Perioperative myocardial ischemia and isolated systolic hypertension in non-cardiac surgery

L’ischémie myocardique périopératoire et l’hypertension systolique isolée en chirurgie non cardiaque

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Abstract

Purpose To determine whether patients with isolated systolic hypertension (ISH) undergoing non-cardiac surgery have a higher incidence of perioperative myocardial ischemia than normotensive patients and hence a greater risk for perioperative adverse events.

Methods After obtaining Research Ethics Board approval, patients were recruited to either an ISH group (systolic blood pressure [SBP] > 140 mmHg with diastolic blood pressure [DBP] < 90 mmHg) or a normotensive group (SBP < 140 mmHg and DBP < 90 mmHg), according to their resting preoperative blood pressure. The primary outcome was the overall incidence of perioperative myocardial ischemia (PMI) as determined by 48-hr ambulatory Holter monitoring. P values ≤ 0.05 were considered to be statistically significant.

Results A total of 312 (150 ISH and 162 normotensive) patients completed the study. Orthopedic surgery was the most frequent surgical procedure in both groups. The overall incidence of PMI was 19.7% in the ISH group compared with 18.8% in the normotensive group (difference 0.9%; 95% confidence interval [CI], −7.9% to 9.8%). The overall incidence of adverse events was 4.0% in the ISH group compared with 1.9% in the normotensive group (difference 2.2%; 95% CI, −1.6% to 5.9%).

Conclusion In this study, we chose to examine ISH as potential cardiac risk factor for patients undergoing non-cardiac surgery. The incidence of myocardial ischemia, a surrogate outcome, was similar in the two groups. The relatively high incidence of myocardial ischemia (19.2%) was of particular interest in this relatively low cardiac risk surgical population. (ClinicalTrials.gov number, NCT01237652).

Résumé

Objectif L’objectif de cette étude était de déterminer si les patients atteints d’hypertension systolique isolée (HSI) présentaient une incidence plus élevée d’ischémie myocardique périopératoire et donc un risque plus élevé d’événements défavorables périopératoires que les patients normotendus subissant une chirurgie non cardiaque.

Méthode Après avoir obtenu l’approbation du Comité d’éthique de la recherche, des patients ont été recrutés et attribués soit à un groupe HSI (tension artérielle systolique (TAS) > 140 avec tension artérielle diastolique (TAD) < 90 mmHg) ou à un groupe normotendu (TAS < 140 et TAD < 90 mmHg), selon leur tension artérielle préopératoire au repos. Le critère de jugement principal était l’incidence globale d’ischémie myocardique périopératoire (IMP) telle que déterminée par monitorage de Holter ambulatoire.
Isolated systolic hypertension (ISH) is recognized as a risk factor for cardiovascular morbidity and mortality.\textsuperscript{1-5} Data from the Multiple Risk Factor Intervention Trial (MRFIT) demonstrated a continuous and graded influence of systolic blood pressure (SBP) on coronary heart disease mortality.\textsuperscript{6} The greatest number of deaths was seen in patients with SBP from 140 to 149 mmHg, and the highest risk of death was noted in patients with SBP $\geq$ 180 mmHg. The MRFIT trial also demonstrated that SBP is a stronger predictor of outcome than diastolic blood pressure (DBP). The seventh report of the Joint National Committee (JNC) on the Detection, Evaluation, and Treatment of Hypertension confirms the close association between ISH and cardiovascular events.\textsuperscript{7} Since ISH was recognized as a separate hypertensive entity only in recent years, analysis on ISH as a separate group would not have been conducted in previous perioperative studies. Some ISH patients with SBP $>$ 160 mmHg (DBP $<$ 90 mmHg) would have been deemed “normal”, while others were deemed hypertensive,\textsuperscript{8-13} thereby diluting the impact of ISH as a risk factor. Patients with ISH and SBP 140 to 160 mmHg (DBP $<$ 90 mmHg)\textsuperscript{14} would often have been included in the normotensive group, further confounding the results. In addition, very few studies measured blood pressure as per JNC guidelines, with two measurements three minutes apart and a prior requisite rest period.\textsuperscript{13} Hence, while previous perioperative studies on hypertension demonstrated minimal or no impact on outcomes, it is difficult to know if the misclassifications could have been responsible. Scattered reports also continued to suggest that hypertension might be one of the risk factors for perioperative cardiovascular morbidity and mortality.\textsuperscript{15-17} A recent study of patients undergoing coronary artery bypass grafting (CABG) found that ISH was an independent cardiac risk factor and was associated with a 40% increase in the likelihood of perioperative cardiovascular morbidity.\textsuperscript{18} Clinically important differences in comorbidities and surgical considerations between cardiac and non-cardiac surgery suggests the need for a similar study in non-cardiac surgery to investigate the incidence of perioperative myocardial ischemia in ISH.

