.

Discussion

The results of this study demonstrate the feasibility and potential of single-session multidetector CT in the etiologic work-up of acute ischemic stroke. Compared with reference-standard methods such as TEE, multidetector CT appears to be feasible and well tolerated. Patient tolerance of multidetector CT is due mainly to the short duration of the examination, which is critical in patients with acute stroke, who may be unstable and agitated.

Figure 3

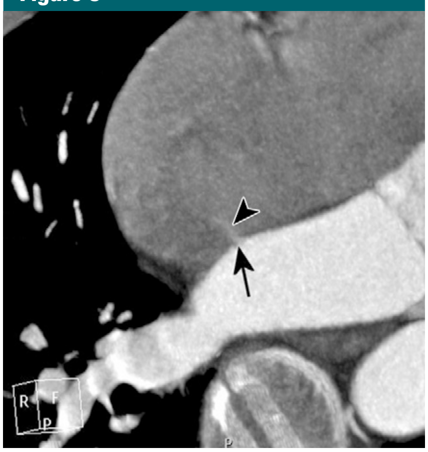

Figure 3: Multidetector CT image (four-chamber long-axis reconstruction) in 59-year-old woman shows patent foramen ovale with distinct flap (arrow) in left atrium at expected location of septum primum and jet of contrast material (arrowhead) from left atrium into right atrium.

Multidetector CT has been reported to have good accuracy for the identification of extra- and intracranial atheromatous disease (4,22). Multidetector CT may also yield information regarding plaque composition, including calcification and plaque attenuation characteristics, both which may be of interest in the assessment of vulnerable plaques (23). Furthermore, multidetector CT has been demonstrated to be effective and reproducible in the detection and quantification of aortic arch atheroma (24,25). In the identification of cardioembolic etiologies, Hur et al (10) achieved a sensitivity of 89% and a specificity of 100%. We achieved lower sensitivity in the current study, which might have been related to differences in the multidetector CT protocols: Hur et al (10) used a prospective ECG-triggered acquisition, the use of which strongly decreases the radiation dose and thus enables one to perform a second delayed acquisition. This acquisition protocol enabled the detection of circulatory stasis (corresponding to spontaneous echo contrast with US), which was systematically missed with our CT protocol.

Regarding the detection of patent foramen ovale and interatrial septal aneurysm, our study results were similar to those of Hur et al (10) but included sensitivity lower than that achieved by Williamson et al (9). This lack of sensitivity of multidetector CT for patent

Figure 4

Figure 4: Multidetector CT image (sagittal reconstruction) of aortic arch in 84-year-old man shows 5-mm-thick atheroma (arrows) of aortic arch with mixed calcified and hypoattenuating components.

foramen ovale and interatrial septal aneurysm detection will be difficult to overcome because the dynamic provocative maneuver performed in TEE to demonstrate the right-to-left shunt would require high temporal resolution and multiple dynamic scanning examinations at the same spatial resolution to be reproduced with multidetector CT and thus lead to an increase in the radiation dose. Finally, the accuracy of CT in the detection of left ventricular aneurysms, kinetic abnormalities, and intracardiac thrombus has been established in several studies (8,10,26–29).

In our study, the minor sources of cardioembolic stroke had the greatest effect on the multidetector CT–based final misclassifications, and lacunar strokes were not considered. Thus, in cases of negative multidetector CT findings, it may be necessary to perform complementary cardiac and brain examinations, ideally with TEE and MR imaging, because these techniques have the highest sensitivity (30,31).

The CT protocol we propose has two main limitations: First, two intravenous contrast material injections are required to study the chest and neck areas. Changing to a single-injection protocol would be more preferable to decrease the total amount of iodine administered. This would necessitate a change in the acquisition mode during scanning because ECG gating is required for the chest examination, but this mode would have to be switched off for the neck examination to decrease the radiation dose. This feature is not available on current clinical CT scanners, and its implementation represents an important challenge for future CT developments.

The second main limitation of our CT protocol is the required radiation dose. Despite an attempt to lower the dose by decreasing the milliampere-second setting (from 300 mAs per section), the retrospective helical mode we used for cardiac examination led to high radiation exposure. The optimal CT protocol for diagnosis and etiologic work-up might include a CT brain perfusion study followed by a single-shot acquisition in the ECG-gated prospective mode in the chest (in the feet-to-head direction) and then a non–ECG-gated acquisition in the neck vessels. Furtado et al (32) recently proposed the use of such a combination with a 64–detector row scanner and a protocol that enables evaluation of the coronary arteries. They reported good overall image quality but a high rate of failed examinations. The use of recently available large-detector CT scanners may address these shortcomings. Nevertheless, this strategy would need further validation—mainly of the accuracy of CT brain perfusion imaging, as compared with brain MR imaging, in identifying lacunar stroke.

Another limitation in our study was related to difficulties in establishing a standard of reference. The equivalence in diagnostic accuracy between multidetector CT and MR imaging for study of the carotid arteries may be well established (4,22), but the capability of multidetector CT for aorta and cardiac analysis is still being debated. In our study, we considered any multidetector CT finding that was not confirmed with TTE or TEE to be false positive. This led us to misclassify two large aortic plaques and one thrombus of the left ventricle that were obvious with multidetector CT, decreasing the overall specificity of the technique. Comparison with another method such as cardiac MR imaging for investigation of cardiac sources or assessment of the combination of multidetector CT and either TEE or TTE would be of interest.

The fact that intra- and interobserver reproducibility was not calculated represents an additional limitation of our study. The design of this open pilot study included a consensual analysis of all images by experienced observers. As such, the accuracy values are probably overestimated. Finally, the delay between CT and the other examinations was variable, and this might have hampered the comparison between CT and the other techniques. However, performing all examinations within 1 day generally is not possible owing to the poor clinical condition of these patients.

In conclusion, multidetector CT is a promising tool in the etiologic screening of ischemic stroke. Multidetector CT may be the first-line imaging modality for identifying acute ischemic stroke causes: It facilitated a correct etiologic classification in up to 83% of the patients in the current study. Negative multidetector CT results should be confirmed with TEE and MR imaging. This imaging strategy should be validated in a larger randomized study involving medical-economic analysis to prove its cost effectiveness in the etiologic work-up of ischemic stroke.

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