Gadolinium-enhanced thoracic CTA: retrospective analysis of image quality and tolerability in 45 patients evaluated prior to the description of nephrogenic systemic fibrosis

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Résumé

Angioscanographie thoracique au gadolinium en TDM multicoupe du thorax : analyse rétrospective de la qualité image et de la tolérance chez 45 patients évalués antérieurement à la description de la fibrose systémique néphrogénique

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Objectif. Évaluer la fiabilité et la tolérance des angioscanographies thoraciques au gadolinium en TDM multicoupe du thorax à 64 coupes par rotation en comparaison avec la technologie TDM à 16 coupes par rotation. Ce travail prospectif ayant été entrepris avant la description des complications de type de fibrose systémique néphrogénique (FSN), une attention particulière a été apportée dans la surveillance à long terme de la population explorée.

Matériel et méthodes. Cette étude était approuvée par le Comité d’Éthique de notre institution avec obtention d’un consentement éclairé pour chaque patient. Quarante-six patients (Groupe 1) (9 hommes et 5 femmes ; âge moyen : 64,3 ans) ayant une contre-indication à l’injection d’un produit de contraste iodé ont bénéficié d’une angioscanographie thoracique (collimation : 32 × 2 × 0,6 mm ; pitch : 1,2) au gadolinium (0,5 mmol/ml) administré à la dose de 0,4 mmol/kg avec un débit de 6 ml/s avec évaluation de la tolérance clinique et biologique du gadolinium. Les résultats de cette population étaient comparés à ceux d’une population de 31 patients (21 hommes ; 10 femmes ; âge moyen : 63,2 ans) (Groupe 2) ayant bénéficié d’une exploration du même type sur un scanner multicoupe à 16 coupes par rotation. L’ensemble de la population a été suivie sur une durée moyenne de 22,6 mois.

Résultats. Pour un volume moyen (déviation standard) non significativement différent (Groupe 1 : 54,8 ± 11 ml ; Groupe 2 : 53,4 ± 6,9 ml) (p = 0,94), les patients du Groupe 1 ont bénéficié d’une angioscanographie sur toute la hauteur du thorax alors que seul le tiers moyen était exploré dans le Groupe 2. Les angioscanographies étaient toutes diagnostiques dans le Groupe 1 et le Groupe 2 ; il existait cependant une proportion significativement plus importante d’angioscanographies interprétables jusqu’au niveau sous-segmentaire dans le Groupe 1 (10/14 ; 72%) que dans le Groupe 2 (6/31 ; 19%) (p = 0,003). Les valeurs moyennes d’atténuation au sein des artères pulmonaires ne différaient pas entre le Groupe 1 et le Groupe 2 (artères centrales : 194,5 ± 51,3 UH vs 180,6 ± 53,8 UH ; p = 0,38) (artères lobaire : 208,5 ± 52,5 UH vs 189,9 ± 60,1 UH ; p = 0,33) (artères segmentaires : 220,4 ± 50,4 UH vs 201,5 ± 54,7 UH ; p = 0,42). Une altération transitoire de la fonction rénale ±

Abstract

Purpose. To assess the accuracy and tolerability of gadolinium-enhanced thoracic CTA using a 64 MDCT compared to a 16 MDCT. Because this study was started prior to the description of NSF, particular attention was paid to long-term follow-up of the patient population.

Materials and methods. The study protocol was approved by the ethics committee of our institution and informed consent was obtained from all patients. Fourteen patients (Group 1) (9 males and 5 females; mean age: 64.3 years) with contraindication to the administration of iodinated contrast material underwent thoracic CTA (collimation: 32 × 2 × 0.6 mm; pitch: 1.2) with gadolinium administration (0.5 mmol/ml) at 0.4 mmol/kg injected at 6 ml/sec with evaluation of clinical and biological tolerability of the gadolinium based contrast agent. Results from this patient population were compared to results from a population of 31 patients (21 males; 10 females; mean age: 63.2 years) (Group 2) imaged on a 16 MDCT. All patients were followed-up for a mean time of 22.6 months.

Results. Using a mean contrast volume (standard deviation) that was not significantly different (Group 1: 54.8±11 ml; Group 2: 53.4±6.9 ml) (p=0.94), patients in Group 1 underwent complete thoracic CTA whereas patients in Group 2 underwent CTA of only the middle third of the thoracic region. All CTA examinations were diagnostic for Group 1 and Group 2 patients; however, evaluation of subsegmental vessels was possible in a significantly larger proportion of patients in Group 1 (10/14; 72%) compared to Group 2 (6/31; 19%) (p=0.003). Mean attenuation values within pulmonary arterial branches were similar for Groups 1 and 2 (central arteries: 194.5±51.3 HU vs 180.6±53.8 HU; p=0.38) (lobar arteries: 208.5±52.5 HU vs 189.9±60.1 HU; p=0.33) (segmental arteries: 220.4±50.4 HU vs 201.5±54.7 HU; p=0.42). Transient alteration of renal function was recorded in one patient from Group 1 with severe pre-existing chronic renal failure. No change in renal function was observed for Group 2 patients. No case of NSF was reported in patients with pre-existing renal failure at the time of enrollment.

