Clin. Cardiol. 29, 65–68 (2006)

Noncardiac Surgery and the Risk of Death and Other Cardiovascular Events in Patients with Hypertrophic Cardiomyopathy

HAITHAM HREYBE, M.D., MALIHA ZAHID, M.D., ALI SONEL, M.D.,* CHESTER B. GOOD, M.D.,* JAMES SHAVER, M.D., SAMIR SABA, M.D.

Cardiovascular Institute, University of Pittsburgh, and *Department of Medicine, VA Hospital, Pittsburgh, Pennsylvania, USA

Summary

Background: There is a paucity of reports evaluating the perioperative risk of noncardiac surgery in patients with hypertrophic cardiomyopathy (HCM).

Hypothesis: The study was undertaken to evaluate the incidence of acute myocardial infarction (MI) and all-cause in-hospital mortality following noncardiac surgery in patients with HCM.

Methods: We searched the National Hospital Discharge Survey database for patients with a diagnosis of HCM who had undergone noncardiac surgery. Cases were matched by age, gender, and year of surgery. Death or acute MI were used as endpoints for analysis.

Results: From 1996 to 2002, 227 patients with HCM were matched with 554 controls (representing national estimates of 25,874 HCM and 50,326 controls patients). Patients with HCM were more likely than controls to have a history of atrial fibrillation (22.7 vs. 10.6%, $p < 0.001$) and of congestive heart failure (CHF) (24.2 vs. 14.1%, $p < 0.001$). The in-hospital incidence of death or MI was higher in patients with HCM than in controls (6.7 vs. 2.5%, $p < 0.001$ for death and 2.2 vs. 0.3%, $p < 0.001$ for MI). After correcting for age, gender, race, presence of hypertension, diabetes mellitus, history of coronary artery-disease, history of CHF, atrial fibrillation, and ventricular arrhythmias in a multivariate binary logistic regression model, the presence of HCM increased the odds of death by 61% (odds ratio [OR] = 1.61, 95% confidence interval [CI] 1.46–1.77, $p < 0.001$), and almost tripled the odds of the combined endpoint of death or MI (OR = 2.82, 95% CI 2.59–3.07, $p < 0.001$).

Conclusion: The presence of HCM significantly increases the risk of death and MI associated with noncardiac surgery. Patients with HCM undergoing elective procedures may require more careful preoperative assessment and perioperative monitoring. The impact of the severity of HCM on outcomes of noncardiac surgery needs further study.

Key words: hypertrophic cardiomyopathy, noncardiac surgery, death, myocardial infarction

Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disorder characterized by histopathologic findings of myocyte disarray and manifesting as unexplained ventricular hypertrophy and an increased risk of sudden death. It is caused by mutations in 1 of 10 or more genes that encode among others the proteins of the cardiac contractile apparatus.[1] Although the majority of patients remain asymptomatic, some exhibit severe limiting symptoms of dyspnea, angina, or syncope, and some may even die suddenly from cardiac causes. Multiple studies have shown that patients with HCM are at higher risk for sudden cardiac death,[2–4] stroke,[2] atrial fibrillation,[2, 5, 6] atrial reentrant tachycardias,[6] syncope,[5, 6] and congestive heart failure (CHF).[3] The mechanisms underlying the morbid consequences of HCM include dynamic left ventricular (LV) outflow tract obstruction, mitral regurgitation, diastolic dysfunction, myocardial ischemia, and cardiac arrhythmias.[1]

Although the risk of noncardiac surgery in patients with coronary artery disease (CAD) is well defined, it remains poorly characterized in patients with HCM. Several studies have attempted to risk stratify patients with HCM undergoing noncardiac surgery by the type of surgery performed, but the results have been inconsistent. Complications such as CHF and myocardial infarction (MI) were prevalent in some studies[7] and scarce in others.[8, 9]

Because of these considerations, we analyzed a nationally representative hospital discharge database to evaluate the inci-

Address for reprints:

Samir Saba, M.D.
Division of Cardiac Electrophysiology
Cardiovascular Institute
University of Pittsburgh Medical Center
200 Lothrop Street, B535 PUH
Pittsburgh, PA 15213, USA
e-mail: sabas@msx.upmc.edu

Received: October 11, 2005
Accepted with revision: October 27, 2005

dence of acute MI and all-cause, in-hospital mortality following noncardiac surgery in patients admitted to United States hospitals with a diagnosis of HCM between 1996 and 2002.

