Original Article

Correlation between hypotension during dobutamine myocardial perfusion imaging and severity of stress-induced ischemia

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Abstract

Objectives: An accurate non-invasive evaluation of coronary artery disease (CAD) is essential in choosing the right management plan. Dobutamine stress myocardial perfusion imaging (MPI) is a substitute test for patients who cannot exercise. This study aimed to assess the relationship between dobutamine-induced hypotension and risk stratification of annual hard cardiac events evaluated by MPI.

Methods: This study is a retrospective study conducted on 1004 patients from October 2015 to august 2019.These patients referred to Rasoul Akram Hospital, because they could not exercise electrocardiography or had contraindications to vasodilator therapy, they were subjected to dobutamine Tc99m-Sestamibi single photon emission tomography (SPECT) protocol. During the protocol, blood pressure was measured with a one-minute interval. From among the participants, 247 patients had decreased blood pressure by more than 20 mmHg during infusion. Then for patients, a gated MPI scan was performed, and MPI with a quantitative and visual interpretation determined the risk stratification of the patients. Multivariable logistic regression model assessed the associations between decrease in blood pressure (above 20 mmHg) and risk stratification.

Results: A total of 1004 patients with a mean age of 59.07 years were studied. Of these patients, 247 had > 20mmHg drop in systolic BP from baseline. This study revealed a significant correlation between hypotension during the dobutamine stress test and high-risk scan patterns in myocardial perfusion scan. Moreover, there was a significant correlation between age increase, smoking, diabetes mellitus, transient ischemic dilation (TID), high baseline blood pressure, and history of CABG or angioplasty with a high-risk scan pattern in MPI.

Conclusions: This study demonstrated that hypotension during the dobutamine stress test is correlated with high-risk scan patterns in MPI.

Keywords: myocardial perfusion imaging, dobutamine, hypotension

Introduction

Non-invasive diagnosis and functional evaluation of CAD must be performed safely and with high accuracy to help the cardiologists to arrange proper management of patients with known or suspected CAD (1, 2). The most common method used for this aim is to exercise stress test. Adding MPI along with exercise stress test, upgrades accuracy for diagnosis and offers prognostic information to clinical and exercise stress test parameters (2).Many subjects are

incapable to do an exercise test due to specific conditions such as osteoarthritis, physical problems, neurologic disease, chronic obstructive pulmonary disease, or peripheral vascular disorder. Furthermore, a significant proportion of the subjects can accomplish only submaximal exercise stress testing (3). An exercise test is often insufficient in these subjects when the scan is negative for myocardial ischemia. In these groups, the best choice is pharmacologic stress testing (4). It is of great importance to identify patients with limited exercise capacity because they usually signify a sicker population and have a higher mortality rate than patients who can exercise. Thus, non-invasive assessment of CAD in patients with limited exercise capacity may recognize a larger ratio of patients at risk of death and hard cardiac events (5). We have good experience with performing MPI with adenosine or dipyridamole. Dobutamine-atropine stress testing, which is an alternative, is usually performed for patients with contraindications for a vasodilator stress test, for instance, asthma or high-grade atrioventricular nodal block (6, 7). Dobutamine stress myocardial perfusion scintigraphy is a reasonable method for the assessment of coronary artery disease in elderly subjects. Hypotension and supraventricular tachyarrhythmias have been observed more frequently in aging patients. However, hypotension during dobutamine stress testing is usually asymptomatic and rarely requires test termination (8). Dobutamine-induced hypotension, defined as > 20mmHg drop in baseline blood pressure, happened in 14% to 20% of the patients that could be related to peripheral vasodilatation and/or evidence of ischemia or infarction on the scan (9).In most patients, an increase in cardiac output compensates for the reduction of systemic vascular resistors induced by dobutamine. The relationship between hypotension and cardiovascular disorder during dobutamine stress testing is debated, due to differences in individuals' response to the dobutamine vasodilation effect. Anticipators of hypotension are high baseline systolic blood pressure, increasing age, high left ventricular ejection fraction, decreased systolic reserve, and dynamic left ventricular obstruction (9). A rise in systolic blood pressure of more than 30 mm Hg throughout dobutamine stress test is related to negligible fixed perfusion defects and a desire to a less annual event rate. Moreover, it is not predictive of the presence or extent of wall-motion abnormality or LV dysfunction and has no prognostic significance

similar to those seen in exercise-induced hypotension.

