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Decreased [99mTc]Sestamibi uptake with dobutamine *versus* dipyridamole stress

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Aim. **Animal studies suggest an interference of dobutamine on [99mTc]sestamibi uptake. In this study dobutamine was compared *to* dipyridamole rest-stress [99mTc]sestamibi uptake ratio (UR).**
Methods. **Twenty-five patients with suspect coronary artery disease (CAD) underwent rest, dobutamine, and dipyridamole [99mTc]sestamibi SPECT at 24-h intervals and coronary angiography. UR was calculated separately for each coronary territory considering injected dose and acquisition delay.**
Results. **There were 38 CAD territories in 20 patients. On a patient basis, dipyridamole SPECT sensitivity was 85%, *versus* 70% for dobutamine. On a territory basis, sensitivity was 66% *versus* 42% (P<0.05), and specificity 92% *versus* 86%, respectively for dipyridamole *versus* dobutamine. In the 38 CAD territories, dipyridamole UR was -4.1±29.4%, and dobutamine UR was -13.1±19.9% (P<0.05). In the 37 no-CAD territories, UR was 34±23.6% for dipyridamole and -0.4±17.8% for dobutamine (P<0.0001). UR difference between CAD *versus* no-CAD territories was larger using dipyridamole (P<0.0001) than dobutamine (P<0.005).**
Conclusion. **The UR comparison confirms that [99mTc]sestamibi uptake underestimates the blood flow heterogeneity induced by dobutamine more than that produced by dipyridamole.**

KEY WORDS: Dipyridamole - Dobutamine - Coronary artery disease.

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In patients unable to perform exercise stress testing and with contraindications to coronary vasodilators, dobutamine is the alternative stress modality for myocardial perfusion imaging.[1-3] Several clinical studies have demonstrated that dobutamine perfusion imaging is reliable for detection and prognostication of coronary artery disease (CAD) and do not report tracer-related differences in diagnostic reliability.[2, 4-9] Animal studies, however, demonstrated that [99mTc]sestamibi underestimates the blood flow heterogeneity induced by dobutamine, possibly because of a direct adverse effect of dobutamine on myocardial [99mTc]sestamibi uptake.[10-13] This could have important implications in patients with mild coronary stenosis.[13] In humans, no data are so far available that support an interference of dobutamine on [99mTc]sestamibi myocardial uptake. The study purpose was to examine quantitatively the changes in [99mTc]sestamibi uptake induced by dobutamine in patients with suspect CAD comparing them with the changes induced by dipyridamole.

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Materials and methods

Patient population and study protocol

The study cohort was consecutively selected among patients referred to our center for evaluation of chest

pain of suspect coronary etiology. Patients with already established diagnosis of CAD, previous myocardial infarction, other cardiac disease including rhythm disturbances, valvular heart disease, and cardiomyopathy or with contra-indications to dipyridamole or dobutamine administration were excluded. The final study group included 25 patients (17 males and 8 females, mean age 60±9 years).

All patients performed resting baseline, dipyridamole and dobutamine [99mTc]sestamibi single-photon emission computed tomography (SPECT) and coronary angiography. The three SPECT studies were performed 24-hour apart, in random order. Coronary angiography was performed according to the study protocol within 15 days of scintigraphic imaging. No patient was receiving cardioactive or xanthine containing drugs. The clinical conditions of all patients remained stable for the whole study. The local Ethics Committee on Human Research approved the study protocol. All patients gave informed consent to participate in the study.

Coronary angiography

Selective coronary angiography was performed in multiple views using the percutaneous transfemoral approach. The degree of lumen narrowing was visually estimated with the aid of calipers. Diameter stenosis was considered significant if ≥50%.

Dipyridamole test

Patients avoided beverages containing xanthine for at least 24 hours before the test. Dipyridamole was infused under electrocardiographic and blood pressure monitoring in a dose of 0.56 mg/kg over 4 min followed by a 4 min interval and then by a second dose of 0.28 mg/kg over 2 min. Thus, the cumulative dose was 0.84 mg/kg over 10 min. Infusion was interrupted at achievement of peak dose, at onset of ischemia (indicated by chest pain associated with horizontal or downsloping ST segment depression ≥0.1 mV at 80 ms after the J point or development of wall motion abnormalities) or at occurrence of remarkable side effects. Technetium-99m sestamibi (740 MBq, 20 mCi) was injected 2 min after the completion of the second dose or earlier if ischemia or side effects requiring the premature termination of the test were registered. Aminophylline (120 mg) was routinely administered i.v. at least 8 min after tracer injection.

