Detection of Amiodarone-Induced Pulmonary Toxicity in Supine and Prone Positions

--- High-Resolution Computed Tomography Study ---

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Background The aim of the present study was to describe the effectiveness and feasibility of high-resolution computed tomography (HRCT) in patients in supine and prone positions to detect amiodarone-induced pulmonary toxicity (APT). With regard to the possible differential diagnosis, our second goal was to emphasize the clinical value of HRCT with the patients in supine and prone positions compared with other paraclinical tests.

Methods and Results Thoracic HRCT taken in both positions for 23 patients who were administrated amiodarone were prospectively evaluated in the current study. High-resolution computed tomography scans obtained with the patient in a prone position were helpful in differentiating dependent opacity from lung disease in 11 out of 23 patients. In another 4 patients, HRCT scans obtained with the patient in a prone position were useful in confirming the presence of subtle ground-glass opacities, considered as APT. Combination of HRCT in supine and prone positions provided a more reproducible method for evaluating the global extent of APT than other paraclinical tests.

Conclusions High-resolution computed tomography used in prone positions as well as a supine position could be an effective technique for reducing false-positive results in detection of APT and preventing the clinically serious pulmonary adverse effects by amiodarone. (Circ J 2005; 69: 466–470)

Key Words: Amiodarone; High-resolution computed tomography; Prone position; Pulmonary toxicity; Supine position

Amiodarone is a unique anti-arrhythmic drug originally developed for angina! Because of its clinically proven effectiveness, amiodarone is now used to control atrial and ventricular arrhythmias. Unfortunately, many adverse effects are related to the use of this agent, especially pulmonary toxicity, so called amiodarone-induced pulmonary toxicity (APT). The condition of APT is extremely serious and difficult to diagnose, with an incidence of up to 13%. Patients with APT may have an associated mortality rate of 10% to 23%. The toxic effects of amiodarone seem to be related to dose and duration of therapy. However, a meta-analysis of studies using low-dose amiodarone revealed that the risk of experiencing pulmonary adverse effects was increased by twofold (1.9% vs 0.7%) compared with placebo treatment. APT can be difficult to diagnose clinically, but early recognition of APT is important because discontinuation of amiodarone could prevent its progression. In clinical practice, despite all radiological tests such as chest X-ray or computed tomography (CT), the diagnosis of APT is often reached by a therapeutic test: corticotherapy, given after the discontinuation of amiodarone.

Since the first report describing the patterns of CT findings in cases of APT 15 years ago, several studies on CT findings have been carried out. Kulhman et al have established the value of CT using standard techniques that provide a means of identifying patients with significant pulmonary accumulation of amiodarone. High-resolution computed tomography (HRCT) is well established for noninvasive evaluation of the thin structural details of the normal and pathological pulmonary parenchyma. Recently, HRCT findings of reversible APT and symptomatic patients with APT were reported.

The technique of HRCT is usually performed in a supine position. Atelectasis is commonly seen in the dependent lung in both healthy and diseased subjects on ordinal HRCT in supine positions, resulting in a ‘dependent density’ or ‘subpleural line’. However, there have been several reports claiming that HRCT in prone positions can be a useful modality to exclude the effect of gravity in patients with asbestosis. Volpe et al reported the usefulness of HRCT in prone positions when chest radiographs show normal findings, possibly abnormal findings, or minimal abnormalities indicative of diffuse lung disease. Therefore, an additional HRCT in prone positions may add important information by counteracting the effects of gravity on pulmonary vascularity. However, there is no study to evaluate APT by HRCT using a combination of supine and prone positions. The aim of the current study was to describe the effectiveness and feasibility of HRCT in patients in supine and prone positions to detect APT.

Serum KL-6 could be a useful maker of APT. A de-
obtained.

tions were performed only when oral informed consent was

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2001, were also included in the present study, because their

patients, who had been given amiodarone before October

Fourteen of the 23 subjects started receiving amiodarone

women (age range: 27–77 years, mean age: 58 years).

Study Protocol

The patient population consisted of 15 men and 8

underlying heart diseases.

