Benefits of combined pharmacologic and submaximal exercise stress on sub-diaphragmatic activity in myocardial perfusion scintigraphy

Original Article

Babak Fallahi[1], Davood Beiki[1], Yalda Salehi[2], Alireza Emami-Ardekani[1], Armaghan Fard-Esfahani[1], Farahnaz Aghahosseini[1], Mohammad Eftekhari[1]

[1]Research Center for Nuclear Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Nuclear Medicine, Vali-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran

(Received 4 April 2018, Revised 26 May 2018, Accepted 28 May 2018)

ABSTRACT

Introduction: Myocardial perfusion imaging (MPI) is an important imaging modality in managing patients with cardiovascular disease. MPI has a significant role in diagnosis and management of cardiovascular disease; however it is subjected to different artifacts. Combining pharmacologic stress with submaximal exercise reduces side effects, improves image quality, and enhances the detection of ischemia, compared with suboptimal exercise or vasodilator stress alone.

Methods: 97 patients (62 males and 35 females) which were randomly allocated into two groups were studied using gated single-photon emission computed tomography (SPECT) imaging. The patients were randomly allocated into two different groups: dipyridamole or dipyridamole combined with submaximal exercise group. Subsequently, they were imaged at 15, 60, 120, and 180 minutes after radiotracer injection.

Results: 97 patients with an average age of 57.1 were compared 15, 60, 120 and 180 minutes after radiotracer injection. Comparing dipyridamole and dipyridamole submaximal exercise group a significant difference in target areas (myocardium, inferior and lateral wall) count ratio to both liver and colon count ratio was observed ($P < 0.05$) up to 120 min; However 180 minutes after the injection the difference between average count ratios of the myocardium to that of the visceral activity was only significant for the colon ($P < 0.05$).

Conclusion: A protocol that combines submaximal exercise with dipyridamole stress is highly effective in improving the average count ratio of myocardial walls compared to visceral activity.

Key words: Sub maximum exercise; Dipyridamole; Sub-diaphragmatic activity; Gated SPECT

Iran J Nucl Med 2018;26(2):105-111
Published: July, 2018
http://irjnm.tums.ac.ir

Corresponding author: Dr. Yalda Salehi, Department of Nuclear Medicine, Vali-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran. E-mail: salehi_y@sina.tums.ac.ir

INTRODUCTION

Cardiac disease is one of the major causes of mortality and morbidity worldwide [1]. Myocardial perfusion imaging (MPI) as an essential imaging modality has a major role in the management of cardiovascular disease. However, different artifacts can hinder the interpretation of the images and in some cases; it may even limit its clinical value. [2]

One of the most prevalent artifacts noted in the MPI is due to sub-diaphragmatic visceral activity. These artifacts are formed as a result of intense accumulation of the radiotracer activity in the liver or gastrointestinal tract which is located just beneath the left ventricle [3]. Sub-diaphragmatic activity mainly affects the inferior wall; however, may cause false positive or false negative results not only on the inferior wall but also on other cardiac walls. Sub-diaphragmatic activities are more prevalent in pharmacologic stress using vasodilators such as dipyridamole or adenosine, largely because of the fact that these agents decrease the systemic vascular resistance, which in turn results in an increased splanchnic blood flow [2, 4].Different solutions have been advised to decline the sub-diaphragmatic activity, one of which is using submaximal exercise in association with dipyridamole infusion [2, 4-8]. However, studies conducted to assess the effectiveness of added submaximal exercise to dipyridamole stress inherent several shortcomings, including lack of randomly chosen control and interventional groups and the absence of any separate assessment of inferior versus other myocardial walls.

The most important drawbacks of these studies would be probably the fact that there is no direct comparison between myocardial activity changes to visceral activity in sequential time images acquired either with dipyridamole alone or in combination with submaximal exercise. Therefore, the main purpose of our study was to assess sub-diaphragmatic activity changes, and to identify the ratio of cardiac uptake to sub-diaphragmatic viscera (liver and colon) in sequential time images taken 15, 60, 120, 180 minutes after the injection of radiotracer, and to compare the results among two groups (dipyridamole versus dipyridamole combined submaximal exercise) to demonstrate the best timing for imaging with ^{99m}Tc-MIBI.