Dobutamine test

Dobutamine was infused intravenously with a mechanical pump at incremental doses of 10, 20, 30, and 40 μg/kg per min every 3 min, under electrocardiographic and blood pressure monitoring; the maximal rate (40 μg/kg per min) was maintained for 5 min. Endpoints of the test were achievement of peak dose, development of ischemia (as previously defined for the dipyridamole test), or the occurrence of severe side effects. Atropine (0.5-1 mg i.v.) was injected in patients in whom at 40 μg /kg per min the heart rate was persistently <85% of the age-predicted maximal value. Technetium-99m sestamibi (740 MBq, 20 mCi) was injected after 1 min of the predetermined maximal infusion rate, and the drug infusion was subsequently continued for 5 min. The tracer injection took place earlier in case of the occurrence of one of the criteria requiring the premature termination of the test. In case of atropine administration, we injected [99mTc]sestamibi after 3 min. Atenolol (up to 2.5 mg in 5 mL) was available to treat side effects.

Technetium-99m sestamibi SPECT

SPECT was collected 60 min after [99mTc]sestamibi injection. We used an Elscint Apex SP4 γ-camera equipped with an ultra-high resolution collimator, with a 20% window centered at the 140 keV photopeak of technetium-99m. Sixty projections of 20 seconds each were acquired in step and shoot mode over a 180° arc, on 64 × 64 matrices using a zooming factor of 1.4. The image reconstruction was performed with filtered backprojection using a Wiener resolution recovery filter. No attenuation or scatter correction was used. The transaxial slices were realigned along the heart axis obtaining short-axis, vertical, horizontal long-axis slices, and polar maps of the regional [99mTc]sestamibi distribution were obtained. Each polar map was normalized for peak myocardial activity and compared with the normal limits obtained in 50 sex-matched subjects with <5% probability of coronary artery disease; pixels with tracer uptake falling more than 2.5 SD below mean normal values were considered abnormal.[14] To make diagnosis of CAD, a coronary artery territory should include at least 10% of abnormal pixels (12% for the right coronary artery territory).[15]

Uptake ratio calculation

For the calculation of the uptake ratio (UR),[16-18] the counts within the resting polar map were corrected by the injected activity and the delay between injection and acquisition time according to the formula:

$$RA_{acq.time} = RA_{inj.time} \cdot e^{-\frac{\ln(2)}{T_{\frac{1}{2}}}(t_{acq} - t_{inj})}$$

where $RA_{acq.time}$ is the activity at the moment of resting SPECT acquisition and $RA_{inj.time}$ the injected activity measured in the syringe before administration with a dose calibrator. Similarly, the stress polar maps were corrected according to the formula:

$$SA_{acq.time} = SA_{inj.time} \cdot e^{-\frac{\ln(2)}{T_{\frac{1}{2}}}(t_{acq} - t_{inj})}$$

where SA = activity at the moment of stress images acquisition (either dipyridamole or dobutamine). The stress counts were further corrected with factors related to normalization and backprojection algorithm according to the formula:

$$SA_{corr} = \frac{K_{rest}}{K_{stress}} SA_{acq.time}$$

where $K_{rest/stress}$ includes all normalization factors used during the procedure of filtered backprojection reconstruction. Finally, UR was derived from the formula:

$$UR = \frac{SA_{corr} * I_s - RA_{acq.time} * I_r}{RA_{acq.time} * I_r}$$

where I_r and I_s are the polar map images of stress and rest, respectively.

UR was shown on a colour coded polar map display on which the three coronary artery territories were identified as usual (Figure 1).[14, 15] For each coronary artery territory the average UR was calculated and expressed as percent of the baseline uptake.

Statistical analysis

Continuous variables were expressed as mean value ± standard deviation and were compared with the Student's t test for paired or independent samples as appropriate, or with the Pearson correlation coefficient; the comparison of proportions was made using the Fisher exact test. A P value <0.05 was considered significant.

Results

General findings

According to coronary angiography, 20 patients were affected by significant CAD (8 1-vessel, 6 2-vessels, and 6 3-vessels CAD) while five had normal coronary arteries. Therefore, a total of 38 coronary artery territories were affected by significant CAD. In resting SPECT, no patient showed abnormal tracer uptake.