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cal tests used to exclude other diagnoses depended on their

was a smoker at the time of the examination. The paraclini-

time of the initial CT evaluation. None of the 23 patients

None of the 23 patients had pulmonary symptoms at the

received 150 mg/day and 1 patient received 100 mg/day.

ence of amiodarone) to see if new changes related to APT

and compared them to the follow-up HRCT (in the pres-

drug administration was started. They otherwise followed

patients had already been receiving amiodarone before the

CT was taken every 3–4 months thereafter. The other 9

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patients had already been receiving amiodarone before the study period began, and did not undergo HRCT before

drug administration was started. They otherwise followed the same study protocol as the other 14 subjects. During the study period between October 2001 and July 2004, we prospectively evaluated the first prone and supine HRCT and compared them to the follow-up HRCT (in the presence of amiodarone) to see if new changes related to APT had occurred.

At the time of initial HRCT evaluation in the presence of amiodarone, 20 patients received 200 mg/day, 2 patients received 150 mg/day and 1 patient received 100 mg/day. None of the 23 patients had pulmonary symptoms at the time of the initial CT evaluation. None of the 23 patients was a smoker at the time of the examination. The paraclinical tests used to exclude other diagnoses depended on their clinical presentation. All patients underwent cardiac echocardiography for evaluation of cardiac function as well as underlying heart diseases.

Chest radiographies and KL-6 were obtained in all

crease in carbon monoxide lung diffusing capacity (DLCO) is also a sensitive indicator of APT in the presence of symptoms and radiological findings. However, it may lack specificity. In addition, DLCO technically depends on the patient’s efforts. In this regard, HRCT in supine and prone positions has a potentially greater ability to detect acute change and subtle structural damage of early stage APT objectively. With regard to the possible differential diagnosis, our second goal was to emphasize the clinical value of HRCT compared to other modalities such as pulmonary function test or KL-6.

Methods

Study Protocol

The patient population consisted of 15 men and 8 women (age range: 27–77 years, mean age: 58 years). Fourteen of the 23 subjects started receiving amiodarone between October 2001 and June 2003, and they underwent HRCT in supine and prone positions before and usually 1 month after initiation of amiodarone treatment. The other 9 patients, who had been given amiodarone before October 2001, were also included in the present study, because their initial HRCT in both positions revealed no apparent abnormal findings. In contrast to the regular scan interval of 10 mm, HRCT scans in prone positions were obtained at 20-mm intervals. This limited the increase in radiation doses up to 1.3 times. Principal investigator (Noriko Oyama) explained the usefulness of additional HRCT in prone positions to each patient, and the HRCT in both positions were performed only when oral informed consent was obtained.