Conclusion. The use of a gadolinium-based contrast agent for thoracic CTA using a 64 MDCT provides diagnostic quality examinations in all patients with improved image quality compared to a 16 MDCT. No complication other than transient alteration of renal
was investigated for thoracic CTA as soon as possible because thoracic CT angiography has become the examination of choice for the diagnostic management of numerous diseases of the thorax, patients with a contraindication to the administration of iodinated contrast agents present a practical problem for obtaining the morphological examination required by the clinician. These limitations of CT Angiography are mainly based on a history of impaired renal function and a severe allergic reaction to the administration of an iodinated contrast agent whose name the CTA patient does not necessarily know. In these cases magnetic resonance imaging is theoretically the alternative imaging technique. However, it is not a viable solution for the management of pulmonary vascular diseases because the results of CT are clearly more precise than MRI (1, 2) as seen by the decrease in prevalence of acute pulmonary embolisms. Despite the technological advances in MRI, the spatial resolution of CT is superior and is a determining factor in the depiction of endo- and perivascular abnormalities especially in the peripheral pulmonary vessels. Moreover, investigation of the pulmonary circulation is impossible without the morphological analysis of other anatomical parts of the thorax, in particular, the lung parenchyma, which cannot be visualized with MRI (3). CT can also provide detailed analysis of the systemic bronchial and non-bronchial collateral circulation, which is abnormally developed in numerous chronic pulmonary vascular diseases.

As a result, the use of gadolinium chelates was investigated for thoracic CTA as soon as the CT acquisition times were reduced. Coche et al were the first authors to report the diagnosis of pulmonary embolism with gadolinium-enhanced spiral CTA in 2001 (4). Following this publication Remy-Jardin, et al. continued these investigations and performed a prospective study of this approach by evaluating the diagnostic effectiveness of gadolinium-enhanced multidetector row thoracic CTA with a 4-detector row scanner (5) then 16-detector-row scanner (6). These studies showed that diagnostic quality examinations could be obtained as long as a 16 detector-row scanner was used because of the small amount of gadolinium administered. The aim of the present prospective study was to continue evaluation of the reliability of and tolerance to gadolinium-enhanced thoracic CTA with multidetector scanners using a 64-detector-row scanner, making it possible to study the entire thorax and compare it to results obtained with 16MDCT. Because this prospective study was begun before complications of NSF (nephrogenic systemic fibrosis) had been described in patients with renal insufficiency (7), we paid special attention when analysing the results and in the long term monitoring of patients in our population who were at risk of NSF.

Material et methods

Investigation protocol

This study was performed as a clinical phase II trial, with direct benefit to the patient, and after obtaining approval from the Comité de Protection des Personnes (Committee for the Protection of Individuals) at the Lille University Hospital. It was preceded by two phases, which investigated respectively, the diagnostic efficacy of and tolerance to gadolinium-enhanced CTA with 4-detector row CT (5) then with 16-detector-row CT (6). The goal of the present study was to evaluate the diagnostic efficacy of and tolerance to gadolinium-enhanced CT angiography with 64MDCT whose characteristics should make it possible to overcome the technological limitations of 16MDCT. The patients who underwent CT angiography with 64-detector-row CT in the protocol described below are the main population in this study (Group 1). The results of this group were compared to the group that underwent CTA under similar conditions with 16MDCT (Group 2). The population in Group 2 included 31 patients in a randomized study that was previously reported by Remy-Jardin, et al. (6). This study, like the preceding studies, received support from the company Schering (Berlin, Allemagne) which provided the contrast agent administered to the patients (gadopentate dimeglumine; Magnevist). An automated dual head injector (Spectris) was provided by Medrad (Pittsburgh, Pa., USA) for this study. Eligibility criteria for patients in the study included:

- An indication for CTA of the pulmonary circulation for the diagnosis or follow-up of a thoracic disease;
• in patients with a contraindication to iodinated contrast agents. Exclusion criteria were clinical instability, pregnancy, breastfeeding, younger than 18, having had or scheduled to have an examination with gadolinium in the 24 hours before or after the present gadolinium-enhanced CTA, impossible to catheterize a peripheral vein with an 18G catheter (necessary for high speed injection of gadolinium in the present study), a history of haemolytic anaemia, or severely impaired renal function without hemodialysis. Evaluation of the reliability of and tolerance to gadolinium was based on the measurement of vital signs and several biological parameters. Informed consent was obtained from each patient before the CT scan was performed.