Dipyridamole test

All patients completed without adverse effects the high-dose infusion protocol. The mean rate-pressure product at the moment of tracer injection was 11 465±1 514 beats/min × mmHg, significantly higher than the corresponding baseline value (9 111±777 beats/min × mmHg, P<0.0001). Anterior chest pain of possible ischemic origin was reported by eight patients and in six of these eight patients and in further two subjects, electrocardiographic modifications suggestive of ischemia were registered. In the dipyridamole images, 28 territories fulfilled the criteria for significant CAD; 25 of these territories showed a significant stenosis in coronary angiography. Therefore, the sensitivity of dipyridamole [99mTc]sestamibi SPECT was 66% for identification of individual affected territories, with 92% specificity. On a patient basis, 17 out of 20 patients were correctly recognized as affected by CAD in at least 1 coronary artery territory (sensitivity 85%).

Dobutamine test

The dobutamine infusion protocol was completed in 18 patients. Of them, four reported anginal pain, one had ischemic electrocardiographic changes and one both angina and ischemic electrocardiographic changes. In seven patients dobutamine infusion was precociously interrupted because of anginal pain (four cases), of ischemic electrocardiographic changes (one case), or of both (two cases). The mean rate-pressure product at the moment of tracer injection was 19 993±3 370 beats/min × mmHg, significantly higher than the related baseline value (8 950±865 beats/min × mmHg, P<0.0001) and than the dipyridamole value (P<0.0001). In dobutamine SPECT, 22 territories showed an abnormal uptake, with 42% sensitivity (P<0.05 *vs.* dipyridamole) and 86% specificity for identification of individual CAD territories. On a patient

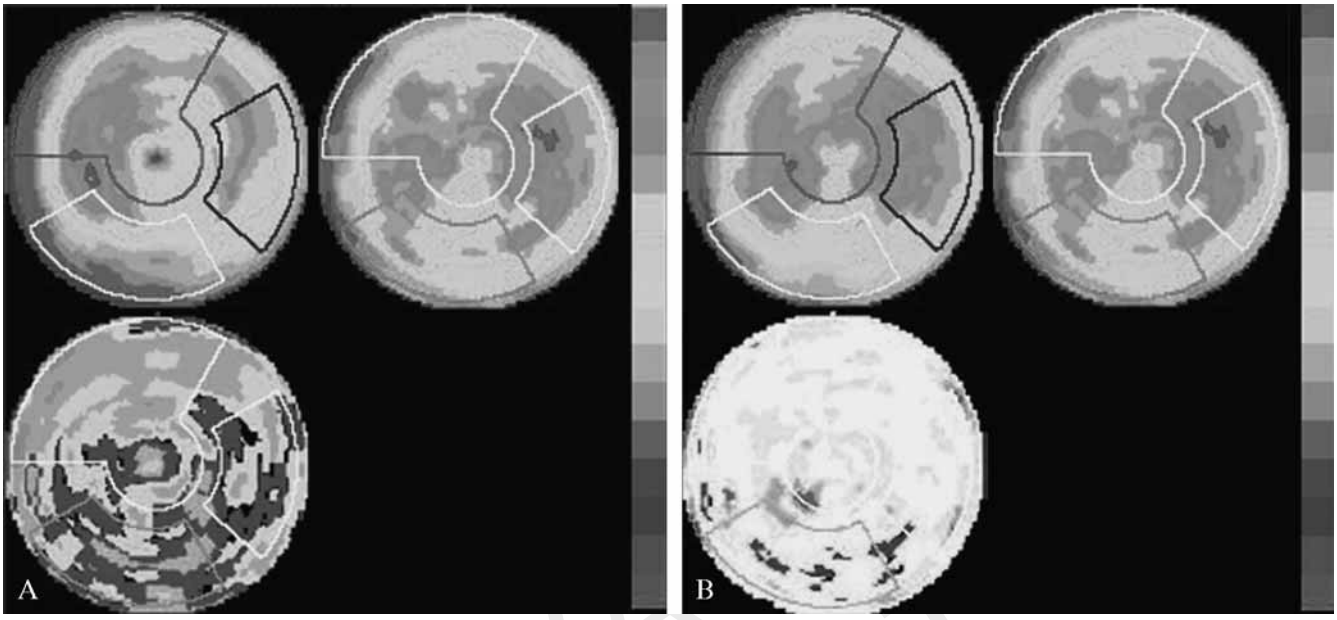

Figure 1.—Example of UR calculation: top left: stress polar map, top right baseline resting polar map; bottom left UR polar map. A) Dipyridamole SPECT showing uptake defects in all coronary artery territories; B) dobutamine SPECT showing an inferior defect only. The more positive UR and the greater contrast in dipyridamole versus dobutamine UR polar map are apparent. In the color scale red=highest activity (or most positive UR), magenta=lowest activity (or most negative UR).