The aim of this study is to investigate the relationship between hypotension during the dobutamine stress test and annual hard cardiac events, risk stratification by detection of ischemia, and infarction during the scan.

Materials and Methods

Consecutive subjects (N = 1004) who underwent dobutamine gated SPECT MPI imaging in the nuclear medicine department of Rasoole Akram hospital from October 2015 to august 2019 were enrolled in this retrospective study. The dobutamine stress test was conducted according to the standard protocol. Patients with poor quality imaging (technical artifact, movement artifact,) were excluded from the study. Echocardiography of patients was evaluated for ruling out the presence of left ventricular outflow tract obstruction (LVOT).

Of all the participants, 247 had decreased blood pressure by more than 20 mmHg during infusion of dobutamine and were enrolled in the study; others were excluded. Dobutamine-induced hypotension was described as decreasing systolic blood pressure more than 20 mmHg from baseline (10, 11).

An injection dose of 740 MBq 99mTc-Sestamibi was infused in each phase of the study (12). For all the patients two series of acquisitions, including post-stress and resting-state acquisitions for comparison, were attempted.

Single-photon emission computed tomographic (SPECT) acquisition was performed in the step-and-shoot mode with 32 thirty-second projections, a zoom factor of 1.46, and in a non-circular 180° arc (45° RAO-to-LPO) with a siemens gamma camera, equipped with low-energy, high-resolution (LEHR) collimators. Moreover, gated myocardial perfusion imaging was assessed for all the subjects in the post-stress phase with an acceptance window of 30%. All the data were recorded in a 64×64×16 computer matrix and reconstructed with three-dimensional ordered subset expectation maximization (3D-OSEM), via two iterations and eight subsets (13). The rotating raw images of all the subjects were evaluated visually, and imaging with motion artifacts or low-count density was dismissed (14).

The reconstructed and reoriented images were then evaluated by an experienced nuclear physician blinded to the results of the ECG. The AutoQUANT® 7.0 software was used for cardiac quantification and functional analysis.

In this research, gated SPECT MPI was used for clinical risk assessment. Prognostic implications of stress perfusion imaging were conducted according to summary recommendations from International Nuclear Cardiology Retreat and guidelines of ACC/AHA 2012 (12).The participants were classified into low, intermediate, and high risk groups. Imaging was evaluated quantitatively according to standard seventeen-segment scoring. Each segment was interpreted as normal (with no perfusion defect), ischemic (with reversible perfusion defect), or infarcted (with persistent perfusion defect) after exclusion of attenuation artifacts. Stress-induced or fixed perfusion defects of small size with normal LVEF were reported as low risk. Participants with the following criteria were identified as bearing intermediate risk: moderate size stress-induced or fixed perfusion defects with no evidence of LV dilation or increased thallium-201 lung uptake or mild to moderate decreased resting LVEF 35%-49%. Following MPI findings were identified as high-risk groups: large size stress-induced perfusion defect (particularly if anterior)- multiple moderate size stress-induced perfusion defects - large, fixed perfusion defect with LV dilation or increase thallium-201 lung uptake- moderate stress-induced perfusion defect with LV dilation, enhancement of thallium-201 lung uptake, or diabetes mellitus or severely decreased LVEF lesser than 35% (5).

All the images visually and semi-quantitatively were evaluated according to seventeen-segment scoring. The summed difference score (SDS) was used for a semi-quantitative assessment of myocardial ischemia, and ischemia was categorized as mild (SDS≤8), moderate (8<SDS≤12), and severe (SDS>13) (15).

Statistical Methods
Data were illustrated as mean ± SD (standard deviation) for the numeric variable of age and were summarized by numbers and percentages for qualitative variables. An independent two-sample t-test was used to compare age, and categorical variables were compared using chi-square or Fisher's exact test, as needed, across risk stratification or reduction in blood pressure groups. Shapiro-Wilk test was also utilized to examine the normal distribution of age in either groups. There was no statistical violation of the assumptions of normality for the age variable in the groups (P>0.05).Multivariable logistic regression model was performed to evaluate associations between reduction in blood pressure (more than 20 mmHg) and risk stratification in presence of potential confounders like age, gender, smoking, hypertension, hyperlipidemia, diabetes mellitus, palpitation, transient ischemic dilation, high baseline blood pressure (more than 135/85 mmHg), and history of CABG or angioplasty. The association of reduction in blood pressure and risk stratification was defined as odds ratios (OR) with 95% confidence intervals (CIs).For the statistical analysis, the statistical software STATA version 14.2 for Windows (College Station, TX, USA) was applied. All p-values were 2-tailed, with statistical significance described by p≤0.05. Written informed consent was taken from all the participants and the protocol was accepted by the local ethics committee.