The Perioperative Myocardial Ischemia in Isolated Systolic Hypertension (PROMISE) study is a prospective observational cohort study of patients undergoing non-cardiac surgery to examine if the incidence of perioperative myocardial ischemia in ISH patients is higher than in normotensive patients, as determined by 48-hr ambulatory ST-segment electrocardiogram (ECG) monitoring. All adverse events were also documented, including myocardial infarction (MI), congestive heart failure (CHF), arrhythmias, cerebrovascular accident (CVA), and cardiovascular deaths.

Methods

After obtaining approval from the Research Ethics Board of The Ottawa Hospital, we screened patients and obtained their written consent. Patients were recruited for the study from the two in-patient campuses of The Ottawa Hospital from September 2006 to January 2009. Following the Canadian hypertension guidelines,\textsuperscript{19} their blood pressures were measured in the preoperative clinic by an automated blood pressure monitor, BPM-300 (VSM Med Tech Ltd, Vancouver, BC, Canada). Following five minutes of rest, a minimum of four blood pressure readings were recorded in the sitting position. Blood pressure readings at three-minute intervals were registered, with an automatic elimination of the first reading. The average blood pressure reading was recorded for each patient. Isolated systolic hypertension was defined as the average SBP $\geq$ 140 mmHg and DBP $<$ 90 mmHg; normotension was defined as SBP $<$ 140 mmHg and DBP $<$ 90 mmHg as per the seventh report of the JNC.\textsuperscript{7} The inclusion criteria were: ages $\geq$ 45 yr, revised cardiac risk index (RCRI) factors $\leq$ 2,\textsuperscript{20} elective non-cardiac surgical procedures, and expected hospital length of stay $\geq$ 48 hr. The exclusion criteria were: atrial fibrillation, left bundle branch block, MI within the previous three months, decompensated CHF, unstable coronary syndrome, hemodialysis, or emergency surgery. We recorded patient demographics, RCRI scores, comorbid
diseases, 12-lead ECG, and preoperative medications. Anesthetic and surgical management were performed as per standard practice at our institution. The patients’ anesthetic charts were reviewed in the postanesthesia care unit (PACU) for intraoperative ischemia or ECG changes (tachycardia, bradycardia, and arrhythmias), hypotension or hypertension, use of vasopressors or β-blockers, and surgical complications. Ischemia was monitored using three-channel (leads II, V3, and V5) continuous ambulatory ECG Holter recorders (Seer MC – MARS version 7.1 GE, Milwaukee, WI, USA). Holter monitoring was applied upon arrival to the operating room or PACU and was continued for up to 48 hr postoperatively. Off-line analysis of the Holter was carried out by a single cardiologist who was blinded to the ISH status. Using the Holter findings, myocardial ischemia was defined as either reversible ST-segment elevation ≥ 1 mm, ST-segment depression ≥ 1 mm, or symmetric inversion of the T wave ≥ 1 mm for at least one minute in one or more of the Holter leads. Each ischemic episode was assessed for magnitude (maximum ST-segment depression), duration and severity (area under the curve), as well as ischemic burden (minutes of ischemia per minutes monitored). The number of ischemic episodes was counted for each patient. Troponin-T levels and 12-lead ECGs were performed on postoperative days (POD) 1, 2, and 3.

A review of the literature has shown that the incidence of ST-segment changes in normotensive subjects is estimated to be 5%.21,22 A power analysis was completed to demonstrate a difference between groups that was triple the rate (15%) in ISH patients. To detect this difference with a level of significance of 0.05 (two-sided) and a power of 80%, we calculated that 159 patients were required in each group. Statistical comparisons between ISH and normotensive groups were made using the Wilcoxon rank-sum test for continuous variables and the Fisher’s exact test for categorical variables. P values of ≤ 0.05 were considered statistically significant. Statistical analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA). All adverse events were recorded. In this study, MI was identified by at least one of the following: a typical rise of a troponin T level or a typical fall of an elevated troponin T level; new pathologic Q-waves in at least two contiguous leads on a 12-lead ECG; and new persistent ST-segment depression or elevation in at least two contiguous leads on a 12-lead ECG; and clinical documentation by the attending physicians. Congestive heart failure was diagnosed by clinical findings, and pulmonary edema was visualized on chest x-ray. Cardiac arrhythmias in this study included either atrial or ventricular arrhythmias that led to hemodynamic instability and required an urgent treatment. Cerebrovascular accident was identified as the presence of neurological deficit as per clinical documentation.

Results

A total of 2,507 patients were screened, and 312 patients were enrolled for the study (150 ISH and 162 normotensive). The overall prevalence of ISH was 6.5% (163 of 2,507 patients, with 13 refusals/withdrawals in the ISH group). Holter data were complete in 307 patients, and off-line analysis findings are described below (Figure).