Methods

Data Source

The National Hospital Discharge Survey collects data on approximately 1% of all discharges from nonfederal U.S. hospitals. Public use files contain demographic data (age, gender, race, marital status), seven diagnostic codes from the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM), four procedural codes, dates of hospital admission and release, sources of payment, and disposition at discharge. These files were collected and merged from 1996 to 2002. Patients with HCM diagnosis were selected using ICD-9-CM code 425.1. Patients who had no surgical procedures or in whom cardiac procedures were performed during hospitalization were excluded. Patients admitted with a primary diagnosis of MI were also excluded. The list of surgical procedure codes was reviewed independently by three investigators (two cardiologists and one internist) and categorized as low, intermediate, or high risk following the guidelines provided by the American College of Cardiology.[10] The three investigators were in agreement as to the risk category of surgical procedures in 60% of cases. For the remaining cases, differences in opinion were resolved through consensus. Patients with procedural ICD-9-CM codes ≥ 8700 were excluded from both cases and control categories, as these codes refer to diagnostic rather than surgical procedures.

For each HCM case, two controls were selected matched by age, gender, and year of surgical procedure. A total of 681 patients (227 with HCM and 554 controls) constituted the surveyed population. For all statistical analyses, the weighing variable provided in the National Hospital Discharge Survey was used to provide complete national census estimates without systematic bias. Data on comorbid conditions likely to affect postsurgical outcome were extracted from the database. These included CHF (ICD-9-CM codes 428.0, 428.1, 428.20, 428.30, 428.40), CAD (ICD-9-CM codes 414.01, 414.02, 414.04, 414.05), diabetes mellitus (ICD-9-CM codes 250.00, 250.01, 250.02, 250.03, 250.70, 250.71, 250.72, 250.73), and hypertension (ICD-9-CM codes 401.0, 401.1, 401.9, 402.00, 402.01, 402.11, 405.11). Atrial fibrillation was defined by its ICD-9-CM code (427.31), and ventricular arrhythmias were defined by any of the ICD-9-CM codes of ventricular tachycardia (427.1), ventricular fibrillation (427.41), or ventricular flutter (427.42). The outcome of interest was acute MI (ICD-9-CM codes 410.11, 410.41, 410.51, 410.61, 410.91) and in-hospital death (as assessed from the discharge status).

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation (SD). Baseline characteristics of patients with and without HCM were compared using the nonpaired *t*-test for continuous variables, and using the chi-square test for categorical variables. Study endpoints were defined as death and MI. Univariate analysis was used to assess the influence of each clinical variable on the study endpoints. Multivariable binary logistic regression was used to assess the independent influence of HCM on study endpoints after correcting for all other significant clinical variables. The outcomes of interest were studied both individually and in combination. For all baseline demographic calculations, as well as univariate and multivariate analyses, the U.S. national estimates were used. A two-tailed p value of < 0.05 was considered significant. All analyses were performed using the Statistical Package for Social Sciences 10.1 version (SPSS, Inc., Chicago, Ill., USA).

Results

Demographic Data

In our data set, 227 patients with HCM undergoing noncardiac surgery were matched with 454 controls by age, gender, and year of surgery. Using the National Hospital Discharge Survey weighing variable, these surveyed patients represent a national estimate of 25,874 patients with HCM and 50,326 controls.

The demographic and clinical characteristics of patients and controls are presented in Table I. When compared with controls, patients with HCM were more likely to carry a diagnosis of CHF (24.2 vs. 14.1%, $p < 0.001$), atrial fibrillation (22.7 vs. 10.6%, $p < 0.001$), or ventricular arrhythmias (2.2 vs. 1.3%, $p < 0.001$), but less likely to undergo high-risk, noncardiac surgical procedures (5.6 vs. 7.7%, $p < 0.001$). There were no clinically significant differences in the prevalence of diabetes mellitus, hypertension, or in the length of hospital stay

TABLE I Demographic and clinical characteristics

Clinical characteristics	Patients with HCM (n = 227)	Controls (n = 554)
Age	67.6 ± 18.8	68.8 ± 17.4
Male gender (%)	38.1	32.4
Hypertension (%)	21.3	23.7
Diabetes mellitus (%)	10.9	12.4
Congestive heart failure (%)	24.2	14.1 [a]
Atrial fibrillation (%)	22.7	10.6 [a]
Ventricular arrhythmias (%)	2.2	1.3 [a]
Length of stay	8.7 ± 9.1	8.3 ± 9.1
Coronary artery disease (%)	6.0	11.4 [a]
White race (%)	62.3	72.2
High risk procedures (%)	5.6	7.7 [a]

$P < 0.001$ for all comparisons between the hypertrophic cardiomyopathy (HCM) and the control groups.