Since the sub-diaphragmatic activity affects the inferior wall the most, and the lateral walls the least, it would be necessary to study these walls separately in addition to the whole myocardium.

In this study we have tried to report some of the limitations of similar studies conducted in the past, such as lack of randomness in assembling patient cohorts, absence of a comparison between sequential images at different time sets, and the absence of a separate analysis for the uptake ratios of whole myocardium and different walls to the sub-diaphragmatic uptake ratio.

METHODS

Study population

Ninety seven patients (62 men, 35 women) who referred to our nuclear medicine department for myocardial perfusion imaging were entered in a clinical trial study.

All patients were able to perform submaximal exercise and they had intermediate pretest probability according to Framingham Risk Score (FRS), without any evidence of left bundle branch block, pace maker, valvular heart disease, or asthma. The study was approved by ethical committee of Tehran University of Medical Science.

Patients signed a written consent and were randomly allocated into two study groups. One group only stressed by dipyridamole (D) and the other by infusion of dipyridamole combined with submaximal exercise (D/SE), as shown in Figure 1.

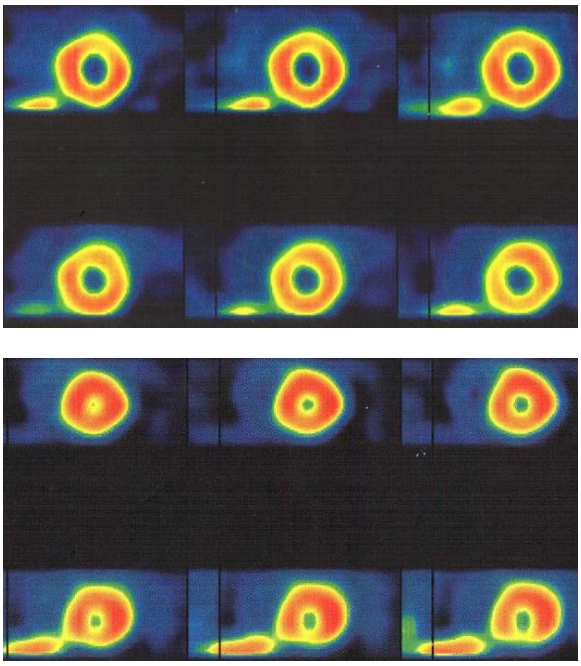


Fig 1. Myocardial perfusion scan stressed by dipyridamole (above) and dipyridamole combined with submaximal exercise.

Patient preparation

All patients were instructed to fast for at least 4 to 6 hours prior to the stress phase, and to avoid nitrates 12 hours prior to the test. They were also requested to refrain from consuming caffeine and long-acting aminophylline 24 hours prior to dipyridamole stress test.

Image acquisition sequence

^{99m}Tc-labeled MIBI for MPI was acquired from a commercial MIBI kit (TCK-Pars-1200, Pars Isotope Co., Tehran, Iran). The standard pharmacological stress was accomplished by intravenous infusion of 0.56 mg/kg dipyridamole over a period of 3 to 4 minutes. Following the infusion of dipyridamole, the participants in D/SE group started to exercise according to Bruce protocol. The exercise was started two minutes before radiotracer injection with warm-up stage and continued up to the completion of stage one. Stress gated MPI was performed in different time sequences including 15, 60, 120 and 180 minutes after the injection of 0.3 mci/kg ^{99m}Tc-MIBI. All images were obtained using a dual-head SPECT gamma camera (ADAC, Solus, Milpitas, CA), prepared with low-energy, high-resolution collimators, with a 15% energy window around the 140 Kev photo-peak. Patients were placed supine. Images were obtained using a 64 × 64 matrix within a 38.5 cm detector mask over a 180-degree arc in a step and shoot mode of rotation. Overall, 32 projections - each lasting 30 seconds - from 45 degrees right anterior oblique to 45 degrees left posterior oblique views were acquired. The rest study was accomplished with comparable dose of radiotracer activity using identical time intervals on the next day.

Image analysis

Images were analyzed using Auto-Quant software. The regions of interest (ROI) were separately put on the whole myocardium as well as on lateral and inferior myocardial walls along with the ROIs around the liver and splenic curvature of the colon. Correspondingly, the ratios of different myocardial walls to the visceral uptake were estimated on the basis of maximum count per pixel for a given ROI in myocardium (i.e. whole, inferior and lateral walls) divided by the maximum count per pixel for a given ROI in visceral activity (i.e. liver and colon). They were calculated for different imaging time sets (i.e. 15, 60, 120, and 180 minutes after radiotracer injection).

