Dynamic enhanced multi-slice spiral CT in evaluation of blood flow patterns of solitary pulmonary nodules with enhancement

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Abstract  Objective  To investigate the methods of dynamic enhanced multi-slice spiral CT in evaluation of blood flow patterns of solitary pulmonary nodules (SPNs) with enhancement.  Methods  Seventy-eight patients with SPNs (≤4 cm) with strong enhancement underwent dynamic multi-slice spiral CT (Marconi Mx8000) scan before and after contrast enhancement by injecting contrast material with a rate of 4 mL/s. For the 40 patients in protocol one, one scan was obtained every 2 seconds during 15-45 and 75-105 seconds after injection, while for the 38 patients in protocol two, one scan was obtained every 2 seconds during 11-41 and 71-101 seconds. For all the patients, one scan was obtained every 30 seconds during 2-9 minutes. The section thickness was 2.5 mm for lesions ≤3 cm and 5 mm for lesions > 3 cm. Standard algorithm was used in the image reconstruction. Precontrast and postcontrast attenuation on every scan was recorded. The perfusion, peak height, ratio of peak height of the SPN to that of the aorta and mean transit time were calculated.  Results  The peak height, perfusion, ratio of peak height of the SPN to that of the aorta and mean transit time in malignant SPNs were 34.85 Hu ± 10.87 Hu, 30.37 ml/(min×100g) ± 11.4 ml/(min×100g), 13.78% ± 3.96%, 14.19 s ± 6.19 s respectively in protocol one, while those in protocol two were 36.62 Hu ± 10.75 Hu, 30.01 ml/(min×100g) ± 8.10 ml/(min×100g), 14.70% ± 4.71%, 13.91 s ± 4.82 s respectively. No statistically significant differences were found between the peak height (t = 0.673, P = 0.503), perfusion (t = 0.152, P = 0.880), ratio of peak height of the SPN to that of the aorta (t = 0.861, P = 0.393) and mean transit time (t = 0.199, P = 0.843) in malignant SPNs measured in protocol one and those measured in protocol two. All mean transit time in protocol two (36/36) were obtained, but only part of them (25/32) were obtained in protocol one.  Conclusion  Dynamic enhanced multi-slice spiral CT is a non-invasive method for quantitative evaluation of blood flow patterns of SPNs with enhancement and scans beginning at 11 seconds after injection of contrast material is suggested.  Key words  MSCT dynamic  Strong enhancement  Solitary pulmonary nodules  Blood flow patterns

Introduction

The solitary SPNs is one of the most common findings on chest radiographs [1]. The blood supply and metabolism of malignant nodules are qualitatively and quantitatively different from those of the most benign nodules [1]. At present, tumors are known to be angiogenesis-dependent [2]. The changes in the tumor vessels cause changes in blood volume, perfusion and capillary permeability [2]. These changes result in change in blood flow pattern and are basis of CT enhancement [2]. Dynamic enhanced computed tomography (CT) is helpful in distinguishing benign nodules from malignant nodules [3,4] and is an applicable method for investigation of tumor angiogenesis in bronchogenic adenocarcinoma [1,2].

With advance of technology, CT can now provides quantitative information about blood flow of neoplasm, which is so called functional CT. MSCT scans patients much faster than single slice CT, with higher temporal resolution and lower radiation doses [5]. It becomes possible to provide more accurately quantitative information
about blood flow patterns of SPNs with MSCT. The aim of this study is to investigate the methods of dynamic enhanced multi-slice spiral CT in the evaluation of blood flow patterns of SPNs with strong enhancement.

2 Materials and methods

2.1 Patient population Patients were selected according to the following criteria: (1) without any therapy before undergoing CT, (2) present of an SPN and smaller than 40 mm with enhancement, (3) absence of contraindication to the administration of contrast material, and (4) probable ability to cooperate with the procedure. The diameter was defined as the average value of the anteroposterior, lateral, and superoinferior diameters on CT scans obtained with a mediastinal window setting. The superoinferior diameter was obtained with a mediastinal window setting on multiplanar reformatting (MPR) image. Ninety patients with SPN met the criteria and underwent multi location dynamic contrast material-enhanced serial CT from April, 2002 to March, 2003. Three patients were excluded from the study because of substantial cardiac motion or beam hardening artifact and nine because of no or slight enhancement (peak height< 20 Hu).