The number of subjects needed in Group 1 was determined by the Department of Medical Statistics at the University of Lille II as set out in the chapter “Statistical Analysis”.

Study population

Group 1

Between June 2004 and July 2005, 14 patients (9 men; 5 women) were included in Group 1. All patients had a relative or absolute contraindication to the injection of an iodinated contrast agent, including those with chronic renal insufficiency alone (n=7) chronic renal insufficiency associated with intolerance to iodinated contrast agents (n=6) and intolerance to iodinated contrast agents (n=1). The history of intolerance to iodinated contrast agents (n=7) included severe skin reactions (n=2), laryngeal edema (n=2) and a malaise immediately after the injection. These patients systematically received medication with histamines and corticosteroids 48 hours before the gadolinium-enhanced CTA was performed. The 13 patients with pre-existing chronic renal insufficiency had chronically elevated serum creatinine levels (>15mg/L) and decreased creatinine clearance values (<70ml/min). Chronic renal insufficiency was classified as moderate in 5 out of 13 patients (creatinine clearance values between 70 and 50ml/min), marked in 4 of the 13 patients (creatinine clearance values between 50 and 30ml/min) and severe in 4 of the 13 patients (creatinine clearance below 30ml/min). None of these patients was receiving hemodialysis. The causes of these 13 cases of renal insufficiency were diabetic nephropathy (n=4), vascular renal disease in 3 patients, one stage III lupus nephropathy, a glomerulopathy of a kidney graft in a renal transplant patient due to nephrotoxicity from the cyclosporin administered for a cardiac transplant, a chemotherapy induced nephropathy in a patient being treated for pulmonary adenocarcinoma and from unknown causes in 3 patients. Indications for CTA included suspected pulmonary embolism (n=8), pre-therapeutic evaluation or follow-up for a tumoral disease of the thorax (n=6).

Group 2

Between September 2002 and March 2004, 31 patients (21 men; 10 women) were included in Group 2. These patients were referred for thoracic CTA with 16-detector-row CT. All patients had a relative or absolute contraindication to the injection of iodinated contrast agents, including chronic renal insufficiency, (n=13), intolerance to iodinated contrast agents (n=12); diabetes (n=2); history of anaphylactic reaction following drug administration (aspirin, penicillin) (a situation which is known to potentially be associated with the risk of life-threatening complications during the administration of contrast agents) (n=2); a recent history of acute renal failure with a return to normal renal function so that clinicians chose to replace iodine with gadolinium for the CTA (n=2). The history of intolerance to iodinated contrast agents included severe skin reactions (n=10) and laryngeal edema (n=2); these patients received specific medication with corticosteroids and histamine 24 hours before undergoing gadolinium-enhanced CTA.

The 13 patients at risk of nephrotoxicity to gadolinium because of pre-existing chronic renal insufficiency had chronically elevated serum creatinine levels (>1.5mg/dl [133μmol/l]) and decreased creatinine clearance values (<50ml/min). The chronic renal insufficiency was classified as moderate in 2 of the 13 patients (creatinine clearance between 70 and 50ml/min), marked in 4 of the 13 patients (creatinine clearance between 50 and 30ml/min) and severe in 7 of the 13 patients (creatinine clearance values below 30ml/min). None of the patients required hemodialysis. The causes of these 13 cases of renal insufficiency included diabetic nephropathy (n=6), post-chemotherapy renal insufficiency (n=2), IgA and IgGk glomerulonephritis (n=2), extended nephrectomy of the left kidney (n=1) and of unknown causes in 2 patients. Indications for CTA included suspected pulmonary embolism (n = 21) and pre-therapeutic evaluation or follow-up of a tumoral disease of the thorax (n = 10). As in Group 1, the patients in this group with a history of an allergic or adverse reaction to iodinated contrast agents systematically received premedication with histamines and corticosteroids 48 hours before gadolinium-enhanced CTA.

CT examination

CT protocol

Group 1

Gadolinium-enhanced CTA was performed in the cranio-caudal direction along the entire length of the thorax with a 64-detector-row CT scanner (Sensation 64, Siemens, Forchheim, Germany), with the following examination parameters: 80-120kV; 90-120mAs; rotation time: 0.33s, collimation: 32×2×0.6mm with a floating focus allowing simultaneous acquisition of 64, 0.6mm slices; pitch: 2, with reconstruction of contiguous transversal 1mm thick slices. Because attenuation of gadolinium increases as tube voltage decreases (8, 9), tube voltage was selected for each patient in relation to his/her weight and based on the following criteria: (a) 80kV for a weight <50kg; (b) 100kV for between 50 et 69kg; (c) 120kV for between 70 and 100kg. No automated dose reduction system was used to avoid introducing noise that could potentially reduce the reliability of examinations performed with low volumes of gadolinium. The mediastinal and lung images were reconstructed respectively with low and high spatial frequency algorithms and viewed in window settings for the mediastinum (width: 350HU; center 30HU) and lung (width 1600HU; center 600HU).