Results
The participants of the present study included a total of 1004 patients (498 women and 506 men) at a mean age of 59.07 years. Of these, 247 subjects had > 20mmHg drop in BP from baseline.

As evidenced by Table 1, a higher proportion of the patients in the intermediate to high-risk group were women. The mean age in the intermediate to high-risk category was 66.91±12.05 years, but in the low-risk category it was 57.17±15.50, which is statistically significant. Factors such as smoking, hypertension, hyperlipidemia, diabetes mellitus, palpitation, transient ischemic dilation, depression of blood pressure above 20 mmHg, and history of CABG or angioplasty were also significantly higher in the intermediate to the high-risk category. There was no significant difference between the low-risk and intermediate to high-risk groups regarding basal hypertension.

Table 1. Demographic and Clinical Variables according to Risk Stratification

Risk stratification Variables	Low (n=769)	Intermediate to high (n=235)	Odds ratio	P-value
Gender				
Male	401(52.1)	105(44.7)	1.349	0.045
Female	368(47.9)	130(55.3)		
Age(year)	57.17±15.50	66.91±12.05	1.052	<0.001
Smoking	114(14.8)	75(31.9)	2.693	<0.001
Hypertension	228(29.6)	111(47.2)	2.124	<0.001
Hyperlipidemia	260(33.8)	108(46.0)	1.665	<0.001
Diabetes mellitus	164(21.3)	103(43.8)	2.879	<0.001
Palpitation	196(25.5)	87(37.0)	1.719	0.001
TID	16(2.1)	46(19.6)	11.454	<0.001
Depress of sys BP 20	143(18.6)	104(44.3)	3.475	<0.001
High base line BP	184(23.9)	49(20.9)	0.838	0.328
CABG or Stent	129(16.8)	87(37.0)	2.916	<0.001

Data are expressed as mean± SD or n (%)

As displayed in Table 2, subjects were divided into the following groups: the group with decreased blood pressure above 20 mm Hg and the group failing to show a blood pressure drop of more than 20 mm Hg. Of the 247 patients with decreased blood pressure, 144 were female (58.3%) and 103 were male (41.7%). This difference was statistically significant, and depression of blood pressure appeared to be more frequent in women than men. The mean age in the group with a decreased blood pressure of more than 20 mmHg was 69.15±8.94 years, but in the other group, it was 56.29±15.64 years, showing to be higher in the first group. Other variables such as smoking, hypertension, hyperlipidemia, diabetes mellitus, palpitation, transient ischemic dilation, risk stratification, and history of CABG or angioplasty were significantly higher in the group with decreased blood pressure>20 mmHg than in the other group.

As can be identified from Table 3, blood pressure depression (more than 20 mmHg) was highly associated with intermediate to high-risk stratification when adjusted for confounders (OR=8.198, CI: 4.663 – 14.412, P<0.001).

Table 2. Demographic and clinical variables according to blood pressure depression >20 mmHg

Blood pressure depression Variables	<20mmHg (n=757)	>20mmHg (n=247)	Odds ratio	P-value
Gender				
Male	403(53.2)	103(41.7)	1.592	0.002
Female	354(46.8)	144(58.3)		
Age (year)	56.29±15.64	69.15±8.94	1.078	0.001<
Smoking	115(15.2)	74(30.0)	2.388	0.001<
Hypertension	189(25.0)	150(60.7)	4.647	0.001<
Hyperlipidemia	231(30.5)	137(55.5)	2.836	0.001<
Diabetes mellitus	161(21.3)	106(42.9)	2.783	0.001<
Palpitation	157(20.7)	126(51.0)	3.980	0.001<
Transient Ischemic Dilation	22(2.9)	40(16.2)	6.456	0.001<
Risk stratification				
Low	626(82.7)	143(57.9)	3.475	0.001<
Intermediate to high	131(17.3)	104(42.1)		
High base line blood pressure	63(8.3)	170(68.8)	24.321	0.001<
CABG or Stent	115(15.2)	101(40.9)	3.862	0.001<

Data are expressed as mean ± SD or n (%)

Table 3. Association between blood pressure depression and risk stratification adjusted for confounding factors

