The effect of aminophylline administration on $^{99m}$Tc-MIBI lung and liver uptake in patients with or without myocardial ischemia*

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**SUMMARY**—This work aims to analyze the influence of aminophylline in the pulmonary and hepatic uptake of $^{99m}$Tc-methoxyisobutylisonitrile ($^{99m}$Tc-MIBI). 72 patients were studied and a myocardial perfusion (MPS) single photon emission computed tomography (SPECT) with $^{99m}$Tc-MIBI was carried out after the administration of dipiridamol. According to the MPS, the patients were classified into 2 groups: Group A: 45 patients without myocardial ischemia and Group B: 27 with ischemia. Each group was divided into 2 subgroups according to whether they had (I) or had not (II) received intravenous aminophylline. The dipiridamol was administered for 4 minutes at a dose of 0.56 mg/kg. If the patients presented any complication, intravenous aminophylline was administered. At 30 minutes p.i., planar images were obtained during a scintigraphy in the interior projection after the injection of $^{99m}$Tc-MIBI. The regions of interest in the heart, hepatic cupula, and most active area of the left lung were outlined and the activity rates were calculated: lung/heart (LHR) and liver/heart (LivHR). No statistically significant differences were observed in the uptake of $^{99m}$Tc-MIBI between subgroups I and II. However, the LHR rates in both subgroups were significantly lower in the patients with ischemia: LHR group A1 vs B1: 0.32 ± 0.08 vs 0.36 ± 0.06, p = 0.03; group AII vs BII 0.31 ± 0.07 vs 0.35 ± 0.07, p = 0.01 respectively. In conclusion, the administration of aminophylline, after the infusion of dipiridamol for MPS, does not modify the pulmonary or hepatic uptake of $^{99m}$Tc-MIBI.

**KEY WORDS:** $^{99m}$Tc-MIBI. Pulmonary uptake. Hepatic uptake. Aminophylline. Ischemia.

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**INTRODUCTION**

Since the last decade, $^{99m}$Tc-Technetium methoxyisobutylisonitrile ($^{99m}$Tc-MIBI) has widely used instead of $^{201}$Thallium ($^{201}$Tl) for myocardial perfusion imaging due its relatively good physical properties such as short physical half life, better image quality, and cost-effectiveness etc. Increased post-stress lung uptake of $^{201}$Tl is a well-known phenomenon reflecting left ventricular dysfunction and/or of severe coronary ar-
cathery disease (CAD). This uptake is postulated to be depending on pulmonary oedema as a consequence of a sudden, exercise-induced increase of left ventricular end-diastolic pressure. Its early increase is defined as an index which is important for the functional evaluation and the prognostication of CAD.

There is limited information concerning the potential value of pulmonary uptake of $^{99m}$Tc-MIBI. The reports, using 1hr post-stress imaging method, about the potential ancillary diagnostic role of $^{99m}$Tc-MIBI lung uptake are conflicting. While some authors noted that it has no value as a diagnostic sign, others suggested that it is possibly helpful at those of it. However, a few studies have suggested that lung uptake of $^{99m}$Tc-MIBI may be a more useful sign of disease when measured on immediate post-stress images compared to standard acquisition at 1hr after injection.

The use of dipyridamole stress is an effective and relatively safe technique for evaluating myocardial ischemia in patients with reduced exercise capacity. Yet, minor complications associated with intravenous dipyridamole administration are relatively common. These complications are usually relieved by intravenous aminophylline administration. The aim of this study was to assess the difference between aminophylline administered and non-administered patients with respect to $^{99m}$Tc-MIBI lung and liver uptake during dipyridamole stress test.

**MATERIALS AND METHODS**

**Patients:** In this study, 72 patients (mean age: 55.94 ± 14.84y, 43 F-29 M); 45 without myocardial ischemia (group A) and 27 with myocardial ischemia (group B) according to dipyridamole stress $^{99m}$Tc-MIBI SPECT myocardial perfusion imaging (MPS) were included. Patients’ data were evaluated retrospectively, and each group was separated into two subgroups: intravenous aminophylline administered (I) and non-administered (II). Patients with previous or recent myocardial infarct and EF of < 50% were excluded. All patients were imaged by same-day stress-rest protocol. Patients with significant valvular of congenital heart disease, cardiomyopathy, intrinsic lung and liver disease were excluded. Only 21 patient with myocardial ischemia accepted and underwent coronary angiography. The number of patients according to affected number of vessel are as follows: 9 one vessel, 6 two vessel, 1 three vessel and 5 normal.