Statistical analysis

SPSS (v. 17.0) commercial software was used for the statistical analysis. All numerical data with normal distribution was expressed as mean ± standard deviation (SD). For different times of acquisition, the ratios of myocardial to visceral uptake for any given myocardial wall in different time of acquisitions were compared among study groups, i.e. D vs. D/SE.

To facilitate data comparison between two independent groups, an unpaired Student-T test was used for normally distributed data and its parametric equivalent, i.e. Mann Whitney U test, was applied for the data which did not show normal distribution. In both groups, multivariable repeated measure analyses were used for within- and between-subject analyses of the myocardial to visceral uptake ratios in both groups over time and the corresponding figures were generated. Between-subject effects determine whether patients on either group (D vs. D/SE) differ on their myocardial to visceral uptake ratios. Within-subject effect, on the other hand, would be a measure of how much individuals tended to change on their myocardial to visceral uptake ratios over sequential time of acquisitions. P values less than 0.05 were considered statistically significant.

RESULTS

Ninety-seven patients (62 men, 35 women) were studied. The average age of the participants was 57.1 ± 8.0 years. 35 men (71.4%) and 14 women (28.6%) were in the dipyridamole group, whereas 27 men (56.3%) and 21 women (43.7%) were put in D/SE group. Despite apparent difference in male to female ratios between groups, the choice of stress was not affected by gender since no statistically significant difference of male and female proportional frequencies was noted between the study groups (P value = 0.142). Also, the average age of the patients in D group was 55.9 ±7.4 years, while that of D/SE group was 58.4 ± 8.5 years, indicating no difference between the studied groups (P value = 0.703). Thus, age and gender were confirmed to have no interfering or confounding effect on the inter-group analyses.

The average ratio of myocardial to visceral uptake obtained from the whole left ventricular myocardium as well as different isolated myocardial walls, including inferior and lateral walls, for the predefined sets of acquisition times, namely 15, 60, 120, 180 minutes after the injection of radiotracer, are respectively compared between two study groups and the results are summarized in Tables 1 to 4.

As noted in these tables in all sets of image acquisitions, the average ratios of myocardial to visceral uptake for the whole myocardium as well as for isolated inferior and lateral walls in relation to both colon and hepatic viscera are higher in D/SE group, as compared with D group, except for similar ratios of whole and lateral wall myocardium to the liver uptake just in imaging set of 180 minutes after radiotracer injection.

A repeated measure analysis was also used to assess the changes in uptake ratios over time, as a within-subject factor, and in separate studied groups, as a between-subject factor.

The results are summarized in Figures 2 and 3. As noted in the Figure 2, the mean myocardial to liver ratios in both groups are rising over time and the between-subject difference was spared up to 120 min while, subsequently, the ratios in group D/SE, but not

Table 1: A comparison between the average count ratio of the whole myocardium to liver uptake 15 minutes post injection in two stress groups.

Ratio	Stress group		p Value
	D *	D/SE **	
Myocardium/Liver	0.57 ± 0.15	0.79 ± 0.33	0.0001
Myocardium/Colon	0.87 ± 0.29	1.28 ± 0.36	0.0001
Inferior wall/Liver	0.47 ± 0.16	1.02 ± 0.53	0.0001
Inferior wall/ Colon	0.77 ± 0.29	1.27 ± 0.35	0.0001
Lateral wall/Liver	0.43 ± 0.13	0.76 ± 0.33	0.0001
Lateral wall/ Colon	0.74 ± 0.25	1.17 ± 0.38	0.0001

*D: Dipyridamole; **: Dipyridamole combined with exercise

Table 2: A comparison between the average count ratio of the whole myocardium to liver uptake 60 minutes post injection in two stress groups.