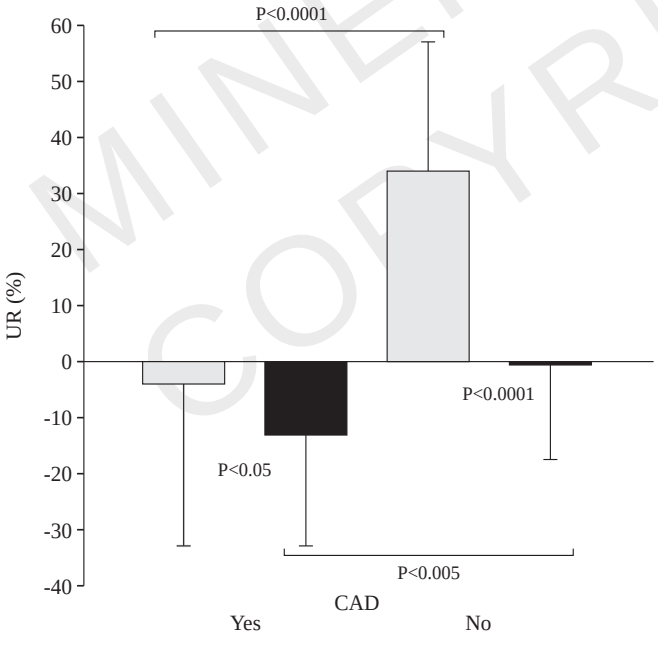

Figure 2.—Histogram showing the UR under dipyridamole (white bars) and under dobutamine (black bars) in the territories with versus those without significant CAD.

basis, 14 out of 20 CAD patients had an abnormal uptake in at least one territory with significant obstruction (sensitivity 70%). Among CAD patients there were two subjects with typical angina and one with typical angina and ischemic electrocardiograohic changes during dobutamine test that had normal tracer uptake in SPECT images. With one single exception, all false negative CAD patients had completed the dobutamine test reaching the target heart ratio.

Uptake ratio

In the 38 territories with significant coronary stenosis, the dipyridamole UR was -4.1±29.4% and the dobutamine UR was -13.1±19.9% (P<0.05). The related values in the 37 coronary territories without obstruction were 34±23.6% for dipyridamole and -0.4±17.8% for dobutamine (P<0.0001). Therefore, a highly significant UR difference was registered between stenotic and normal territories using dipyridamole (P<0.0001). The UR difference between stenotic and normal territories was slightly less significant using dobutamine (P<0.005) (Figure 2).

There was a significant inverse correlation between

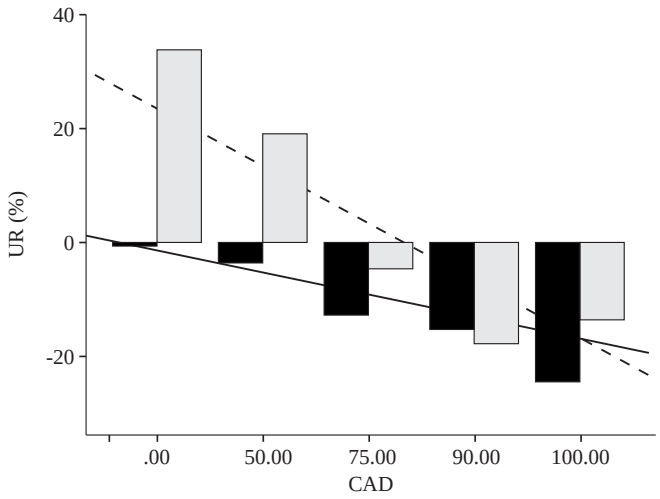

Figure 3.—Correlation between severity of CAD (percent lumen obstruction) and UR under dipyridamole (white bars, dashed line) and under dobutamine (black bars, solid line). Bars show the mean UR for each degree of CAD.

extent of abnormal uptake and UR both using dipyridamole (r=-0.58, P<0.0001), and using dobutamine (r=-0.46, P<0.0001). There was a significant inverse correlation as well between degree of coronary artery obstruction and dipyridamole UR (r=-0.64, P<0.00001), and this correlation was significantly closer (P<0.05) than the corresponding correlation with dobutamine UR (r=-0.38, P<0.001) (Figure 3).

