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Original Article

Poor myocardial blush grade accompanies to higher sudden death risk scores of hypertrophic cardiomyopathy

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Abstract

Aim: Hypertrophic cardiomyopathy (HCM) is predominantly inherited as an autosomal dominant disease. The aim of our study was to evaluate angiographic microvascular flow and predictors of poor MBG in patients with HCM.

Material and Methods: Patients with poor MBG (MBG 0/1, n=43), and patients with normal MBG (MBG 2/3, n=15) were included retrospectively.

Results: Family history and left ventricular end-diastolic diameter were significantly higher in the poor MBG group (p = 0.025, p=0.021). Left atrium diameter and moderate to severe mitral regurgitation (MR) were significantly higher in the normal MBG group (p=0.034, p=0.002). Percentage of SCD risk was significantly higher in patients with poor MBG (p=0.014). Moderate and severe mitral regurgitation (odds ratio =0.013, p=0.004) and HCM-SCD risk score (odds ratio = 0,398, p=0.009) were found to be independent parameters for predicting poor myocardial blush grade. The cut-off value of HCM-SCD risk score obtained by ROC curve analysis was 3.10 for the prediction of poor myocardial blush grade (sensitivity: 76.2%, specificity: 76.7%). The area under the curve (AUC) was 0.712 (p=0.016).

Conclusions: Our study results demonstrated the increased risk of sudden cardiac death accompanies poor myocardial blush grade in patients with HCM. If confirmed by further studies, poor MBG may convey SCD-HCM risk of higher rates.

Keywords: Hypertrophic cardiomyopathy; microvascular disease; sudden cardiac death risk score.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is predominantly inherited as an autosomal dominant disease. Other etiologies such as genetic syndromes, neuromuscular diseases, storage diseases may also be presented as HCM (1). While it is an inherited disease, HCM incidence is much lower below the age of twenty-five and with a rate of 0.2% in adult population. Cardiomyopathy is a term for structural myocardial pathologies in which other cardiac disruptors such as hypertension, coronary artery disease (CAD) are absent, whereas severe coronary artery disease may accompany HCM cases in about 25% of the adult HCM population (2). Disruption of coronary blood flow and/or myocardial structure occurs in HCM by not only the obstruction of left ventricular (LV) outflow but also thickened ventricular muscle mass, increased oxygen demand, coronary obstruction and microvascular disease responsible for myocardial ischemia (3). Diminished coronary blood flow may precede ischemia and heart failure, which are the best-known etiologies of cardiac morbidity and mortality (4). To improve survival, evaluation of risk scores for HCM is recommended before the implantation of implantable cardioverter defibrillators (ICD). The criteria used in HCM-SCD risk score are family history, age, left atrial diameter, ventricular tachycardia, syncope, LV outflow gradient and maximum LV thickness (1). Increased sudden cardiac death (SCD) risk presents the necessity of ICD in patients whose score is above 4% according to the mentioned criteria. Although risk of severe CAD in patients' survival and concominant CAD in patients with HCM have been reported by several studies, there is continuing debate

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regarding the coexisting CAD risk profile on scores and further management (2,5). These small number of studies evaluated epicardial coronary flow via critical lesion by coronary angiography, helical flow by MRI and ischemia by thallium-201 scintigraphy (6,7). Nonetheless, whether there is an influence of microvascular flow grade on the pathological structure and SCD risk of HCM has not been reported yet. Microvascular disease involvement in HCM is a result of relatively small arterioles because of thickened myocardium, reduced vasodilator capacity, and increased collagen deposition (3). Myocardial blush grade (MBG) is a visual evaluation method via assessment of the entrance and existence of coronary microvascular flow and myocardial opacification. Poor MBG (MBG 0/1 grade out of 3) and impaired microvascular flow despite non-critical epicardial flow have been shown to be the predictors for unfavorable survival (8,9). The aim of our study was to evaluate microvascular flow and the predictors of poor MBG in patients with HCM.

MATARIAL AND METHODS

Study population

Our study population consisted of patients with HCM who had coronary angiography scans who were admitted to the coronary clinic in 2011-2018, retrospectively. Patients with MBG 0/1 were served as group 1 and poor MBG (n=43). Patients with MBG 2/3 were served as group 2 and normal MBG (n=15). We excluded patients who were not at the range of adult population, aortic stenosis, and patients without coronary angiography scans.