Ratio	Stress group		p Value
	D *	D/SE **	
Myocardium/Liver	0.84 ± 0.38	1.10 ± 0.44	0.003
Myocardium/Colon	0.91 ± 0.38	1.53 ± 0.68	0.0001
Inferior wall/Liver	0.69 ± 0.29	1.06 ± 0.42	0.0001
Inferior wall/ Colon	0.83 ± 0.40	1.30 ± 0.59	0.0001
Lateral wall/Liver	0.68 ± 0.44	1.08 ± 0.48	0.0001
Lateral wall/ Colon	0.87 ± 0.48	1.27 ± 0.56	0.0001

*D: Dipyridamole; **: Dipyridamole combined with exercise

Table 3: A comparison between the average count ratio of the whole myocardium to liver uptake 120 minutes post injection in two stress groups.

Ratio	Stress group		p Value
	D *	D/SE **	
Myocardium/Liver	1.06 ± 0.58	1.59 ± 0.60	0.0001
Myocardium/Colon	0.89 ± 0.45	1.47 ± 0.73	0.0001
Inferior wall/Liver	1.07 ± 0.58	1.56 ± 0.56	0.0001
Inferior wall/ Colon	0.77 ± 0.43	1.48 ± 0.64	0.0001
Lateral wall/Liver	1.04 ± 0.53	1.37 ± 0.55	0.004
Lateral wall/ Colon	0.77 ± 0.40	1.36 ± 0.68	0.0001

*D: Dipyridamole; **: Dipyridamole combined with exercise

Table 4: A comparison between the average count ratio of the whole myocardium to liver uptake 180 minutes post injection in two stress groups.

Ratio	Stress group		p Value
	D *	D/SE **	
Myocardium/Liver	1.53 ± 0.59	1.56 ± 0.52	0.8
Myocardium/Colon	1.13 ± 0.50	1.78 ± 0.85	0.0001
Inferior wall/Liver	1.31 ± 0.60	1.58 ± 0.52	0.0180
Inferior wall/ Colon	0.99 ± 0.50	1.66 ± 0.74	0.0001
Lateral wall/Liver	1.32 ± 0.61	1.45 ± 0.50	0.0001
Lateral wall/ Colon	0.91 ± 0.47	1.63 ± 0.77	0.25

*D: Dipyridamole; **: Dipyridamole combined with exercise

in group D, reaching a plateau and the between-subject difference was decreased at the end of imaging sequence (i.e. 180 min) leading to a rather similar whole and lateral myocardial to liver uptake ratios in both groups at this time; however, the inferior myocardial wall to liver uptake ratio remained significantly higher in D/SE group even by 180 min. The patterns of whole and isolated myocardial walls to colon uptake ratios (as shown in Figure 3) are somewhat different from myocardial to liver ratios. In both studied groups, the myocardial to colon uptake ratios are gradually and insignificantly increased in the sequential 15, 60 and 120 min images while the incremental curves of these ratios are steeper following 120 min especially for whole myocardium and inferior wall.

The P values for both between- and within-subject effects are also shown in each figure. Referring to the inter-subject effect of P value, we can see whether patients in the two studied groups with different protocols of pharmacologic stress have correspondingly different myocardial to visceral uptake ratios. In addition, intra-subject effect of intercept group*time interaction and the corresponding P value determine if the pattern of time-dependent changes in myocardial to visceral uptake ratios differ across the two studied groups (D vs. D/SE).