**$^{99m}$Tc-MIBI SPECT imaging:** Dipyridamole (DP) subjects underwent scintigraphy after intravenous infusion of 0.56 mg/kg over 4 min. If the patients had any complications, 120 mg intravenous aminophylline was administered, at least 5 minutes after. After the injection of 370 MBq $^{99m}$Tc-MIBI at 20th min an anterior planar image with a matrix of 128 × 128 for 5 minutes and at 60th min after SPECT images were obtained. The subjects’ blood pressure, heart rate, 12 lead ECG and symptoms were monitored throughout the study. 4 hours after the completion of DP, 740 MBq $^{99m}$Tc-MIBI was injected and SPECT imaging was repeated 45 min. later. A gamma camera equipped with a high-resolution collimator and a 20% window centred at the 140 keV photopeak of $^{99m}$Tc, 32 projections, 20 sec. each, were acquired in step-and-shoot mode over a 180° arc and 64 × 64 matrices. The image reconstruction was performed with filtered backprojection using the combination of Ramp and Metz filter. No attenuation or scatter correction was used. Transaxial slices were realigned along the heart axis obtaining short-axis, vertical and horizontal long-axis slices.

**Image Analysis:** The $^{99m}$Tc-MIBI LHR and LivHR were obtained from anterior planar image taken 20 minutes after DP administration. $^{99m}$Tc-MIBI heart, lung and liver uptake were quantified by drawing a 5 × 5 pixel rectangular region of interest (ROI) on a myocardial segment of myocardium with the maximum count density (Fig. 1), and on the left upper lung and right upper liver area. The LHR and LivHR were calculated by dividing the mean counts Per pixel in the lung and liver ROI to those of the heart.

Patients were scored visually according to $^{99m}$Tc-MIBI uptake in myocard perfusion images. 0: normal (group A: n = 45, patients without myocardial ischemia); 1: mild defect (n = 0); 2: moderate defect (n = 5); 3: severe defect (n = 3).

**Echocardiography:** For echocardiographic evaluation patients were studied at rest in left lateral decubitus position. According to American Society of Echocardiography, echocardiographic examinations were obtained from parasternal long axis and apical four-chamber views. Left ventricular ejection fraction (EF), end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated by classic formula assuming an idealised ellipsoidal model and utilising the Teichholtz correction.

Statistical Analysis: All measured parameters were reported as mean ± sd. The relationship between scintigraphic and ECO parameters were evaluated using Pearson’s r coefficient. ANOVA test was used for statistical analysis. A probability (p) of < 0.05 was considered statistically significant.

RESULTS

In table I, 99mTc-MIBI LHR and LivHR values of both aminophylline administered and non-administered subgroups were presented. There was no difference in 99mTc-MIBI indices between both subgroups, statistically. However, LHR values in subjects with normal myocardial perfusion were significantly lower than patients with abnormal perfusion in both subgroups (LHR group AI vs BI: 0.32 ± 0.08 vs 0.36 ± 0.06, p = 0.03; AII vs BII: 0.31 ± 0.07 vs 0.35 ± 0.07, p = 0.02 respectively). LivHR values in subjects who had abnormal myocardial perfusion were greater than patients with normal perfusion in both subgroups, but the difference was not significant (p > 0.05).

There were no difference in echocardiographic parameters between aminophylline administered and non-administered subgroups, statistically (table II). However, in both of them, EF and SV values in subjects with normal myocardial perfusion were significantly greater than those with abnormal perfusion. EDV values in subjects with normal perfusion were lower than those with abnormal perfusion. There was invert correlation between LHR and EF in the whole group (r = -0.51, p = 0.01).

The hemodynamic parameters measured at rest, 4 minutes during the DP infusion, and 4 minutes post-DP infusion for both groups are reported in table III. The rate of aminophylline side effects in groups A and B were as follows; in group A: 23% headache, 19% flushing, 17% nausea, 4% anginal attack; in group B: 19% headache, 14% nausea, 9% flushing and 3% anginal attack.