Hypertrophic cardiomyopathy patients was defined as those with a wall thickness of ≥ 15 mm in any LV segment/segments and those patients were chosen from the database according to the recent reports.[1] Patients with increased left ventricular thickness and the absence of other flow overloading etiologies that increased afterload were included as suitable data providers. The local ethics committee's approval was obtained for the study (No: 07 on 08/02/2018).

Laboratory and echocardiographic evaluation

Since the current study has a retrospective feature, we obtained the data of laboratory and echocardiography from the database of the computer system. We included patients with HCM who had ventricular outflow obstruction or not, and regardless of the localization of the hypertrophic segment. There were no patients with a prosthetic valve and patients' data were obtained before further invasive treatment (such as ICD, alcohol septal ablation and/or surgery for gradient or valve).

Coronary angiography

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score was calculated from the angiographic analysis of coronary lesions with ≥50% stenosis in vessels of ≥1.5 mm in diameter (10).

Myocardial blush grade was assessed using the best view of each coronary artery. At least three cardiac cycles were viewed for a conclusion. Grading of myocardial blush was as follows; MBG 0: Minimal or no blush of the myocardium, MBG 1: Dye slowly enters but fails to exit the microvasculature (dye is visible for at least 30 seconds), MBG 2: Input and output of dye in myocardium is delayed (dye is visible at least for 3 cardiac cycles). MBG 3: Normal entry and exit of dye from the microvasculature. MBG 0/1 patients served as the poor myocardial perfusion group, MBG 2/3 patients served as normal myocardial perfusion according to the previous report (11). Hypertrophic cardiomyopathy sudden death risk score was assessed according to the latest suggestions (1).

Statistical analysis

The variables were divided into two groups as categorical and continuous. Categorical data were expressed as numbers and percentages and compared with the chi-square test. Continuous variables were expressed as mean ± SD. The normal distribution of continuous variables was calculated by the Shapiro-Wilk test. Normally distributed continuous variables were compared with the independent samples T test, not normally distributed variables were compared with Man Whitney U Test. Binary logistic regression analysis was performed with the variables which were found to be significant in univariate analysis. Independent predictors of poor myocardial blush grade were determined via the logistic regression analysis. Results were expressed as the p value and Odds ratio (OR) in CI of 95%. Statistical analyses were calculated with the SPSS 20.0 software (SPSS Inc., Chicago, IL, United States) and $p < 0.05$ was considered significant.

RESULTS

Comparison of variables between poor and normal myocardial blush grade groups

Demographic data except for family history (age, gender, diabetes mellitus, smoking and hypertension) were similar between the groups ($p>0.05$). Laboratory parameters were similar between the groups ($p>0.05$). In terms of transthoracic echocardiographic parameters, while left atrium diameter and moderate to severe mitral regurgitation (MR) were significantly higher in the normal MBG group ($p=0.034$, $p=0.002$; respectively), left ventricular end-diastolic diameter was significantly higher in the poor MBG group ($p=0.021$). Epicardial coronary artery involvement was similar between the groups ($p>0.05$). Percentage of SCD risk was significantly higher in patients with poor MBG ($p=0.014$). After checking the patients' survival rate from the database, it was seen that the mortality rates were similar between the groups up to now ($p>0.05$). Table 1 shows the variables between the poor and normal myocardial blush grade groups. Scatter plot diagram of HCM-SCD risk score of patients with poor and not poor myocardial blush is shown in Figure 1.

Table 1. Comparision of variables between poor and normal myocardial blush grade groups

Variables	Group 1 (n = 43)	Group 2 (n = 15)	P-value
Age (years)	48.4 ± 10.9	50.7 ± 12.4	NS
Female sex (%)	46.5	60	NS
Diabetes mellitus (%)	23	13	NS
Hypertension (%)	23	13.3	NS
Family history (%)	53	20	0.025
Smoking (%)	46.5	33.3	NS
LDL–C (mg/dL)	132.6 ± 36.1	130.4 ± 40.6	NS
HDL–C (mg/dL)	34.0 ± 9.5	33.7 ± 5.8	NS
Triglycerides (mg/dL)	169.0 ± 97.1	174.8 ± 77.8	NS
Glucose (mg/dL)	108.9 ± 40.2	97.9 ± 33.8	NS
eGFR (mL/min/1.73 m^2)	100.3 ± 14.6	101.6 ± 10.5	NS
Maximal LV diastolic wall thickness (mm)	22.3 ± 3.8	21.2 ± 2.4	NS
LV maximal to posterobasal ratio	2.4 ± 0.6	2.4 ± 0.5	NS
Left atrium (mm)	38.2 ± 6	41.8 ± 3.5	NS
Maximum LVOT gradient (mmHg)	74.4 ± 32.5	84.8 ± 36.2	NS
LVEDD (mm)	45.6 ± 3.2	43.3 ± 3.2	0.021
EF(%)	59.6 ± 5.6	62.3 ± 4.2	NS
Modarate-severe MR (%)	14	53	0.002
CAD (absent/mild-modarate/ severe %)	72/14/14	74/13/13	NS
SYNTAX score	13.5 ± 6.7	13.5 ± 6.3	NS
Atrial fibrillation (%)	14	33	NS
SCD risk (%)	5.4 ± 2.9	3.3 ± 1.7	0.014
Mortality (%)	0.7	0	NS