The ISH patients were slightly older than the normotensive patients, but all other characteristics were similar between the two groups. Demographic data are presented in Table 1. Patients with RCRI scores ≤ 2 represented 97.3% of the ISH group and 98.8% of the normotensive group, respectively. Orthopedic surgery represented the majority (58.7%) of all surgical procedures in both groups, while vascular surgery represented the least (6.5%). The majority of the orthopedic procedures were performed using regional techniques (90.2%).

During 14,736 patient-hours of monitoring, myocardial ischemia occurred in 29 (19.7%) patients in the ISH group and in 30 (18.8%) patients in the normotensive group (difference = 0.9%; 95% CI, −7.9% to 9.8%) (Table 2). The characteristics of the ischemic events in both groups are presented in Table 3. During ischemia, there was an increase in the heart rate by a mean standard deviation (SD) of 21.3 (11.2) beats-min⁻¹ and 24.0 (12.9) beats-min⁻¹ in the ISH and normotensive groups, respectively. All myocardial ischemia in this study was in the form of ST-segment depression and occurred postoperatively. The mean (SD) peak of ST-segment depression was −1.4 (0.3) mm in the ISH group and −1.3 (0.2) mm in the normotensive group, respectively (difference = −0.04; 95% CI, −0.17 to 0.09; P = 0.95). The daily 12-lead ECG demonstrated ischemic changes in 13 (8.7%) patients in the ISH group and in seven (4.3%) patients in the normotensive group.

Although the study was not powered to detect a difference in the secondary adverse events, nine patients had adverse cardiovascular outcomes, six (4%) patients in the ISH group and three (1.9%) patients in the normotensive group (difference 2.2%; 95% CI, 1.6% to 5.9%). In the normotensive group, myocardial ischemia did not precede any adverse events, while 50% of ISH patients with adverse events demonstrated ischemia. Two patients in the ISH group showed evidence of an elevated cardiac troponin T level and documented MI. They further developed CHF. These patients experienced myocardial ischemia with a total duration of 294 min and 569 min, respectively. No patients in the normotensive group showed evidence of a high troponin T level or MI. An additional patient in the ISH group developed CHF with no evidence of myocardial ischemia. Postoperative arrhythmias associated with hemodynamic instability and requiring treatment were
documented in two patients in the ISH group. One of those patients demonstrated ischemia that lasted for a total of 102.75 min. One patient in the ISH group had CVA with residual weakness. In the normotensive group, one patient developed CHF; another patient experienced cardiac arrhythmias that required treatment, and there was one death (Table 4).

Discussion

This is a prospective perioperative study to examine ISH in patients undergoing non-cardiac surgery. The overall incidence of myocardial ischemia was similar in ISH patients as compared with normotensive patients (19.7% vs 18.8%, respectively). However, the confidence interval for the difference ranged from 8% lower to 10% higher in the ISH group, indicating the imprecision of our results. In addition, as a low-risk group, the incidence of adverse events in the ISH population (4.0%) was high compared with results suggested previously in the literature.16

Prevalence of perioperative ISH in non-cardiac surgery patients

The prevalence of perioperative ISH in our study was 6.5%, which correlates with the Canadian Heart Health Survey of 6.4% prevalence in the Canadian population.23 Isolated systolic hypertension is the most frequent subtype of hypertension and has been described as a disease of the elderly. In this study, the ISH group was slightly older than the normotensive group. In the third National Health and Nutrition Examination Survey,24 65% of the uncontrolled or untreated hypertensive population had ISH. In our study, 60% of the ISH patients were receiving antihypertensive medications, but their blood pressure remained uncontrolled. On the other hand, about 60% of the patients in the normotensive group were on antihypertensive medications and their blood pressures were well-controlled. The absence of a difference in myocardial ischemic events between groups may be attributed to the fact that a significant number of patients in the normotensive group had a past medical history of hypertension which may have
carried the same potential risk of developing myocardial ischemia as in the ISH group.

Prevalence of myocardial ischemia in this study vs other perioperative studies

In general, the incidence of myocardial ischemia depends on the patient’s cardiac risk factors, surgical procedure (cardiac vs non-cardiac), and mode of detection. The overall incidence of myocardial ischemia in our study was 19.2%. Our initial estimation of the myocardial ischemia prevalence in the normotensive group was 5%, based on the prevalence of myocardial ischemia in healthy subjects when exposed to stress tests. Little is known about the prevalence of myocardial ischemia in low-risk patients with hypertension. In one study of patients who had a history or were at risk of coronary artery disease, the incidence of myocardial ischemia was reported to be 20% and was significantly higher in other perioperative studies. The reason for the relatively high incidence of myocardial ischemia observed in this study is unclear. Since perioperative studies of hypertensive “low-risk” patients are uncommon, this may be an underrecognized phenomenon. Furthermore, previous studies that reported results from two-lead Holter monitoring systems would be expected to have reduced sensitivity for ischemia detection as compared to the three-lead (II, V3, & V5) Holter used in this study.