[a] Baseline variables that exhibit clinically relevant differences (relative difference > 20%) between the patients with HCM and controls.

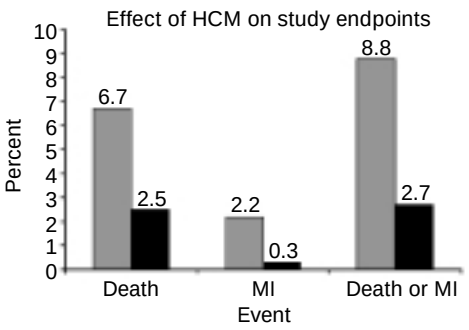

FIG. 1 Bar graph of the incidence of clinical events of death, acute myocardial infarction (MI), and the combination of death and acute MI for patients with a diagnosis of hypertrophic cardiomyopathy (HCM) and for controls. Note the higher incidence of all clinical events in the patients with HCM ($p < 0.001$ for all comparisons). ▒ = HCM, ■ = controls.

between cases and controls. It was surprising that the prevalence of CAD was lower among patients with HCM (6.0 vs. 11.4%, $p < 0.001$).

Univariate and Multivariate Predictors of Cardiac Events

Using univariate analysis, patients with HCM were more likely to die (6.7 vs. 2.5%, $p < 0.001$) or to sustain an MI (2.2 vs. 0.3%, $p < 0.001$). The combined endpoint of death or acute MI was significantly higher in patients with HCM than in controls (8.8 vs. 2.7%, $p < 0.001$) (Fig.1).

After correcting for age, gender, race, presence of hypertension, diabetes mellitus, history of CAD, history of CHF, atrial fibrillation, and ventricular arrhythmias in a multivariate binary logistic regression model, the presence of HCM increased the odds of death by 61% (odds ratio [OR] = 1.61, 95% confidence interval [CI] 1.46–1.77, $p < 0.001$), and almost tripled the odds of the combined endpoint of death or MI (OR = 2.82, 95% CI 2.59–3.07, $p < 0.001$).

The Effect of Surgical Risk

With increasing risk of the surgical procedure performed, there was no consistent increase in the endpoints of death, MI, or their combination. For each risk category, however, the presence of HCM significantly increased the risk of the combined endpoint. This was most pronounced in the low (10.6 vs. 2.9%) and high (16.4 vs. 1.1%) surgical risk categories, but comparisons for all-risk categories were highly significant ($p < 0.001$).

Discussion

Our results indicate that patients with HCM undergoing noncardiac surgery are at increased risk of perioperative death or MI. This relationship persisted after correcting for differences in gender, race, and other associated diseases such as diabetes mellitus, hypertension, CAD, and CHF.

The finding of increasing perioperative risk in patients with HCM is in agreement with multiple reports in the literature.[7–9] Most of the reported studies demonstrated an increase only in nonfatal MI, with no significant effect of HCM on total mortality as is shown in our present study. There are various possible reasons for these discrepancies, perhaps the most important of which is the size of the reported studies compared with ours. All prior studies suffered major drawbacks from being small case series and lacking control groups. The largest of these studies by Haering *et al.* included only patients with asymmetric septal hypertrophy, and showed a 40% rate of adverse events other than death.[8] These figures exceed our numbers manyfold and are hard to explain. Of note, however, is the fact that the study by Haering *et al.* included only patients with septal hypertrophy; hence their results may not be applicable to all patients with HCM included here. Unlike these other studies, our current analysis is representative of the nationwide HCM population admitted to large tertiary care centers as well as to small community hospitals in rural areas. It also represents patients of both genders, of all ages, and of all ethnic and racial backgrounds. These unique features in our study make its results applicable to the population of patients with HCM at large. The lack of detailed clinical information such as echocardiographic data prevents, however, meaningful risk stratification within our study population.