Group 2

It was not possible to obtain a CTA of the entire thorax with the 16MDCT technology because of the low volume of contrast agent administered. As a result, CTA of the pulmonary circulation was limited to scanning the region of interest extending from the aortic arch to the inferior pulmonary veins as quickly as possible. Therefore, unenhanced images of the entire thorax were obtained before performing gadolinium enhanced CTA so images of the upper and lower regions of the thorax could be obtained. CTA was performed with a 16-detector-row CT scanner (Sensation 16, Siemens, Forchheim, Germany) with the following parameters: 80-120kV; 70-

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120mAs; rotation time: 0.5s; collimation: 16x1,5mm; pitch: 1.5 with reconstruction of contiguous transversal 2mm thick slices. Tube voltage was adapted to each patient according to his/her weight based on the following criteria:
- 100kV (80kV when possible on the machine) for <70kg;
- 120kV for ≥ 70kg.

No automated dose reduction system was used. The CT examinations with and without enhancement were performed in the craniocaudal direction. The mediastinal and lung images were respectively reconstructed with a low- and high- spatial frequency algorithms in window settings for viewing the mediastinum (width: 350HU; center: 30HU) and lungs (width: 1600HU; center: –600HU).

**Gadolinium administration**

The protocol for administration of gadolinium was similar in both groups of patients. Each patient received a dose of 0.4mmol/kg of gadolinium (gadolinium concentration: 0.5mmol/mL) (contrast agent: gadopentate dimeglumine – Magnevist - Schering). The corresponding volume of contrast agent was administered with an automated injector at a rate of 6ml/sec using the same evaluation procedure as in the previous studies (5, 6). The injection of gadolinium was followed by a 15ml injection of saline flush in all patients at a rate of 3ml/s. Automatic bolus-triggering software (Care Bolus software; Siemens Medical Solutions; Forchheim, Germany) was systematically used with a region of interest on the pulmonary artery trunk. The threshold for triggering sequences was between 50-70HU. When this threshold was reached, another 4 second interval was necessary before scanning began as the table moved to the pulmonary apex.

**Evaluation of tolerance to and efficacy of gadolinium-enhanced CTA**

Parameters evaluated in Groups 1 and 2:

**Parameters to evaluate tolerance**

Because adverse reactions have been reported after gadolinium administration (10), we systematically evaluated clinical and biological tolerance to gadolinium. The occurrence of adverse effects such as a burning sensation at the injection site, local pain (from extravasation of gadolinium), minimal to moderate allergic reactions such as nausea, vomiting, headache, flushing, allergic skin reactions, severe anaphylactic reactions and/or convulsions were investigated for the 24 hours following gadolinium administration. Biological tolerance was investigated in blood samples obtained 24 hours before (T0) and 24 hours after (T1) gadolinium administration. The latter criterion was chosen from the time intervals reported in the literature to define contrast-induced nephropathy (11) and in agreement with the nephrologists participating in this study (PhD). C creatinine, iron, haptoglobin, white blood cell count, and reticulocytes were measured in serum. To evaluate renal tolerance to gadolinium, the primary variables were changes in creatinine levels in serum after gadolinium injection in patients with normal renal function, and changes in creatinine clearance values after gadolinium injection in patients with pre-existing alterations in renal function. In patients with normal renal function before CTA, acute gadolinium-induced changes in renal function were defined as an increase of at least 5mg/l in creatinine levels in serum in the 24 hours following gadolinium injection. An acute change in renal function secondary to gadolinium administration in patients whose renal function was impaired prior to CTA was defined as a reduction in creatinine clearance values of at least 10% in the 24 hours after gadolinium-enhanced CTA was performed. Creatinine clearance rate was estimated by the Cockcroft formula [(140 - the patient’s age) x patient’s weight] divided by [7.2 x creatinine serum concentration]; for female patients, the result was multiplied by a factor of 0.85. The volume of gadolinium administered to each patient was systematically noted. Clinical signs of NSF were looked for including the presence of erythematous patches, subcutaneous edema, pruritis, a burning sensation, pain and paresthesia during gadolinium administration and in the weeks following CT.