Variables	Odds ratio	95% CI for OR	P-value
Gender Female vs Male	1.307	0.912 - 1.875	0.145
Age(year)	1.048	1.033 – 1.064	<0.001
Smoking	2.398	1.527 – 3.766	<0.001
HTN	1.370	0.920 – 2.041	0.121
HLP	0.834	0.551 – 1.263	0.392
DM	1.617	1.081 – 2.419	0.019
Palpitation	1.475	0.954 – 2.280	<0.080
TID	4.854	2.414 – 9.758	<0.001
Blood pressure depression >20 mmHg	8.198	4.663 – 14.412	<0.001
High base line blood pressure	0.035	0.016 – 0.074	<0.001
CABG or Stent	2.622	1.703 – 4.036	<0.001

This study revealed a significant correlation between hypotension during the dobutamine stress test with high-risk scan patterns in MPI. There was also a significant correlation between age increase, smoking, diabetes mellitus, TID (enlargement of the left ventricular cavity throughout stress), high baseline blood pressure (systolic blood pressure more than 130 mm Hg or diastolic blood pressure ≥80 mm Hg), and history of CABG or angioplasty with a high-risk scan pattern in MPI. Interestingly, after adjusting the variables to reduce their confounding effect on each other, the odds ratio of decreased blood pressure turned out to be higher than 20 mmHg once dobutamine infusion increased (8.198 vs. 3.475). After adjustment, variables such as gender, hypertension, hyperlipidemia, and palpitation (sensations by a person that they are having hard, rapid, or irregular heartbeats or a combination of these sensations) proved no significant association with a high-risk scan pattern in MPI.

Discussion

The results of this study indicate that the incidence of hypotension during the dobutamine stress test is associated with severity of ischemia and presence of infarction in myocardial perfusion scan, and increased risk of annual hard cardiac events. Complicating hypotension during dobutamine infusion is a common episode in about 20% of the subjects. However, it is transient and infrequently needs discontinuation of the test. Hypotension during exercise stress indicates severe coronary artery disease, but hypotension throughout dobutamine infusion cannot be an indicator of the severity of coronary disease (16). Reasons for hypotension during dobutamine infusion have addressed dobutamine-induced cavity obliteration and vasovagal mechanisms, but the exact hemodynamic changes during hypotension are not known (11).

Geleijnse et al. examined the prognostic significance of systolic blood pressure alterations during the dobutamine stress MPI test. A decline in systolic BP ≥ 20 mm Hg was depicted in 16% and was related to increasing age and high baseline systolic BP. Gender, history of previous myocardial infarction or congestive heart failure, and the use of *β*eta blockers, angiotensin-converting enzyme inhibitors, or diuretics were not related to depression of systolic BP response. Based on the results, there were no considerable discrepancies among patients with and without systolic BP decrease during the dobutamine stress test and events during follow-up reviews (17). Elhendy et al. also detected that dobutamine-induced hypotension is associated with the number of ischemic segments on myocardial perfusion imaging in patients with prior MI (18).

Day et al. demonstrated that hypotension during dobutamine stress echocardiography is predictive of perioperative cardiac events and can be used in risk stratification before vascular or noncardiac thoracic surgery (19). Dhond et al. also found out that the incidence of hypotension during dobutamine stress echocardiography is low (3%) and appears to predict a poor prognosis for subsequent hard cardiac events (20).

In this study, we evaluated a considerable number of patients with blood pressure decline during dobutamine infusion and used risk stratification of hard cardiac events in this population. Our results suggest that decreased blood pressure more than 20 mmHg after dobutamine infusion is related to a higher risk of cardiac event classification.

Limitations
Our results are based on data collected from a population of subjects who had referred to our department for SPECT MPI study. Therefore, the generalization of the results to a broader population can be questionable. Besides, the current study is retrospective, in the face of the prospective collection of the data.
Finally, this study was performed in only one nuclear cardiology center.

Conclusion
The results of this study demonstrated that hypotension during the dobutamine stress test is correlated with a high-risk imaging pattern in MPI, so this is an important finding that can be considered in the management of patients with CAD.