Discussion

Coronary vasodilators, such as dipyridamole or adenosine, induce maximal increase in coronary blood flow, with measured values 4- to 5-fold the baseline level.[19] In stenotic territories, flow may increase to a more limited extent, or be actually decreased because of coronary steal mechanisms.[20] Inotropic stimulators like dobutamine produce at high dosage an increase in oxygen demand, mainly because of increase in heart rate and myocardial contractility. Consequently, they induce coronary dilatation to meet the increased demand, with a rise in coronary blood flow in normal territories that has been reported to range from 3- to 5-times the baseline value.[21, 22] In territories subtended with stenotic vessels true ischemia is to be expected, and can be identified both by perfusion and by functional imaging, mainly echocardiography.[23]

Various animal studies, however, suggest a possible interference of dobutamine on [99mTc]sestamibi uptake, and this would imply that other tracers should be preferable to [99mTc]sestamibi in case of dobutamine stress.[10-13] The hypothesized mechanism is a dobutamine-induced calcium influx into the mitochondria, with consequent reduction of the mitochondrial negative transmembrane potential.[24, 25] Although there are enough clinical reports about dobutamine [99mTc]sestamibi imaging to indicate that this potential interference has limited importance in clinical practice,[2, 6-8] the issue has been never completely clarified. A main reason for this is the difficulty to quantify in humans the [99mTc]sestamibi uptake under dobutamine. To overcome this problem, we examined a relative parameter, the stress-rest UR, and we compared it in the same patients using both dipyridamole and dobutamine. Although UR is just a coarse parameter that does not define the absolute value of tracer uptake in the myocardium, we thought that by assessing it in normal and stenotic territories of the same subjects, and having as reference the values obtained using dipyridamole, our data could be of some interest.

We could demonstrate that in coronary territories without epicardial vessel obstruction, the increase in [99mTc]sestamibi uptake induced by dobutamine was significantly lower than that induced by dipyridamole. Because positron emission tomography studies indicate that there are no differences in the maximal flow that can be achieved using dipyridamole or dobutamine our data would confirm some interference of dobutamine on [99mTc]sestamibi uptake. In the presence of coronary stenosis, there was on average a slight decrease in [99mTc]sestamibi uptake with both dobutamine and dipyridamole. Because most of our patients had severe coronary stenoses this finding is not completely surprising, since in these cases even dipyridamole may induce true ischemia. It would have been reasonable to expect more pronounced decreases using a stressor with ischemic properties such as dobutamine, but this was not the case. Consequently, we observed that the difference in stress-induced uptake changes between normal and stenotic coronary artery territories was clearly greater using dipyridamole than dobutamine.

When these data were compared with the capability of the two stressors to identify significant CAD using a standardized quantitative approach to SPECT evaluation, dobutamine SPECT was found to quite effective in CAD detection on a patient basis, and this

is in agreement with the several reports that examined the reliability of [99mTc]sestamibi dobutamine SPECT.[2, 6-8] However, it appeared that on a coronary artery basis dipyridamole was superior to dobutamine in terms of sensitivity, without major differences in specificity.

The small and selected patient population is a first limitation of our study. However, this study was not aimed to compare the diagnostic power of the two stressors, but to the comparison of their URs, and to the best of our knowledge this comparison had never been performed before. We did not use gated SPECT in this study, and therefore we cannot define how far the evaluation of left ventricular function could influence the diagnostic performance of the two stressors and possibly help to overcome some limits of dobutamine.[26] On the other hand, most of the literature about [99mTc]sestamibi dobutamine SPECT is based on nongated data.[2, 6-9] UR remains a very coarse method to measure the true tracer uptake by the myocardium. By evaluating the UR under dipyridamole in the same patients we tried to partly overcome this limitation. Given the heterogeneity of the reported myocardial blood flow values under dobutamine,[21, 22] the lack of flow measurements in our patients precludes the possibility to definitely demonstrate that the lower UR was not related to a lower flow increase. Finally, our study does not give any data about the mechanisms that cause the interference of dobutamine on [99mTc]sestamibi uptake.

Conclusions

In conclusion, our data suggest that using dobutamine the disparity in [99mTc]sestamibi uptake between normal and stenotic coronary artery territories is relatively less marked than using dipyridamole and that this difference could imply a less accurate detection of individual CAD territories with possible underestimation of CAD extent. This study supports to restrict the use of dobutamine stress for [99mTc]sestamibi myocardial perfusion SPECT to the few cases in which it is indicated by the current recommendations.[3]

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