Seventy-eight patients (55 men, 23 women; age range 35-76 years old, mean age 56 years old) with SPNs 8.5-39.7 mm (mean, 25.7 mm) were studied. Final diagnosis were confirmed histologically by means of surgery, CT-guided transthoracic needle aspiration biopsy, or transbronchial lung biopsy in 71 patients. In other seven patients, the diagnosis was based on resolution of the lesions on CT images after antibiotic treatment. Among the 78 patients, the diagnosis was malignant in 68 patients (adenocarcinoma in 46 patients, squamous cell carcinoma in 6 patients, bronchioloalveolar carcinoma in 5 patients, adenocarcinoma in 4 patients, small cell lung cancer in 5 patients and metastatic tumor from carcinoma of colon in 2 patients) and inflammatory in 10 patients. (Final diagnosis were confirmed histologically by means CT-guided transthoracic needle aspiration biopsy in three patients. In seven patients, the diagnosis was based on resolution of the lesions on CT images after antibiotic treatment.)

2.2 Protocol Patients were divided into two groups sequentially. The odd numbers made up of group one examined by protocol one (scans were obtained beginning at 15 seconds after injection of contrast medium) and the even numbers made up of group two by protocol two (scans were obtained beginning at 11 seconds after injection of contrast medium). Before the examination began, the patients were carefully instructed in and practiced the breathing technique to reproduce precisely the same degree of inspiration for each scan series.

Before dynamic scanning, control scans were obtained from which the scan level that best showed the SPN, close to the nodular equator, was selected. Multi location dynamic scans were obtained at the selected section with Marconi Mx8000 MSCT (Marconi Medical Systems, Ohio, America). Iodinated, low-osmolar, nonionic contrast material (ioversol injection, 300 mg iodine per milliliter, Mallinkrodt Inc., St. Louis, USA) was administrated via the antecubital vein at a rate of 4 mL/s for a total 90 ml by using an autoinjector. The section thickness was 2.5 mm for the nodule with a diameter less than 3 cm and 5 mm for the nodule with a diameter between 3 and 4 cm. Sixteen series CT scans were obtained beginning at (16 scans each for the first and second series and one scan each for the rest series) 15, 75 (40 patients, protocol one) or 11, 71 (38 patients, protocol two) 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510 and 540 seconds after injection of contrast medium. The scanning time was 0.75 second and the scanning interval was 1.25 second. Interseries delay was 30 seconds except for interseries delay between the second and the third which was 45 (protocol one) or 49 seconds (protocol two). Four images without contrast material enhancement and 184 dynamic contrast material-enhanced images were obtained during a 540-second scanning period for each patient. A normal reconstruction algorithm without edge enhancement (window width, 350 Hu; window level, 40 Hu) was used for dynamic scanning.

2.3 Data analysis Time attenuation curves were created from regions of the interest drawn over the SPN images with the biggest area, aorta (or common carotid artery if the aorta was not included in the sections) and inflammatory in 10 patients. The region of interest was as large as possible to minimize noise but with care to avert partial volume effect. According to this criterion, the area of the region of interest was about 60% of the area of the lung nodule but with care to avert calcification and necrosis. If there was substantial artifact from cardiac motion or beam hardening from adjacent bone to create rapid changes of attenuation, the image was eliminated from data analysis.

Time attenuation curves were created by using Time Lapse software in MxView workstation. Perfusion and mean transit time were calculated by using
functional CT software in MxView workstation.

Peak height (ie, the maximum value of the time attenuation curve, PH), defined as total attenuation minus baseline precontrast attenuation, was determined and the following ratio of peak height of the SPN to peak height of the aorta was calculated: \( \frac{\text{PH}_{\text{SPN}}}{\text{PH}_{\text{aorta}}} \times 100\% \).

Perfusion of the SPN was calculated by applying an unclear medicine data processing technique to the time attenuation data; this technique based on the general equation\(^6\): \( P = \frac{\text{TAC}_{\text{SPN}}}{\text{PH}_{\text{AA}}} \), where \( P \) = perfusion in milliliters of blood flow per minute per unit of tissue, \( \text{TAC}_{\text{SPN}} \) = the maximum gradient of the SPN time attenuation curve in Hounsfield units per minute and, and \( \text{PH}_{\text{AA}} \) = peak height of aortic attenuation in Hounsfield units.