DISCUSSION

Early 201Tl lung uptake is a well-known phenomenon. Although exercise was preferred as stress in the majority of studies, in their study on 201Tl lung uptake, Villanueva y cols.14 suggested that dipyridamole has comparable diagnostic value. 99mTc-MIBI has been widely used in myocardial perfusion imaging for several years, however, there is limited information concerning the potential value of its pulmonary uptake. Saha y cols.5 reported that there is no value of lung uptake as an ancillary diagnostic sign on conventional 99mTc-MIBI.
images obtained 1 hr after stress. While some authors pointed out that its value is reduced in comparison to $^{201}$Tl$^{8,9}$, others accepted it as helpful as those of $^{99m}$Tc-MIBI.

In pharmacologic stress with dipyridamole, the scintigraphic findings may differ due to different stress hemodynamics, tracer kinetics and imaging techniques. Another important characteristic of $^{99m}$Tc-MIBI is its slow myocardial washout which ameliorates concern regarding the prolonged imaging time associated with SPECT. A few studies have suggested that lung uptake of $^{99m}$Tc-MIBI may be a more useful sign of disease when measured on immediate post-stress images compared to standard acquisitions at 1 hr after injection.$^{7,8}$

This study examined the influence of aminophylline administration during dipyridamole stress on $^{99m}$Tc-MIBI lung and liver uptake in subject with known or suspected CAD. No difference was found in echocardiographic or hemodynamic parameters between the two groups. Although individual variability in liver clearance of $^{99m}$Tc-sestamibi$^{15}$ was noted before, in our study aminophylline administration after dipyridamole stress did not effect $^{99m}$Tc-MIBI lung and liver uptake. However, we found that myocardial ischemia had an important role in increased lung uptake.

Hurwitz y cols.$^{7}$ also found a relationship between 1 hr post-stress dipyridamole lung uptake and ischemic perfusion defects. They started the imaging 20 min after $^{99m}$Tc-MIBI injection when blood pool phase and adequate myocardial uptake completed. Since $^{99m}$Tc-MIBI redistribution started after 2 hr$^{16}$, increased $^{99m}$Tc-MIBI lung uptake might be prolonged due to myocardial ischemia. Our results were also supported by the findings of Hurwitz y cols.

Giubbini y cols.$^{11}$ studied subjects with recent anterior myocardial infarction undergoing $^{99m}$Tc-sestamibi first-pass ventriculography and SPECT perfusion imaging. They found inverse correlation between LHR values and left ventricular ejection fraction measured on first-pass study. A similar inverse correlation between LHR and left ventricular ejection fraction measured on echocardiography was found in our study.

Our study suggested that LivHR values in subjects who had abnormal myocardial perfusion were slightly greater than patients with normal perfusion in both aminophylline administered and non-administered subgroups. To our knowledge, there is no study in the literature assessing $^{99m}$Tc-MIBI liver uptake in patients with heart disease. Increased liver uptake of an agent in LV systolic dysfunction may be explained by lower then normal right atrial emptying fraction, as the LV myocardium is the principal muscle responsible for active pulling of atrio-ventricular ring.$^{17}$ Decreased emptying of right atrium results in increased intra-atrial volume and pressure with consequent hepatic congestion. In addition, left and right ventricles are functionally and structurally interdependent. Therefore, abnormalities of LV can disturb right ventricular diastolic function which results in higher than normal right atrial pressure and liver congestion. However, in our study the LivHR difference between patients with- and without myocardial ischemia was found not to be significant. Hence, to determine its value in myocardial perfusion imaging, further studies are needed to be performed either with larger number of patients, or in patients with previous MI and/or severe left ventricular dysfunction.

In conclusion, we found that in patients with and without myocardial ischemia, who had no previous

**Table III**

THE HEMODYNAMIC PARAMETERS OF PATIENTS

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<td>95 ± 15</td>
<td>101 ± 17</td>
<td>184 ± 39</td>
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<td>101 ± 16</td>
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r-HR: resting heart rate, HR-DYP: Heart rate 4 minutes into the DP infusion, HR-4-DYP: Heart rate 4 minutes post-DP infusion, r-SBP: resting systolic blood pressure, SBP-DYP: systolic blood pressure 4 minutes into the DP infusion, SBP-4-DYP: systolic blood pressure 4 minutes post-DP infusion, r-DBP: diastolic blood pressure, DBP-DYP: diastolic blood pressure 4 minutes into the DP infusion, DBP-4-DYP: diastolic blood pressure 4 minutes post-DP infusion.
MI and no severe left ventricular dysfunction, the lung and liver $^{99m}$Tc-MIBI uptake are not affected byaminophylline administration.

REFERENCES