EF: ejection fraction, eGFR: estimated glomerular filtration rate, HDL-C: high density cholesterol, LDL-C: low density cholesterol, LVEDD: left ventricular end-diastolic diameter, MR: mitral regurgitation, SCD: sudden cardiac death

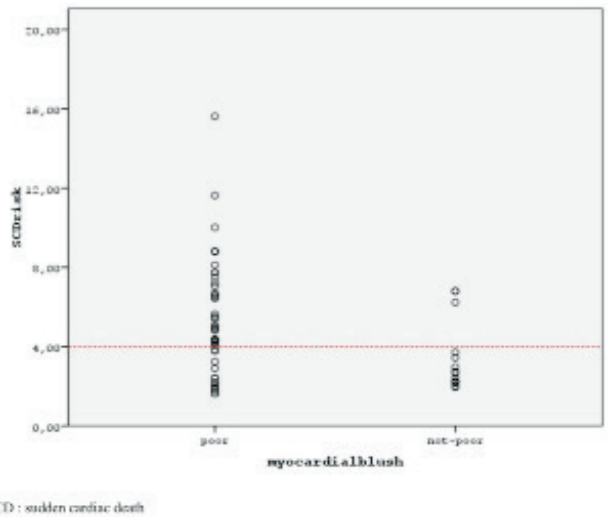


Figure 1. Scatter plot diagram of HCM-SCD risk score for patients with poor and non-poor myocardial blush

Binary logistic regression analysis

Moderate and severe mitral regurgitation (odds ratio = -0,013, p=0.004) and HCM-SCD risk score (odds ratio = 0,398, p=0.009) were found to be independent parameters for predicting poor myocardial blush grade. Independent predictors in logistic regression analysis are shown in Table 2.

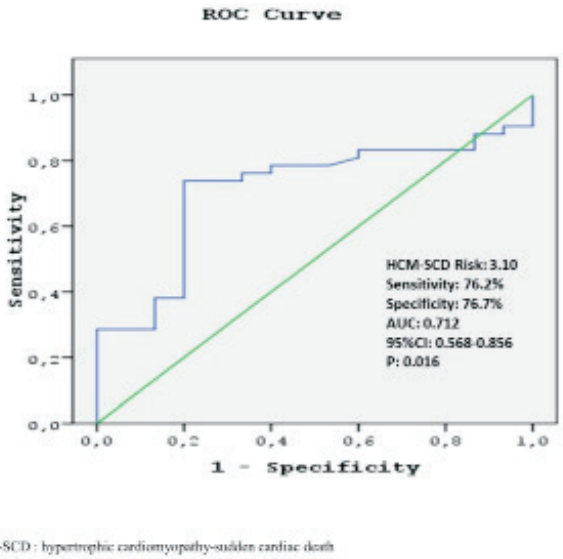
Table 2. Drugs used by patients

Variables	Odds ratio	P-value
HCM-SCD risk score	0.398	0.009
Moderate-severe mitral regurgitation	–0.013	0.004

HCM-SCD: hypertrophic cardiomyopathy-sudden cardiac death

ROC curve analysis to determine the predictive value of HCM-SCD risk score for poor myocardial blush grade

The cut-off value of HCM-SCD risk score obtained by ROC curve analysis was 3.10 for the prediction of poor myocardial blush grade (sensitivity: 76.2%, specificity: 76.7%). The area under the curve (AUC) was 0.712 (p=0.016) (Figure 2).