All values were expressed as a mean \( \pm \) standard error. The significance of the difference between groups was analyzed by means of \( T \)-test. A \( P \) value less than 0.05 was considered statistically significant. All the statistical analysis were performed by SAS software.

3 Result

The results in this studies were showed in table one and table two. The time attenuation curve of the bronchogenic carcinomas usually showed a gradual increase to the peak height where it maintained plateau. The peak level of enhancement of the bronchogenic carcinomas was almost executing in 1 minute. No statistically significant differences were found between the peak height \( (t = 0.673, \ P = 0.503) \), perfusion \( (t = 0.152, \ P = 0.880) \), ratio of peak height of the SPN to that of the aorta \( (t = 0.861, \ P = 0.393) \) and mean transit time \( (t = 0.199, \ P = 0.843) \) in malignant SPNs measured in protocol one and those measured in protocol two (Fig 1, A-D). All mean transit time in protocol two \( (36/36) \) were obtained. Only part of them \( (25/32) \) were obtained in protocol one, because seven of the 32 malignant nodules had showed enhancement (peak height> 5 Hu) when the first scan began. Only one mean transit time in ten active inflammatory nodules was measured (Fig 2, A-D).

Fig 1 Dynamic CT scans in a 60-year-old man with adenocarcinoma of the right lower lobe. (A) The attenuation value was 33.3 Hu on the precontrast scan, (B) 67.5 Hu on the scan obtained 40 seconds after administration of contrast material, (C) perfusion value was 23.96 ml/(min 100 g), (D) mean transit time was 16 s.
Fig 2 Dynamic CT scans in a 65-year-old man with inflammatory nodule of the right lower lobe. (A) The attenuation value was 31.5 Hu on the precontrast scan, (B) 77.8 Hu on the scan obtained 71.8 seconds after administration of contrast material, (C) perfusion value was 60.88 ml/(min*100 g), (D) mean transit time was 16.1 s.

Tab 1 Nodule characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Malignant (n = 68)</th>
<th>Active inflammatory (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (cm)</td>
<td>2.57±0.82</td>
<td>2.30±0.64</td>
</tr>
<tr>
<td>Precontrast attenuation (Hu)</td>
<td>40.70±7.19</td>
<td>34.01±7.14</td>
</tr>
<tr>
<td>Peak height (Hu)</td>
<td>35.79±10.76</td>
<td>29.76±4.59</td>
</tr>
<tr>
<td>SPN to aorta (%)</td>
<td>14.27±4.37</td>
<td>18.51±2.71</td>
</tr>
<tr>
<td>Perfusion [ml/(min*100 g)]</td>
<td>30.18±9.58</td>
<td>36.44±4.37</td>
</tr>
<tr>
<td>Mean transit time (s)</td>
<td>14±5</td>
<td>(4-26)</td>
</tr>
</tbody>
</table>

All values were expressed as a mean ± standard deviation. Numbers in parenthesis were range for each parameter.

Tab 2 Malignant nodule characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group one (n = 32)</th>
<th>Group two (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak height (Hu)</td>
<td>34.85±10.87</td>
<td>36.62±10.75</td>
</tr>
<tr>
<td>SPN to aorta (%)</td>
<td>13.78±3.96</td>
<td>14.70±4.71</td>
</tr>
<tr>
<td>Perfusion [ml/(min*100 g)]</td>
<td>30.37±11.14</td>
<td>30.01±8.10</td>
</tr>
<tr>
<td>Mean transit time (s)</td>
<td>14.19±6.19</td>
<td>13.91±4.82</td>
</tr>
</tbody>
</table>

4 Discussion

At present tumor has been proved to be a kind of disease depending on angiogenesis\[^2,7\]. Angiogenesis research is now being translated from laboratory to clinical application. There is an increasing need to locate an angiogenic site, to quantify angiogenesis, and to develop end points for clinical trials of antiangiogenic therapy for cancer patients. Currently microvessel density (MVD) count is considered the standard for quantification of angiogenesis in histologic studies\[^2\]. The primary quantifiable parameters that can be derived with dynamic CT are perfusion, peak height and mean transit time in the study of angiogenesis in bronchogenic adenocarcinoma\[^2\].