Our data demonstrate an increased risk of death in patients with HCM associated with noncardiac surgery. The risk associated with HCM was increased in all surgical categories, but was most pronounced in the low- and high-risk categories compared with the intermediate-risk group. Furthermore, there was no consistent increase in the risk of death or MI as the risk of surgery increased in the patients with HCM or in the controls. The explanation for these findings is not clear.

Possible mechanisms responsible for the increased incidence of MI in patients with HCM include persistently elevated LV pressures as well as limited blood flow and oxygen delivery through the perforating arteries during periods of increased myocardial oxygen demand. In addition, patients with HCM are also at risk of ventricular tachyarrhythmias in the setting of disturbed ventricular conduction caused by myofibrillar disarray and the resulting anisotropy. Both ischemic and arrhythmic events are therefore likely mechanisms for the significantly higher mortality observed in patients with HCM.

Limitations

The present study has several important limitations. The data are derived from hospital discharges from across the U.S. and their accuracy depends on accurate coding. This limitation may be even more important in a heterogeneous disease such as HCM, in which only severe cases may have been given the ICD-9-CM code for the disease, leading to an overestimation of the effect of this condition on mortality and MI perioperatively. No information can be derived from the potentially different outcomes between the variants of HCM because ICD-9-CM coding does not differentiate between the various forms of this disease. In addition, the severity of HCM could not be

assessed because of the same coding limitation. Furthermore, the database does not allow an assessment of the impact of specific medications such as beta blockers on the outcome. The benefit of large numbers allowed us to correct for major comorbidities identified; however, given the retrospective nature of the study, other potential confounders or biases cannot be excluded.

Conclusion

Patients with HCM undergoing noncardiac surgeries remain at an increasing risk of death or perioperative MI in this era of improved surgical techniques and anesthesia. The overall absolute mortality rate is 4.2% higher in patients with HCM than in controls. Further studies are required to assess the effect of specific therapeutic interventions on reducing the surgical risk in patients with HCM.

References

1. Nishimura RA, Holmes DR Jr: Hypertrophic obstructive cardiomyopathy. *N Engl J Med* 2004;350:1320–1327
2. Maron BJ, Chaitman BR, Ackerman MJ, Bayés de Luna A, Corrado D, Crosson JE, Deal BJ, Driscoll DJ, Mark Estes NA III, Araújo CGS, Liang DH, Mitten MJ, Myerburg RJ, Pelliccia A, Thompson PD, Towbin JA, Van Camp SP, for the Working Groups of the American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention; Councils on Clinical Cardiology and Cardiovascular Disease in the Young: Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation* 2004;109: 2807–2816
3. Maron BJ: Hypertrophic cardiomyopathy: A systematic review. *J Am Med Assoc* 2002;287:1308–1320
4. McKenna WJ, Mogensen J, Elliott PM: Role of genotyping in risk factor assessment for sudden death in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;39:2042–2048
5. Fananapazir L, Chang AC, Epstein SE, McAreavey D: Prognostic determinants in hypertrophic cardiomyopathy. Prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiological findings. *Circulation* 1992;86:730–740
6. Fananapazir L, Tracy CM, Leon MB, Winkler JB, Cannon RO III, Bonow RO, Maron BJ, Epstein SE: Electrophysiologic abnormalities in patients with hypertrophic cardiomyopathy: A consecutive analysis in 155 patients. *Circulation* 1989;80:1259–1268
7. Kuroiwa M, Arai M, Ueno T, Takenaka T, Okamoto H, Hoka S: Perioperative cardiovascular complications in patients with hypertrophic cardiomyopathy. *Masui* 2003;52:733–739
8. Haering JM, Comunale ME, Parker RA, Lowenstein E, Douglas PS, Krumholz HM, Manning WJ: Cardiac risk of noncardiac surgery in patients with asymmetric septal hypertrophy. *Anesthesiology*. 1996;85:254–259
9. Chang KH, Sano E, Saitoh Y, Hanaoka K: Anesthetic management of patients with hypertrophic obstructive cardiomyopathy undergoing non-cardiac surgery. *Masui* 2004;53:934–942
10. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froelich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr: ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2002;39:542–553