**Parameters evaluating efficacy**

The CT parameters evaluated in groups 1 and 2 included:
- Attenuation in the pulmonary arteries based on the placement of a circular region of interest (ROI) on the 3 pulmonary arteries (central pulmonary artery, right and left interlobar pulmonary arteries) (average surface of the region of interest 1.5cm²); the mean value of these 3 measurements defined the level of enhancement in the central pulmonary arteries.
- Attenuation in the lobar arteries based on a circular region of interest (ROI) placed on the 4 lobar arteries (mediastinal artery of the upper right lobe, culminal artery, right and left inferior pulmonary arteries) (average surface of the region of interest 0.2cm²); the mean value of the 4 measurements defined the level of enhancement of the lobar pulmonary arteries.
- Attenuation in the segmental arteries based on a circular region of interest placed on the 4 segmental arteries (right and left anterior segmental arteries; right and left inferior segmental arteries) (average surface of the ROI, 0.1cm²); the mean value of these 4 measurements was used to determine the level of attenuation of the segmental pulmonary arteries as long as there was no supero-inferior attenuation gradient, a parameter which was confirmed for each patient. These segmental arteries where chosen because their respective orientation on the horizontal and vertical planes provided reliable density measurements, with no partial volume effect.

The density measurements of the subsegmental pulmonary arteries of the anterior segment of the right superior lobe and the posterior segment of the right inferior lobe were not obtained because of the small size of these vascular sections, and the risk of error. Attenuation at the subsegmental level was therefore classified as similar to or inferior to that of the segmental level that they originated from. Objective attenuation measurements from CTA images of the central, lobar and segmental pulmonary arteries were preformed by a radiologist (MRJ; 15 years of experience in thoracic CTA). These measurements were all obtained after data acquisition, during clinical management of the patient. To rate the confidence level of interpretation of CTA results (possibility of detecting an endo or periluminal abnormality), there were 3 grades of attenuation for the central, subsegmental and segmental arteries: excellent (attenuation >150HU), good (attenuation between 100 and 150HU) and poor (<100HU). A CTA was considered to be interpretable up to:
- The subsegmental level (grade 1) in case of good or excellent enhancement of the
central, segmental and subsegmental arteries;
- The segmental level (grade 2) in case of good or excellent enhancement of the central, segmental arteries with poor enhancement of the subsegmental arteries.
- The central level (grade 3) when a reliable analysis could only be made of the lobar and central arteries with good enhancement for this region and poor opacification elsewhere;
- Grade 4 was characterized by poor opacification of the central arteries to the segmental arteries, making it impossible to detect endo and/or perivascular abnormalities.

Grades 1 to 3 corresponded to diagnostic quality CTA while grade 4 corresponded to non-diagnostic examinations. The height of the scanned thorax and acquisition times were noted for each examination.

### Conditions for the evaluation of clinical, biological and CT parameters

During the investigation period, clinical and biological tolerance to gadolinium-enhanced CTA was monitored first by the radiologist in charge of the examination, then by the physician who had referred the patient. An observation notebook was systematically filled out by the principal investigator (MRJ), which included clinical, biological and CT data. To evaluate immediate tolerance during the examination, each patient was monitored during and after the examination (immediately after and 30 minutes following the injection). All CT examinations were interpreted prospectively to provide appropriate patient management. Prospective analysis of biological tolerance to gadolinium was performed by a nephrologist participating in the study (PhD). For the present retrospective analysis, gadolinium enhanced CTA results were reinterpreted by consensus by 2 radiologists, one University Hospital radiologist with 15 years experience in thoracic CTA (MRJ) and another junior radiologist (LS) with 5 years experience in CT. The readers were aware of the conditions of the CT examination but had no information about general tolerance, in particular about renal function at the time of the CTA. CTA reliability scores were obtained from a consensus of the two readers (MRJ; LS). Finally, the investigation of NSF type complications in patients with pre-existing renal insufficiency was performed retrospectively because this complication had not been described when the patients were included in the study. The duration of clinical follow-up was noted for each patient.

### Statistical analysis

#### Calculation of the number of subjects necessary in Group 1

To obtain a rate of interpretable CTA above 0.7 (70%), 35 subjects were needed for Group 1 for a classic 1 step analysis (12), with the following data:
- risk of type 1 error = 10% and risk of type 2 error = 5%,
- null hypothesis $p_0=0.7$, alternative hypothesis $p_a=0.9$.