After the initial HRCT subsequent to amiodarone admin-

Table 1 Patient Characteristics and Summary Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Underlying heart disease</th>
<th>Index arrhythmia</th>
<th>Treatment (months)</th>
<th>Dose (mg/day)</th>
<th>KL-6 (U/ml)</th>
<th>%DLCO</th>
<th>CT finding</th>
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<tbody>
<tr>
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<td>GGO (2)</td>
</tr>
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<td>p-AF</td>
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<td>(–)</td>
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</tr>
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<td>NSVT</td>
<td>15</td>
<td>200</td>
<td>219</td>
<td>(–)</td>
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<tr>
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<td>VT/VF</td>
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<td>200</td>
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<tr>
<td>8</td>
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<td>HCM</td>
<td>VF/p-AF</td>
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<td>200</td>
<td>188</td>
<td>19%</td>
<td>GGO (18)</td>
</tr>
<tr>
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<td>DCM</td>
<td>NSVT</td>
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<td>200</td>
<td>149</td>
<td>(–)</td>
<td>DO</td>
</tr>
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<td>OMI</td>
<td>VT</td>
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<td>501</td>
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</tr>
<tr>
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<td>DCM</td>
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<td>556</td>
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<td>VT</td>
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<td>DO</td>
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<tr>
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<td>M</td>
<td>OMI</td>
<td>VT</td>
<td>22</td>
<td>200</td>
<td>205</td>
<td>37%</td>
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</tr>
<tr>
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<td>M</td>
<td>OMI</td>
<td>VT</td>
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<td>150</td>
<td>496</td>
<td>Low</td>
<td>DO</td>
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<tr>
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<td>40</td>
<td>F</td>
<td>DCM</td>
<td>NSVT</td>
<td>25</td>
<td>100</td>
<td>318</td>
<td>16%</td>
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<tr>
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<td>34</td>
<td>F</td>
<td>DHCM</td>
<td>VT</td>
<td>27</td>
<td>150</td>
<td>209</td>
<td>36%</td>
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</tr>
<tr>
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<td>37</td>
<td>F</td>
<td>HCM</td>
<td>VF</td>
<td>33</td>
<td>200</td>
<td>145</td>
<td>(–)</td>
<td>N</td>
</tr>
<tr>
<td>18</td>
<td>27</td>
<td>M</td>
<td>HCM</td>
<td>VF/p-AF</td>
<td>35</td>
<td>200</td>
<td>133</td>
<td>(–)</td>
<td>N</td>
</tr>
<tr>
<td>19</td>
<td>63</td>
<td>F</td>
<td>DCM</td>
<td>VF/p-AF</td>
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<td>187</td>
<td>Normal</td>
<td>DO</td>
</tr>
<tr>
<td>20</td>
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<td>DCM</td>
<td>VT</td>
<td>42</td>
<td>200</td>
<td>654</td>
<td>Normal</td>
<td>N</td>
</tr>
<tr>
<td>21</td>
<td>74</td>
<td>M</td>
<td>DCM</td>
<td>VT/VF</td>
<td>42</td>
<td>200</td>
<td>252</td>
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<td>DO</td>
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<tr>
<td>22</td>
<td>76</td>
<td>M</td>
<td>DHCM</td>
<td>VT</td>
<td>55</td>
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<td>223</td>
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<tr>
<td>23</td>
<td>52</td>
<td>M</td>
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<td>VF</td>
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<td>200</td>
<td>202</td>
<td>Low</td>
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</tbody>
</table>

A low value carbon monoxide lung diffusing capacity in %DLCO indicates that the baseline %DLCO was less than 80% without significant decrease during amiodarone therapy. (–) in %DLCO represents absence of the data. Number in parentheses of computed tomography finding indicates the interval from the beginning of amiodarone administration. Nine patients (cases 4, 8, 17–23) had been given amiodarone before the present study began.

M, male; F, female; OMI, old myocardial infarction; HCM, hypertrophic cardiomyopathy; AVR, aortic valve replacement; DCM, dilated cardiomyopathy; DHCM, dilated HCM; VF, ventricular fibrillation; VT, ventricular tachycardia; NSVT, non-sustained VT; p-AF, paroxysmal atrial fibrillation; GGO, ground glass opacity; DO, dependent opacity; N, normal.

Table 2 High-Resolution Computed Tomography Findings in Amiodarone-Induced Pulmonary Toxicity

<table>
<thead>
<tr>
<th>Case</th>
<th>CT finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right lower lobe, ground-glass opacity, diffuse distribution</td>
</tr>
<tr>
<td>2</td>
<td>Bisasilar areas, ground-glass opacity with reticulation</td>
</tr>
<tr>
<td>3</td>
<td>Right lower lobe subpleural areas, ground glass opacity with reticulation</td>
</tr>
<tr>
<td>4</td>
<td>Right lower lobe, ground-glass opacity, focal distribution</td>
</tr>
</tbody>
</table>
patients at the time of the follow-up period. A KL-6 value above 400 U/ml was defined as abnormal, as it is our institutional criteria. Percentage DLCO (%DLCO) was also measured at the time of HRCT evaluation if the patient's condition was stable. A 20% decrease in %DLCO from the initial examination was defined as a positive indicator of APT.