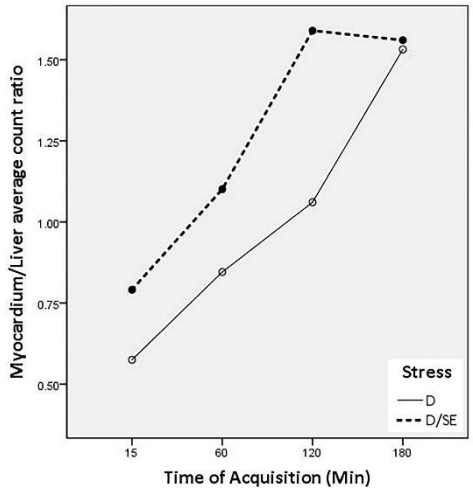
DISCUSSION

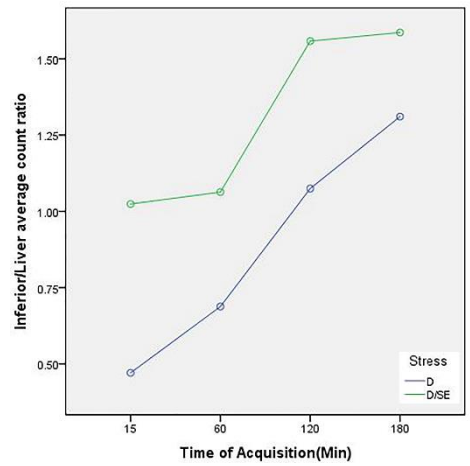
Although in most studies, adding submaximal exercise to pharmacological stress has been associated with dramatic increase of cardiac to liver ratio [7-11], they suffer several drawbacks. In some studies patients were placed in two stress groups. One group was only subjected to dipyridamole, while in the other dipyridamole was accompanied by submaximal exercise in a non-randomized way. Moreover, most studies merely analyzed the ratio of cardiac to liver activity and did not consider the colon activity. Another limitation of the previous studies is that the activity ratio of the lateral wall, as a cardiac wall with the minimum impressibility from the sub-diaphragmatic activity, was not included. Besides, the inferior wall as the most prominent distinct wall to be influenced by the sub-diaphragmatic activity [2] had not been independently evaluated on the basis of multiple images obtained over different time sets.

Only a limited number of studies have been conducted to assess the effect of submaximal exercise in addition to dipyridamole stress in relation with the changes of cardiac to sub-diaphragmatic activity ratios during a time series of imaging. In a study by Cullom et al. [12] limited populations of 30 patients were allocated in two separate groups including 15 patients who were stressed with adenosine and 15 with the combination of adenosine and submaximal exercise. The image was acquired less than 6 minutes after the injection of radiotracer. The results of this study showed a significant difference between the ratios of cardiac to sub-diaphragmatic activity in both times sets.

Another study [13] showed that in stress phase with exercise, 15 to 180 minutes after the injection, Tc-99m tetrofosmin activity in the myocardium remained in its peak. Furthermore, during the entire time the ratio of activity in the myocardium to the sub-diaphragmatic organs was above 1.

We, on the other hand, studied 97 patients (62 males, 35 female) with an average age of 57.13 ± 8.04. There was no substantial statistical difference regarding the distribution of either age or gender among two stress groups (D vs. D/SE), which is indicative of standard randomization among two groups.





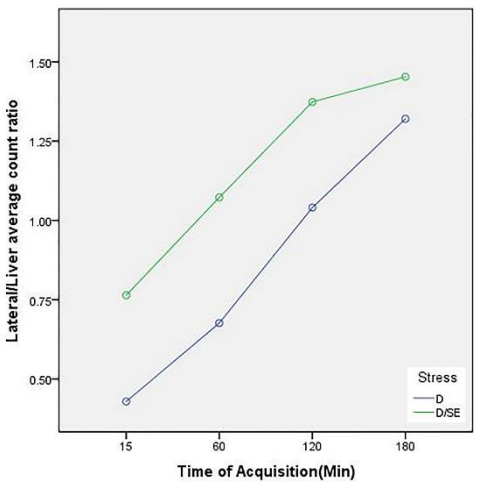
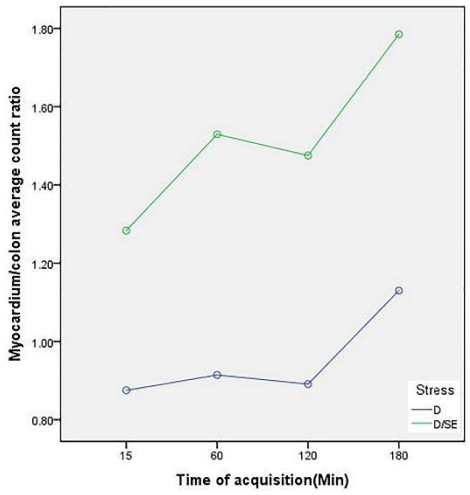
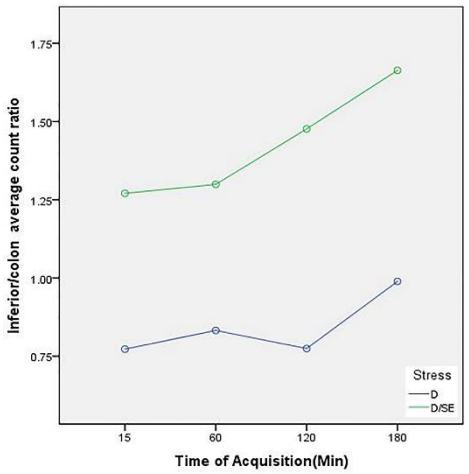