The number of subjects needed for Group 1 was determined using the methodology of phase II clinical trials. To minimize the number of patients to be included if the new strategy (gadolinium-enhanced CTA with 64MDCT) was more effective, or on the contrary less effective, the use of a grouped sequential method with a triangular test was especially well adapted (13, 14). For this trial, we chose to evaluate inclusions and calculate the success rate (percentage of diagnostic CTA) in groups of 7 patients. Based on the above hypothesis, a maximum of 35 subjects was needed for the triangular sequential plan, thus 5 potential intermediary tests (7 subjects then 14, 21, 28 and 35 subjects), but with a very strong probability of concluding before this, because that is the goal of triangular plans.

Patients were included by groups of 7. A first analysis was performed in the first 7 patients, with the number of successes (rate of diagnostic CTA) and E the number of failures (E+S=7). We then calculated $V=7p_0 (1-p_0)$ and $Z=S-7p_0$. There were three possible results:
- the point is located in the area of “proven efficacy”: we discontinue patient inclusion and efficacy is considered to be above 70%,
- the point is located in the area of “efficacy too low”: we discontinue inclusion and efficacy is considered to be below 70%,
- the point is located in an area of uncertainty: we continue inclusion.

If inclusion continues after the first analysis, a second analysis is performed on another 7 patients with the same rules for stopping and this continues until a maximum of 35 patients have been included. This method makes it possible to determine either the usefulness of gadolinium (success rate more than 70%) or to abandon its use because the success rate is too low.

### Results

#### Characteristics of the studied populations

Group 1 included 14 patients because of the 100% success rate (number of diagnostic CTA) in 7 then 14 patients. Group 2 included 31 patients. Table I shows the characteristics of both groups. There was no significant difference between the two groups for weight, height or age. CT was indicated for:
- investigation of pulmonary embolism (Group 1: n=8; 57%; Group 2: n=21; 68%);
- evaluation/follow-up of tumoral disease (Group 1: n=6; 43%; Group 2: n=10; 32%).

#### Effectiveness of gadolinium-enhanced CTA

Table II shows the technical characteristics of the gadolinium-enhanced CTA protocol in Groups 1 and 2. The average acquisition times and thoracic heights measurements were significantly greater in Group 1 than in Group 2. There was no significant difference in mean gadolinium volumes administered to the two groups. There were significantly more low voltage CTA examinations performed in Group 1 than in Group 2 (fig. 1 et 2).

Table III shows the attenuation in the pulmonary arteries in Groups 1 and 2. There was no significant difference in mean attenuation between the 2 groups in any of the anatomical areas studied. Table IV shows the results for reliability of interpretation of gadolinium-enhanced CTA.
CTA in Groups 1 and 2. It should be noted that all examinations were coded as being of diagnostic value in both groups. However, there was a significant difference in the qualitative rating of the CT angiogram results between the two groups (p=0.003) with more CT angiograms that could be interpreted at the subsegmental level in Group 1 (p=0.003), than in Group 2 (fig. 3).

No pulmonary embolisms were detected in the 29 patients with suspected pulmonary embolisms. CT angiograms for evaluation or follow-up of treatment for tumoral diseases were successful in all 16 patients referred for this indication allowing the evaluation of disease progression necessary to make therapeutic decisions.

Tolerance to gadolinium-enhanced CTA

No adverse reactions occurred after gadolinium injection, in particular no allergic reactions occurred in patients with a history of intolerance to iodinated contrast agents. The injections were not painful and no gadolinium extravasation was observed. Table V summarizes renal tolerance to gadolinium.

In group 1:
- 13 patients had pre-existing renal insufficiency before CTA and 1 patient had normal renal function;
- After CTA: (b-1) there was no significant reduction in creatinine clearance values; (b-2) however, one patient with pre-existing renal insufficiency had a transitory alteration in renal function (clearance before CT: 39ml/min; clearance after CT: 30ml/min) which returned to baseline in 48 hours.

In Group 2:
- 18 patients had normal renal function before gadolinium-enhanced CTA and 13 patients had pre-existing renal insufficiency;
- After CTA: (b-1) there was no significant change in creatinine clearance values; (b-2) however, no adverse reactions occurred in patients with a history of intolerance to iodinated contrast agents. The injections were not painful and no gadolinium extravasation was observed.

Table V summarizes renal tolerance to gadolinium.

Discussion

This study shows that 64-detector-row CT provides higher quality gadolinium-enhanced thoracic CTA results than those obtained with 16-detector-row CT. Because the diagnostic reliability increases as the confidence level of the analysis of the peripheral parts of the pulmonary arterial tree increases, it is interesting to note that 72% of the examinations in Group 1 could be interpreted up to the subsegmental level (vs 19% of those in Group 2). If segmental and subsegmental readings are grouped together, this study shows that there is a high level of confidence in the analysis of the peripheral arterial bed in 93% of patients, while only 54% of the CTA obtained with 16-detector-row CT reached this confidence level. Several improvements in the imaging technology can explain these differences. First, temporal resolution has improved with 64-detector-row CT, making it possible to scan the entire thorax in Group 1 – at the risk of having a longer average acquisition time – while only the middle third of the thorax could be explored in Group 2.