HCM-SCD : hypertrophic cardiomyopathy-sudden cardiac death

Figure 2. ROC curve analysis of HCM-SCD risk score for poor myocardial blush grade

DISCUSSION

ın terms of microvascular insufficiency that is the main ischemic disruption in patients with HCM, we analyzed the risk profile of patients with HCM according to their routine echocardiographic parameters, concomitant coronary diseases if there were any, the SCD scores and interpreted those values with their MBG. The main findings of our study were as follows;

1. Although epicardial vessel involvement was similar between the groups, SCD risk score was markedly higher in patients with poor MBG. This difference made it necessity for ICD implantation from low risk to intermediate risk.

2. Although 5-year SCD risk was higher in the poor MBG group, the mortality rate was not different between the two groups.

3. More than mild MR was significantly higher in the normal MBG patients.

While hypertrophic cardiomyopathy is a relatively common hereditary disease, studies in which coexistence with coronary artery diseases were insufficient (1). Patients with hypertrophic cardiomyopathy may present with various textural disorders in the heart chambers depend on the seriousness of their LV hypertrophy and volume status of LV cavity. Disarrangements of cellular structure and fibrosis follow myocardial hypertrophy, increased LV diastolic /left atrial pressure, LV outflow tract obstruction and mitral regurgitation (MR) concluded as diastolic dysfunction, myocardial ischemia, arrhythmias, heart failure and the most feared one is SCD if diagnosis delayed (12). As SCD is the initial finding, patients may be admitted with various types of symptoms due to the mentioned pathological disarrays of ventricular myocardium and cavity.

While obvious atherosclerotic disease of epicardial coronary arteries is the most common etiology of myocardial ischemia in the general population, patients with HCM are exposed to ischemia via several pathological pathways such as elevated ventricular wall tension, inadequate diastolic filling pressures due to arrhythmias, left ventricular outflow tract (LVOT) obstruction and microvascular fibrosis. The last etiology gives the inevitable result of ischemia by increasing the ratio of myocardium to micro vessels (3,13). Enhanced myocardial force creates a resistance not only by pressing out of the epicardial vessels, but also its intramyocardial capillaries are restricted during systole. Thus, ischemia occurs regardless of an atherosclerotic occlusion (14). Value of myocardial blush grade in patients with acute coronary syndromes was reported by Arnoud et. al (15). They analyzed MBG and myocardial viability, ventricular function and long-term mortality. While the value of MBG decreased, their mortality rate increased exponentially (24%) in patients with poor MBG, as it was 3-6% in patients with normal MBG). They also showed the favor of MBG that was an independent predictor of mortality after adjusting other well-known major cardiac events' risk factors (ejection fraction, infarct size, TIMI- Thrombolysis in Myocardial Infarction- flow etc.). Our study population consisted of patients without acute coronary syndromes, however, De Caterina et. al (16) analyzed coronary microvascular function angiographically in patients with Tako-Tsubo syndrome (TTS) that is of apical wall motion abnormalities and non-obstructive epicardial arteries. They showed that diminished microvascular flow rate was higher in patients with TTS compared to patients with myocardial infarction in whom TIMI 0-2 grade was obtained. In another study, the researches reported significantly lower MBG in patients with Syndrome X compared to the control group (17). These studies showed the effectiveness of MBG calculation in patients with non-obstructive epicardial coronary vessels. In our study, while mortality was not seen in the normal MBG group, 3 patients died in the poor MBG group; however, no statistical significance was achieved. Increased patient population may create a significant mortality result between the groups.

In HCM, mortality often occurs as SCD, frequently due to ventricular arrhythmias in asymptomatic patients below the age of 35. Hence risk evaluation is carried out by using some clinical criteria (mentioned in the introduction