Fig 2. Comparison between myocardial to liver uptake ratios in different study groups over sequential times of acquisitions for whole myocardium (above), inferior wall (middle) and lateral wall (below). The dotted line represents the changes in myocardial to liver uptake ratios over time in the pharmacologic stress group with submaximal exercise (group D/SE) and black line represents the corresponding ratios in the group using dipyridamole alone (group D).





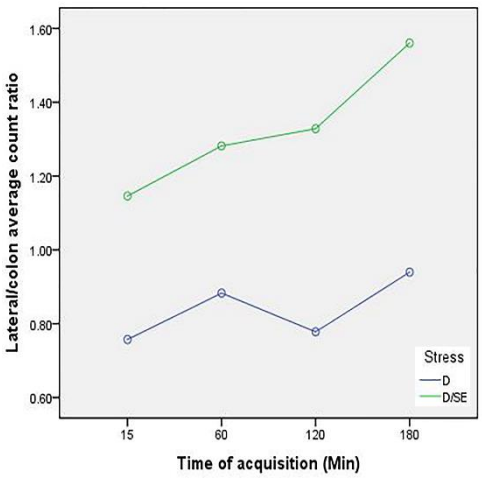


Fig 3. Comparison between myocardial to colon uptake ratios in different study groups over sequential times of acquisitions for whole myocardium (above), inferior wall (middle) and lateral wall (below). The dotted line represents the changes in myocardial to colon uptake ratios over time in the pharmacologic stress group with submaximal exercise (group D/SE) and black line represents the corresponding ratios in the group using dipyridamole alone (group D).

It was shown that in different sequential time sets such as 15, 60 and 120 minutes after the injection of radiotracer, the average cardiac uptake ratio (including the inferior and lateral walls) to liver and colon activity differed significantly between two stress groups (D vs. D/SE). On the other hand, 180 minute after the radiotracer injection, the only significant statistical difference was noted in the ratio of myocardium uptake together with the inferior and lateral walls to colon uptake ratio; but myocardial to liver ratio was only significant in the inferior wall.

This study also demonstrates that adding submaximal exercise to dipyridamole for the improvement of cardiac uptake ratio to sub-diaphragmatic visceral uptake has the highest effectiveness on the colon uptake and as it was shown by repeated measure analysis that the myocardial to colon uptake ratio increases slowly up to 120 min in both stress groups with a sharp rise in 180 min and between- subject difference was spared up to the 180 min. On the other hand, the result of this intervention on the myocardial uptake ratio to liver ratio decreases gradually over the time; Despite the fact that during the first 2 hours there is a significant statistical difference between two stress groups (D versus D/ SE), 180 minutes after the injection, the effectiveness of submaximal exercise in the improvement of cardiac uptake ratio to liver ratio decreases significantly as these ratios are similar in two groups.

These results show that bowel activity is more as a result of gastric mucosal secretion rather than hepatobiliary excretion. First, because it does not match the timing of activity arriving from duodenum to splenic flexure of colon, and second, due to the fact that it unexpectedly decreases by elapsed time. These results suggest that submaximal exercise is most effective in decreasing colon activity, and its effect does not decrease over time, while the effectiveness of this intervention on liver activity is much lower and it is more prominent at the early time stages (maximum up to 2 hour).

CONCLUSION

A protocol that combines symptom-limited exercise and dipyridamole stress with gated SPECT imaging is highly effective on improvement of average count ratio in myocardial walls compared to visceral activity. Since the greatest benefit of adding submaximal exercise to dipyridamole stress in improving the quality of cardiac SPECT images is to decrease the colon activity, in patients with high probability of artifacts due to colon activity (patients with decreased bowel movement) or in patients in which due to colon activity the scan should be repeated and are not a good candidate for stress by exercise, adding submaximal exercise to dipyridamole can improve image quality.

Acknowledgements

This study has been part of a nuclear medicine specialty thesis and supported by Tehran University of Medical sciences, Tehran, Iran, Grant No. 9882.

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