It should be noted that the mean volume of contrast medium was not significantly different between the two groups. There was no significant difference in the enhancement density in the pulmonary arteries between the two groups. These results...
were possible thanks to both improved temporal resolution and also a larger selection of low tube voltages for the images in Group 1. Unlike Group 2 where most patients were scanned at 120kV (64% of patients), 78% of patients in Group 1 were explored at between 100 and 80kV. This situation is very favourable for gadolinium-enhanced CT (8). Finally, the CTA in Group 1 were obtained with an inframillimetric collimation and reconstruction of 1mm thick slices while collimation was 16x1.5mm with reconstruction of 2mm slices in Group 2. Thus, the quality of CT examinations with the technical parameters in Group 1 is comparable to that obtained with multidetector CTA with an iodinated contrast agent (15-19). Although the results of this study confirm that diagnostic thoracic CTA can be obtained in patients who cannot receive iodinated contrast agents, certain limitations must be mentioned in the present study. The first, the dose of gadolinium used in this study (0.4mmol/kg) is above the existing maximum accepted doses (0.3mmol/kg). In a preliminary study, we found that the diagnostic efficacy of thoracic CTA was better with a dose of 0.4mmol/kg than with 0.3mmol/kg, mainly because of the increased volume of contrast agent administered (6). There were no adverse effects on renal function at that dose in any of the 13 patients presenting with chronic renal insufficiency at inclusion. In the present study, one case of...
transitory acute renal insufficiency occurred in a patient in Group I. The occurrence of this type of complication may have been underestimated because biological testing was performed within 24 hours after gadolinium injection while the most common interval for monitoring usually extends from 24 to 72 hours. However, this limitation was compensated by the fact that our patients, who were all hospitalized for CTA, underwent periodic biological testing. None of the tests within 8 days after CT showed changes in renal function, in particular in patients with pre-existing impaired renal function. It should be remembered that official approval for administration of a triple dose of gadolinium in MRI does not exist except for the diagnosis of brain metastases. Despite this, gadolinium administration at doses of 0.3, 0.4 and 0.5 mmol/kg have been reported in the literature both in angio MR and CT angiography, and other exploratory radiographic examinations with no deleterious effects. (20-27). The third limit to our study concerns the population selected for gadolinium-enhanced CT angiography. In 2008, this population could no longer include patients with severe renal insufficiency, whose creatinine clearance value was below 30 ml/min, because they are at high risk of developing NSF. It should be remembered that this complication which was previously known as nephrogenic fibrosing dermopathy was described in
1997, but the relationship between this entity and gadolinium contrast agents was not described until 2006 (7). The development of clinical symptoms of NSF can occur on the day of the injection and up to 2 to 3 months after gadolinium administration. Because our study is retrospective, we included systematic follow-up of all patients with impaired renal function at gadolinium administration. During an average follow-up of 22.6 months, no complications of this type occurred. It should be noted that the incidence of NSF varies depending on the type of contrast agent administered because of the physicochemical differences, and differences in stability of the different contrast agents. The incidence of NSF with gadopentate dimeglumine which was used in this study, is estimated to be between 0.1 and 1% in high risk subjects, including not only patients with severe chronic renal insufficiency but also dialysis patients and patients with impaired renal function who have are waiting to have a liver transplantation (28). Based on existing knowledge, moderate to severe renal insufficiency should be criteria for taking special care, or even exclusion from gadolinium enhanced CT angiography. Evaluating the risk-benefit of a diagnostic examination with a contrast agent is the key issue when deciding upon this indication in this population. The second target population for thoracic gadolinium-enhanced CT angiography is patients with a history of severe intolerance to iodinated contrast agents. Patients with a history of a drug-induced anaphylactic reaction may also be concerned. Indeed, this situation is known to be potentially associated with life-threatening complications during administration of iodinated contrast agents. In particular, results of examinations with gadolinium have not been shown to be better than those with low iodine contrast agents. In our clinical practice (excluding patients with renal insufficiency) when gadolinium enhanced CT angiography is the only diagnostic investigation, clinicians and radiologists discuss the risk-benefit to decide whether to perform this examination. If the indication for this procedure is maintained, our institution approves occasional gadolinium-enhanced thoracic CT angiographies, as long as the patient is informed of the reasons the test has been indicated and that this is noted in the medical file. This situation fulfills the criteria for the use of contrast agents “outside marketing approval” which was recently mentioned in the literature (29). Angio MRI is an interesting alternative in these patients, because the doses of gadolinium are lower than those used in this study. As a recent study shows, results up to the segmental level in the study of the pulmonary arterial bed make it appropriate for the diagnosis of pulmonary embolism in patients with contraindications to iodinated contrast agents (30).