Myocardial ischemia in the ISH group vs the normotensive group

In the ISH group, 50% of patients with adverse events experienced prolonged myocardial ischemia with a total duration of > 100 min. There were three patients in the normotensive group with myocardial ischemia > 100 min vs five patients in the ISH group. Prolonged myocardial ischemia in the ISH group led to MI in two patients and a cardiac arrhythmia in another (60% of the ISH patients with prolonged myocardial ischemia), but no adverse event was reported in the remaining two patients with prolonged ischemia. Previous studies have shown that cardiac morbidity in patients undergoing major vascular surgery is best predicted by myocardial ischemia. In a meta-analysis, postoperative myocardial ischemia confers a 10.3-fold increase in the odds of a cardiac event. Landesberg et al. found that ischemia lasting > two hours was associated with a 32-fold increase in the risk of morbid cardiac events. Others have stated that several minutes of myocardial ischemia not only increases the risk of cardiac events but also increases perioperative mortality rates.
In this study, prolonged ischemia in the normotensive group did not precede any cardiovascular events. On the other hand, ISH patients seemed to have a lower threshold (60% incidence) to develop adverse events as result of prolonged myocardial ischemia.

Perioperative ISH patients in cardiac surgery vs non-cardiac surgery

Perioperative ISH as a cardiovascular risk factor was examined in patients undergoing CABG surgery. The Multicenter Study of Perioperative Ischemia Research Group examined 5,436 CABG patients and 382 patients with pulse pressure > 80 mmHg. Postoperative MI was 20/382 (5.2%) vs 344/4,419 (7.8%) (odds ratio [OR], 0.65 [0.41-1.04]; P = 0.07). In an earlier study, Aronson et al. examined 2,417 patients undergoing CABG with 612 patients identified as having ISH. The definition of ISH, however, was based on a single preoperative measurement. Myocardial infarction was not one of the outcomes, but left ventricular dysfunction was a finding (OR, 1.3 [1.0 to 1.6]). Those studies had higher sample sizes than our study, and they involved high-risk cardiac surgical patients. In our study, although myocardial ischemia was evaluated as a surrogate outcome, we demonstrated previously that it predicts an increased risk for postoperative myocardial ischemic hard outcomes (OR, 10.3 [6.4 to 16.5]).

Therefore, our finding is consistent with the cardiac surgical population in that ISH does not predict an increased risk in MI.

PROMISE study; low-risk group

All patients in this study were low-risk, with RCRI ≤ 2 and no history of ischemic heart disease. High-risk patients in previous perioperative studies suggested an incidence of 3.9% (95% CI, 3.3 to 4.6) cardiac events. Thus, in our study, the 4.0% incidence of cardiovascular events in a low-risk group is relatively high. The estimated postoperative cardiac events of 97.3% RCRI of ≤ 1 is < 1%. However, emerging evidence suggests that low-risk patients could be at a higher risk of perioperative morbidity and mortality than originally thought. The use of Lee’s RCRI to audit and predict perioperative outcomes was challenged in a recent study which found that perioperative cardiac events were higher than described by Lee et al. in patients with RCRI of 2. In a retrospective cohort study examining the use of beta blockers in non-cardiac surgery, Kaafarani et al. found that none of the deaths occurred among the patients at high cardiac risk. The findings of this study highlight the fact that the low-risk patients deserve more attention and more studies to identify the magnitude of the problem. In the ISH group, the average age was significantly higher than in the normotensive patients. However, the reason for the high incidence of adverse events remains unclear. Finally, the American College of Cardiology and the American Heart Association considers that hypertension is not an independent risk factor for perioperative cardiovascular complications when SBP < 180 mmHg. However, if SBP ≥ 180 mmHg, the potential benefits of delaying surgery to optimize the effects

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<th>Table 3 Characteristics of the ischemic episodes</th>
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SD = standard deviation; CI = confidence interval

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<th>Table 4 Adverse cardiovascular events</th>
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<td>Adverse events</td>
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<td>Mortality</td>
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TriT = cardiac troponin T; CHF = congestive heart failure; CVA = cerebrovascular accident

a This included two patients with the documented myocardial infarction in the isolated systolic hypertension group.
of antihypertensive medications should be weighed against the risk of delaying the surgical procedure. Our findings demonstrated a high incidence of cardiovascular events with SBP of 150.6 ± 9.0 mmHg. Further studies may be warranted to examine myocardial ischemia in ISH patients compared with normotensive patients without a prior history of hypertension. Also, a much larger prospective study is warranted to determine whether ISH produces a higher rate of perioperative cardiovascular events.

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Competing interests None declared.

References