References
1. Malek H, Hedayati R, Yaghoobi N, Behnia M, Rastgou F, Bitarafan Rajabi A, et al. The relationship between retinopathy in diabetes mellitus type 2 and severity and extent of myocardial ischemia in myocardial perfusion imaging. Iranian Heart 2013;13(4):6-14.
2. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). J Am Coll Cardiol. 1999; 33(7):2092-197.
3. Lee J, Chae SC, Lee K, Heo J, Iskandrian AS. Biokinetics of thallium-201 in normal subjects: comparison between adenosine, dipyridamole, dobutamine and exercise. J Nucl Med. 1994; 35(4): 535-41.
4. Malek H, Hedayati R, Yaghoobi N, Firoozabadi H, Rastgou F, Bitarafan Rajabi A. Association Between Blunted Heart Rate Response to Dipyridamole and Myocardial Ischemia in Diabetic Patients as Compared With Nondiabetic Patients. Iranian Heart . 2020; 21(1):67-74.
5. Schinkel AF, Elhendy A, Van Domburg RT, Bax JJ, Vourvouri EC, Sozzi FB, et al. Prognostic value of dobutamine-atropine stress myocardial perfusion imaging in patients with diabetes. Diabetes Care. 2002; 25(9):1637-43.
6. Pennell DJ, Underwood SR, Ell PJ. Safety of dobutamine stress for thallium-201 myocardial perfusion tomography in patients with asthma. Am J Cardiol. 1993; 71(15):1346-50.
7. Dakik HA, Vempathy H, Verani MS. Tolerance, hemodynamic changes, and safety of dobutamine stress perfusion imaging. J Nucl Cardiol. 1996; 3(5):410-4.
8. Elhendy A, Valkema R, van Domburg RT, Bax JJ. Safety of dobutamine-atropine stress myocardial perfusion scintigraphy. J Nucl Med. 1998; 39(10):1662-6.
9. Geleijnse ML, Elhendy A, Fioretti PM, Roelandt JR. Dobutamine stress myocardial perfusion imaging. J Am Coll Cardiol. 2000; 36(7):2017-27.
10. Rallidis LS, Moyssakis IE, Nihoyannopoulos P. Hypotensive response during dobutamine stress echocardiography in coronary patients: A common event of well-functioning left ventricle. Clin Cardiol. 1998; 21(10):747-52.
11. Tanimoto M, Pai RG, Jintapakorn W, Shah PM. Mechanisms of hypotension during dobutamine stress echocardiography in patients with coronary artery disease. Am J Cardiol. 1995; 76(1):26-30.
12. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol. 2016; 23(3):606-39. Journal of Nuclear Cardiology. 2016;23(3):606-39.
13. Malek H, Samiei N, Yaghoobi N, Bavaghar N, Firoozabadi H, Rastgou F, et al. Assessment of LV diastolic dysfunction in myocardial perfusion imaging: a correlative study with transthoracic echocardiography. Nucl Med Commun. 2021; 42(9):979-983.
14. Dorbala S, Ananthasubramaniam K, Armstrong IS, Chareonthaitawee P, DePuey EG, Einstein AJ, et al. Single photon emission computed tomography (SPECT) myocardial perfusion imaging guidelines: instrumentation, acquisition, processing, and interpretation. J Nucl Cardiol. 2018; 25(5):1784-1846.
15. Bitarafan-Rajabi A, Rastgou F, Hosseini S, Firoozabadi H, Malek H, Amouzadeh H, et al. Assessment of myocardial viability in patients with left ventricular dysfunction: Correlation between CT-based attenuation correction and uncorrected quantification analysis in thallium201 (201Tl) rest-redistribution SPECT study. Iranian Heart J. 2013; 13(4):15-20.

16. Wang C-H, Cherng W-J, Hung M-J. Dobutamine-induced hypotension is an independent predictor for mortality in patients with left ventricular dysfunction following myocardial infarction. Int J Cardiol. 1999; 68(3):297-302.

17. Geleijnse ML, Elhendy A, van Domburg RT, Rambaldi R, Reijs AE, Roelandt JR, et al. Prognostic significance of systolic blood pressure changes during dobutamine-atropine stress technetium-99m sestamibi perfusion scintigraphy in patients with chest pain and known or suspected coronary artery disease. Am J Cardiol. 1997; 79(8):1031-5.

18. Elhendy A, Bax JJ, Poldermans D. Dobutamine stress myocardial perfusion imaging in coronary artery disease. J Am Coll Cardiol. 2000; 36(7):2017-27.

19. Day SM, Younger JG, Karavite D, Bach DS, Armstrong WF, Eagle KA. Usefulness of hypotension during dobutamine echocardiography in predicting perioperative cardiac events. Am J of Cardi. 2000;85(4):478-83.

20. Dhond MR, Whitley TB, Singh S, Nguyen TT, Bommer WJ. Incidence and significance of profound hypotension during dobutamine stress echocardiography. Clin Cardiol. 2000; 23(1):47-50.