**Conclusion**

This study shows that high quality diagnostic pulmonary CT angiograms can be obtained of the entire thorax using ga-

<table>
<thead>
<tr>
<th>Table III</th>
<th>Quality of arterial enhancement during CT angiography.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td>MDCT</td>
</tr>
<tr>
<td>64 slice/rot</td>
<td>14 patients</td>
</tr>
<tr>
<td>Central pulmonary arteries, HU</td>
<td></td>
</tr>
<tr>
<td>Average (median)</td>
<td>194.5 (192)</td>
</tr>
<tr>
<td>(range)</td>
<td>(102.7-279.7)</td>
</tr>
<tr>
<td>Lobar pulmonary arteries, HU</td>
<td></td>
</tr>
<tr>
<td>Average (median)</td>
<td>208.5 (208.6)</td>
</tr>
<tr>
<td>(range)</td>
<td>(104.8-307.1)</td>
</tr>
<tr>
<td>Segmental pulmonary arteries, HU</td>
<td></td>
</tr>
<tr>
<td>Average (median)</td>
<td>220.4 (230.7)</td>
</tr>
<tr>
<td>(range)</td>
<td>(124.2-300.1)</td>
</tr>
</tbody>
</table>

HU: Hounsfield units; δ: Wilcoxon test for independent samples.

Fig. 3: Patient with lupus disease referred to search for a pulmonary embolism (160cm; 55kg). Gadolinium-enhanced CT angiography was indicated because of chronic renal insufficiency. The image obtained at the level of the culmen shows the excellent quality of enhancement at the segmental (large arrow) and subsegmental levels (small arrows). The CTA does not show any endoluminal abnormality in the central or peripheral arterial bed.

The least toxic gadolinium chelate is recommended. The frequency of NSF is different depending on the gadolinium chelates used, use of rate of NSF is different depending on the gadolinium chelates used, use of gadolinium. There are no definitive recommendations for this diagnostic strategy, which should exclude patients with severe renal insufficiency because of NSF. Safety and effectiveness of gadolinium-enhanced multislice spiral CT angiography of the chest: preliminary results in 37 patients with contraindications to iodinated contrast agents. Radiology 2005; 235: 819-26.


Reference


Table IV
Reliability of interpretation of CT angiograms in Group 1 and 2.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT 64 slice/rot</td>
<td>CT 16 slice/rot</td>
</tr>
<tr>
<td>CT Angiography interpretable to the subsegmental level (Grade 1 CTA)</td>
<td>10 (72%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>CT Angiography interpretable to the segmental level (Grade 2 CTA)</td>
<td>3 (21%)</td>
<td>11 (35%)</td>
</tr>
<tr>
<td>CT Angiography interpretable to the lobar level (Grade 3 CTA)</td>
<td>1 (7%)</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>Non-diagnostic CTA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There is a significant difference in the distribution of the reliability of interpretation of CT angiographies between Groups 1 and 2 (p=0.003; Fisher’s exact test).

Table V
Renal tolerance to gadolinium in Groups 1 and 2.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDM 64 slices/rot</td>
<td>TDM 16 slices/rot</td>
</tr>
<tr>
<td>Patients with normal renal function before gadolinium enhanced CT Angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients, n</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Serum creatinine before gadolinium average (median) (range) (mg/L)</td>
<td>9</td>
<td>9.8 (9.5) (6-14)</td>
</tr>
<tr>
<td>Serum creatinine after gadolinium average (median) (range) (mg/L)</td>
<td>10</td>
<td>10 (9.5) (6-14)</td>
</tr>
<tr>
<td>Number of patients with an increase in serum, n creatinine levels &gt;5mg/L</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Wilcoxon test for paired samples.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDM 64 slices/rot</td>
<td>TDM 16 slices/rot</td>
</tr>
<tr>
<td>Patients with pre-existing renal insufficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients, n</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>creatinine clearance before gadolinium average (median) (range) (mg/L)</td>
<td>39.2 (35.9)</td>
<td>29.6 (24.2)</td>
</tr>
<tr>
<td>creatinine clearance after gadolinium average (median) (range) (mg/L)</td>
<td>(6.2-67.7)</td>
<td>(7.10-61.10)</td>
</tr>
<tr>
<td>Number of patients with decreased creatinine clearance ≥ 10% after the examination, n</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Wilcoxon test for paired samples.
Gadolinium-enhanced thoracic CTA: retrospective analysis of image quality and tolerability in 45 patients evaluated