The peak height is helpful in distinguishing benign nodules from malignant nodules\[^3,6\], while no help in differentiating active inflammatory nodules from malignant nodules\[^6\]. The changes in the tumor dysfunctional new vessels cause changes in blood volume, perfusion and capillary permeability\[^2,7\]. Flow of contrast material through intravascular space in an active inflammatory nodule takes place through relatively straight vessels with a normal configuration\[^8\]. Thus, perfusion value is high. The quantitative information about blood flow patterns is helpful in differentiating malignant nodules.
from active inflammatory[14].

In studies by Swensen et al[9], four spiral acquisitions at 1-minute intervals were obtained. Zhang et al[6] obtained 20 single scans at 2-second intervals during 105-second scanning period. Taking advantage of merits of MSCT[5], the authors modified the scanning procedure used by Zhang and Kono[6] and obtained encouraging results. The scanning procedure performed in this study has one distinct merits: High frequency recorded data with 0.75-second scanning time and 1.25-second intervals, which was more ideal theoretically[6] in providing quantitative information about blood flow patterns of SPNs.

Many researchers have found that a higher injection rate is more effective in increasing peak and overall contrast enhancement[6]. Yamashita et al[6] found that some lung carcinomas reached peak enhancement late, at 5 minutes, with an injection rate of 2mL/s, which may indicate that these lung carcinomas have a wide extravascular fluid pool because at that time more than 80% of the contrast material remains outside the blood vessels[10]. A relative lower injection rate may be responsible for such a late enhancement, because a slower injection rate results in not only a long time to peak enhancement but also a more proportional extravascular distribution at peak enhancement[6]. In this study, the authors used a technique having been used by Zhang et al[6] of intermittent bolus injection of 4mL/s.

The vascular supply of most pulmonary cancer is from the bronchial arterial system[11]. In most of the inflammatory pulmonary processes, because of diffuse thrombosis at the arterioles of the pulmonary circulation, the vascular supply is actually from the bronchial arterial system[6]. Transport time after injection reveals contrast material beginning to enter the intravascular space in the lung in 11–19 s via the bronchial artery[1]. Some malignant nodules would show enhancement on the scan obtained 15 seconds after injection of contrast material, as this results revealed. Miles[12] measured perfusion of some solid organs with dynamic computed tomography and obtained encouraging results. Zhang et al[6] measured perfusion of SPNs with the application of this technique in 1997. In study of Zhang et al[6], the first scan was obtained at 15 seconds. In order to found when scans begin after injection of contrast material was more rational the authors examined patient by two protocols. All mean transit time in protocol two were obtained, but only part of those were obtained in protocol one.

1–2 minutes after injection, most iodine molecules will be distributed in the extravascular space of issue rather than in vessels[13]. Thus, a bolus injection will provide sufficient vascular characterization only on the first few scans after injection[13]. In this study, the authors used a technique which had been used by Zhang et al[6] of intermittent bolus injection of 4mL/s. Thus, in early-phase scanning (15–45 seconds or 11–41 seconds), the authors could achieve high-quality studies with purely intravascular agents, without extravascular distribution[6]. The authors considered that measurement perfusion of SPNs with dynamic CT is possible, because with this intermittent bolus injection of 4mL/s, 0.75-second scanning time and 1.25-second intervals, data of the entire pass of one injected contrast bolus could be obtained.

The scanning procedure with shorter scanning intervals was more ideal theoretically in measuring the maximum gradient of the SPN time-attenuation curve and peak height of aortic attenuation accurately. The mean perfusion value of malignant nodules measured by Zhang and Kono[6] was 0.7ml/(min•ml) and by this study 30.18ml/(min•100g) which approximated to that [13.6–29.8ml/(min•100g)] measured with a single photon emission CT (SPECT)[14]. A shorter scanning interval may attribute to the difference.

No statistically significant differences in the peak height, perfusion, ratio of peak height of the SPN to that of the aorta and mean transit time were found between protocol one and protocol two. All mean transit time in protocol two were measured, but only part of those were measured in protocol one. Scans beginning at 11 seconds after injection of contrast material was suggested.

In this study, an 19-gauge mainline needle was used, by monitoring the progress of the injection visually and with palpation, no extravasation occurred.

Overall, this study suggests, with intermittent bolus injection of 4mL/s, 0.75-second scanning time and 1.25-second intervals, dynamic enhanced multislice spiral CT is a kind of noninvasive methods for quantitatively evaluation of blood flow patterns of SPNs with strong enhancement...
References


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