During the follow-up period, detection of APT by HRCT in both supine and prone positions prompted us to stop amiodarone treatment if an abnormality in either the %DLCO or KL-6 was present. Patients with neither %DLCO nor KL-6 abnormality continued to receive amiodarone and were closely monitored and evaluated clinically.

Results

Table 1 shows the baseline characteristics of the 23 patients: case numbers, their age, sex, underlying heart disease, index arrhythmia, length of treatment, dosage of amiodarone, KL-6, %DLCO, and CT findings. The length of treatment (defined as the period from the beginning of drug administration until study completed) was 25±3 months (mean±SE). The underlying heart diseases were ischemic heart disease in 13 patients, cardiomyopathy in 9 patients and 1 patient who had had aortic valve replacement. Intravenous injection of amiodarone for loading was used only in case 16. None of the patients showed abnormality on chest radiographs and none had a history of respiratory disease prior to starting treatment with amiodarone.

In 8 (35%) of the 23 patients, HRCT scans obtained with the patient in a supine position showed normal findings, and the HRCT scans obtained with the patient prone did not provide any additional information. Of the remaining 15 (65%) patients, HRCT scans obtained with the patient supine showed possibly abnormal findings. On HRCT scans obtained with the patient prone, these abnormalities persisted in 4 patients and completely disappeared in the other 11. Abnormalities in these 4 patients were all ground-glass opacities (GGO) in the lower lung. They did not show other abnormalities such as consolidation, reticulations, honeycombing, micronodules, or nodules. Overall, HRCT scans obtained with the patient prone were helpful in 15 patients, excluding (n=11) or confirming (n=4) the presence of subpleural abnormalities in the posterior part of the lung.

Using our criteria, two (cases 13 and 16) showed a great-
er than 20% decrease of %DLCO compared with the data before administration. However, APT was ruled out in these 2 cases using HRCT. Administration of amiodarone could be safely continued in these patients and no adverse events have occurred to date.

Four patients (cases 1, 3, 6 and 8) were diagnosed as APT based on the HRCT findings (Table 2). Two of them (cases 3 and 6) showed no abnormalities in %DLCO and KL-6 level. As case 6 refused the implantation of Implantable Cardioverter Defibrillator, amiodarone has been carefully continued without deterioration of pulmonary function or the worsening of HRCT findings at the 9-month follow-up. However, in case 3 whose index arrhythmia was paroxysmal atrial fibrillation, administration of amiodarone was stopped. However, GGO was still present 4 months later. The other 2 cases (cases 1 and 8) were also forced to stop amiodarone. Elevation of KL-6 up to 653 U/ml was observed in case 1, whereas case 8 showed a marginal (19%) decrease in %DLCO without abnormality in the KL-6 level. The follow-up HRCT at approximately 6 months showed absence of GGO in both cases (see below). In this way, during the study period (average 25 months) using HRCT in supine and prone positions, no serious pulmonary side effects of amiodarone were clinically documented.

Representative Cases

Case 1 High-resolution computed tomography of a 43-year-old male who was administrated 200 mg/day amiodarone for 2 months showed GGO in his right lower lung field (Fig 1A). Since these findings were reproduced in the prone position (Fig 1B), we diagnosed APT at an early stage even though he was totally asymptomatic. Amiodarone administration was stopped immediately and the follow-up CT after 7 months revealed complete recovery from APT (Fig 1C). The KL-6 value was also normalized.

Case 13 and 16 A decrease in %DLCO of over 30% was observed after 5 months administration in a 62-year-old male (case 13). Another 34-year-old female (case 16) also showed a greater than 30% decrease in %DLCO compared to before treatment. In both cases, APT was definitively ruled out using HRCT in the supine and prone positions, and the patients were able to safely continue taking amiodarone.

Case 21 A high density area was found in the subpleural area in an ordinary supine position HRCT of a 74-year-old male (Fig 2A). The finding was clearly revealed as a ‘false positive’ by the prone position scan which showed no abnormalities (Fig 2B). The finding was thought to be a so-called ‘dependent opacity’ or ‘dependent density’.