section) for primary prevention. The criteria included age, echocardiographic criteria (left atrial diameter, maximum LV thickness, LVOT gradient), family history, syncope and ventricular tachycardia (12). Our study population consisted of middle-aged patients in whom SCD risk was decreased by means of increased age, however, indication of existing patients with coronary angiography results prevented us from analyzing the young adult population (age of 18-35). Although there has been quite distinct results for ICD requirement criteria between American and European models (60% vs 26%), coronary flow evaluation has not been used for further management up-to-date (1,18). Our study showed a deviation, from low to intermediate in the SCD risk zone associated with decreased MBG (from 2/3 grade to 0/1). The lower the MBG, the higher the risk of SCD. In terms of echocardiographic parameters, our results showed that increased LV end diastolic diameter accompanied poor MBG. Moreover, higher values of left atrial diameter and MR accompanied normal MBG in our study. Logically, the higher grades of MR, the higher filling pressure that triggers the enlargement of left atrium and diastolic impairment. And this last result brings to the mind that impaired diastolic dysfunction precedes diminished microvascular flow. Rossi et al. (19), however, explained that MR did not have any effects on the strongest proven echocardiographic parameter of LV end diastolic pressure, the time difference between mitral and pulmonary vein A waves (20). These results showed that MR may not be coexisting with impaired diastolic ventricular functions and coronary flow. Additionally, increased LV end diastolic volume causing a decrease in LVOT gradient, is the unequivocally pathophysiological condition that prevents mitral cusps from banging to the interventricular septum and higher rate of MR (21). These study results may explain our findings in which higher grade of MR was significantly lower and not coexisting with LV enlargement in patients with poor MBG. In the light of all these results, we can investigate whether poor myocardial flow leads to an increase in sudden cardiac death risk in HCM. As we know, there are several mutations which have been defined in the pathogenesis of HCM. Beta-myosin heavy chain (MYH7), myosin-binding protein C (MYBPC3), cardiac troponins (TNNI3, TNNT2), tropomyosin alpha-1 chain (TPM1) and myosin light chain 3 (MYL3) are defined as mutations which are the causes of HCM and these account for 60% of all HCM cases, with the exception of about 10% HCM patients who suffered from metabolic, storage and mitochondrial disorders (1). Besides, Olivotto et. al (22) studied myofilament genes mutations, MYBPC3, MYH7, light chain and thin filament proteins, associated with the presence of HCM. Their results showed diminished dipyridamole MBG in patients who suffered from mutation compared to patients without mutation ($p = 0.019$). They evaluated MBG by positron emission tomography. In our study, patients with poor MBG were more likely to have a family history in terms of SCD in first-degree relatives below the age of 40. Although, in our study we did not know if any mutation was responsible for HCM progression in each patient, it is certain that the mutations mentioned above are inherited. Besides that, family history of sudden cardiac death is a proven risk score assessment for SCD in HCM (1). Many more patients with family history in our poor MBG group may be responsible for increased HCM-SCD risk score (from low to intermediate risk zone) when compared with normal MBG.

Along with these results, Femenia et al. (23) showed fragmented QRS as a novel risk stratification in HCM via surface 12-lead ECGs records. Their retrospective study demonstrated that fragmented QRS is associated with arrhythmic events in patients with HCM. Additionally, in other reports HCM was shown to coexist with higher troponin levels mimicking acute myocardial infarction (13,24). Since troponin is a primary marker for the diagnosis of myocardial infarction and is correlated with the extent of myocardial necrosis and survival, ischemia in HCM raises suspicion that it endangers survival. A recently published article by Gawor et. al (25). addressed some biomarkers, soluble suppression of tumorigenicity (sST2) and galectin-3 (Gal-3), which were reported for the prognosis of heart failure, also associated with non-sustained ventricular tachycardia, syncope and family history but without the HCM SCD-risk in patients with HCM. In a different way, our evaluation method MBG seemed as a fast and conceivable marker for assessing HCM SCD-risk range. As these researches show, SCD risk may be an ongoing process, influenced not only by traditional markers but by also other pathognomical factors.

The first limitation of this study was the small number of the study population. Primary prevention risk models were created and these were compatible for a 5-year risk evaluation. While our retrospective data screening encompassed 5-years (2012-2017), some patients have not still fulfilled this range, so longer follow-up periods should be taken into consideration. Since it was a retrospective study, we did not know the responsible mutation, metabolic and/or mitochondrial disorders of all patients, if any was defined. The mere presence of poor MBG does not imply that diminished microvascular flow is a only risk factor of HCM. Our study population, which consisted of middle-aged adults in which a relatively higher age may play a role in potentiating poor MBG when we take into account the general HCM population in which there is a higher risk for SCD. Hence, studies with young adult HCM patients may be analyzed in terms of poor MBG and its risk of SCD, if coronary angiography was performed for an indication.

CONCLUSION

Our study results demonstrated that increased risk of sudden cardiac death accompanies poor myocardial blush grade in patients with HCM. If confirmed by further studies, poor MBG may convey SCD-HCM risk of higher rates.

Conflict of interest is not declared. There was not any funding for this study. This study was performed according to the Helsinki Human Rights Declaration.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Mustafa Kemal University clinical ethics committee approved the study (No: 07 on 08/02/2018).

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