Discussion

The toxic effects of amiodarone appeared to be related to dose and duration of therapy. However, a meta-analysis of studies using low-dose amiodarone revealed a significant risk of the pulmonary toxicity compared to placebo.7 No treatment for amiodarone pulmonary toxicity has been proven to be effective, but most investigators advocate discontinuation of amiodarone and the use of corticosteroids. Amiodarone-induced pulmonary toxicity can be difficult to diagnose clinically, but early recognition of APT is important because discontinuation of amiodarone could prevent its progression. However, we should be cautious about termination of amiodarone, because it may result in the recurrence of life-threatening arrhythmias leading to fatalities.

The problems related to APT are lack of satisfactory monitoring methods and its definite diagnostic criteria.22,23 Therefore, in the present study, 3 monitoring methods for detecting APT were used: (i) abnormal HRCT findings; (ii) 15% and more decrease in %DLCO; and (iii) high KL-6 value (ie, above 400 U/ml). Suspected APT was defined as presence of at least 1 abnormality in these parameters, and we considered it definite APT if there were more than 1 abnormal results of them. In addition, both congestive heart failure and infection were excluded by echocardiography, blood examinations, and clinical courses in all patients with definite APT.
lung is typically involved earlier and to a greater degree than the anterior part of the lung in patients with this disease. In the study by Aberle et al, HRCT scans obtained with the patient prone enabled basal abnormalities to be reliably distinguished from gravity-dependent attenuation in 25 out of 29 patients with a clinical diagnosis of asbestosis. Scanning with the patient prone has also been suggested for evaluation of other interstitial lung diseases that tend to involve the posterior lower part of the lung.

In the current study, HRCT scans obtained with the patient prone were helpful in differentiating dependent opacity from lung disease in 11 patients in whom HRCT scans obtained in the supine position showed subtle abnormalities in the posterior lower lobes. In another 4 patients, HRCT scans obtained with the patient in a prone position were useful in confirming the presence of subtle GGO in the posterior part of the lung, which were considered to be a possible abnormality on the HRCT scans obtained with the patient supine. Therefore, we have shown the potential effectiveness and feasibility of HRCT in supine and prone positions for detection of APT.

Vernhet et al reported HRCT findings of reversible APT. They stated that honeycombing was not present in their patients with reversible APT and that subpleural GGO were characteristic of APT. In addition, Standertskjold-Nordenstam et al reported 2 asymptomatic patients with APT whose spatial distribution was mainly located peripherally in the posterobasal area and close to the interlobar fissures. These are in agreement with the findings for our patients with APT as well as those with asbestosis! We speculate that the initial finding of APT is GGO and that this is a potential clue for detection of APT in an early and reversible stage.

The diagnostic value of %DLCO as a possible marker of APT has been reported. This respiratory examination requires not only patients’ cooperation but also forced breathing to obtain a consistent, steady score. Some patients, especially elderly patients, might have difficulty maintaining steady respiration and the %DLCO score can fluctuate in each examination. In this respect, %DLCO might be inferior as a method for detecting and monitoring APT as compared with HRCT in supine and prone positions, which is highly reproducible without effort. Case 13 and 16, as a matter of fact, suffered substantial fluctuations in %DLCO score, but could safely continue amiodarone administration after obtaining completely normal images in supine and prone positions.

In some of our patients with a high KL-6 value, amiodarone was able to be continued without serious side effects if no abnormal HRCT findings were present (cases 7, 10, 11, 14 and 20). Moreover, in our hospital, the value of serum KL-6 is reported a few days later after the blood sampling. However, we also believe that the serum KL-6 is a potential new marker for APT as previously reported and that it would be a simple method for screening APT.

In conclusion, this is the first report of the usefulness of HRCT in supine and prone positions to detect APT and to rule out false positive overestimations that can occur with the commonly used HRCT in a supine position. HRCT with patients in supine and prone positions could be superior to pulmonary function test in regards to reproducibility and objectivity. Combination of supine and prone positions is a useful and more reliable method to precisely evaluate HRCT findings in patients taking amiodarone.

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References