Preoperative Serum Potassium Levels and Perioperative Outcomes in Cardiac Surgery Patients

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Potassium plays a central role in the maintenance of cellular polarization, and is critical to transmission of electrical impulses through the myocardium. Alterations in the normal balance between intracellular and extracellular potassium concentrations can lead to serious arrhythmias. The adverse association between hypokalemia and arrhythmia in animal models appears to be more significant in the presence of acute myocardial ischemia. In patients with acute myocardial ischemia, low serum potassium levels obtained on hospital admission are associated with the development of ventricular tachycardia or fibrillation. In noncardiac surgical patients with a history of coronary artery disease, 1 study suggested that a preoperative serum potassium level of less than 3.5 mmol/L is independently associated with perioperative mortality.

Combined, these findings suggest that a preoperative diagnosis of hypokalemia should delay surgery until repletion is achieved. Although potassium is critical for normal electrophysiology, the association between abnormal preoperative serum potassium level and perioperative adverse events such as arrhythmias has not been examined rigorously.

Objective To determine the prevalence of abnormal preoperative serum potassium levels and whether such abnormal levels are associated with adverse perioperative events.

Design and Setting Prospective, observational, case-control study of data collected from 24 diverse US medical centers in a 2-year period from September 1, 1991, to September 1, 1993.

Patients A total of 2402 patients (mean [SD] age, 65.1 [10.3] years; 24% female) undergoing elective coronary artery bypass grafting who were not enrolled in another protocol. The study population was identified using systematic sampling of every nth patient, in which n was based on expected total number of procedures at that center during the study period.

Main Outcome Measures Intraoperative and postoperative arrhythmias, the need for cardiopulmonary resuscitation (CPR), cardiac death, and death due to any cause prior to discharge, by preoperative serum potassium level.

Results Perioperative arrhythmias occurred in 1290 (53.7%) of 2402 patients, with 238 patients (10.7%) having intraoperative arrhythmias, 329 (13.7%) having postoperative nonatrial arrhythmias, and 865 (36%) having postoperative atrial flutter or fibrillation. The incidence of adverse outcomes was 3.6% for death, 2.0% for cardiac death, and 3.5% for CPR. Serum potassium level less than 3.5 mmol/L was a predictor of serious perioperative arrhythmia (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.2-4.0), intraoperative arrhythmia (OR, 2.0; 95% CI, 1.0-3.6), and postoperative atrial fibrillation/flutter (OR, 1.7; 95% CI, 1.0-2.7), and these relationships were unchanged after adjusting for confounders. The significant univariate association between increased need for CPR and serum potassium level less than 3.3 mmol/L (OR, 3.3; 95% CI, 1.2-9.5) and greater than 5.2 mmol/L (OR, 3.0; 95% CI, 1.1-8.7) became nonsignificant after adjusting for confounders.

Conclusions Perioperative arrhythmia and the need for CPR increased as preoperative serum potassium level decreased below 3.5 mmol/L. Although interventional trials are required to determine whether preoperative intervention mitigates these adverse associations, preoperative repletion is low cost and low risk, and our data suggest that screening and repletion be considered in patients scheduled for cardiac surgery.

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versed. However, such a recommendation is controversial since in 2 other studies no increase in incidence of intraoperative arrhythmias occurred in patients with low vs normal serum potassium levels. These last 2 studies are, however, limited in ways that preclude definitive conclusions. First, the inclusion of any electronically detected arrhythmia may overrepresent the true incidence of serious rhythm disturbances; moreover, these electrocardiac perturbations may not represent a true adverse outcome. Second, these studies are inadequately powered to assess the association between preoperative hypokalemia and serious adverse outcome. Third, hypokalemia is arbitrarily defined as any potassium level less than 3.5 mmol/L, making it difficult to generalize a possible threshold for risk. Fourth, few investigators have focused on patients undergoing myocardial revascularization, a subset of patients who may be particularly vulnerable to hypokalemia. Finally, most studies have been conducted at a single institution and thus may incorporate, unintentionally, a bias of individual institutional practice.

Data regarding the association between elevated serum potassium levels and perioperative arrhythmias are virtually nonexistent in the literature. Severe hyperkalemia (potassium level > 7.0 mmol/L) reduces the resting membrane potential to the point in which conduction of electrical impulse ceases, but data regarding the effect of more moderate levels of hyperkalemia on the development of perioperative arrhythmias are limited.

The present study by the Multicenter Study of Perioperative Ischemia Research Group attempted to overcome these limitations by prospective evaluation of historical and laboratory variables from 2417 patients undergoing elective coronary artery bypass graft surgery. Our study population was drawn from a diverse group of 24 academic, federal, and health maintenance medical centers in the United States. Our goals were to determine the prevalence of abnormal serum potassium levels preoperatively and the incidence of adverse perioperative events in this population, and to determine if there is a level of serum potassium that is associated with increased risk of adverse outcome.

**METHODS**

Patients eligible for this multicenter observational study were defined as those undergoing coronary artery bypass grafting on an elective basis, with or without concurrent valvular surgery, who were not enrolled in another research protocol. With appropriate institutional review board approval, data were collected over a period of 2 years (September 1, 1991, to September 1, 1993) at 24 institutions (listed at the end of this article). The study population was identified using a systematic sampling scheme incorporating every nth patient, in which n was based on the expected total number of procedures performed at each center over the study period. Enrollment ranged from 100 to 108 patients per site. The study database included a standardized preoperative set of historical, demographic, physical examination, and catheterization data, as well as perioperative surgical, anesthetic, and adverse outcome data. Three 12-lead electrocardiograms were obtained, the first within 1 week prior to surgery, the second within 3 days after, and the third within 10 days after surgery. Diagnosis of perioperative Q-wave myocardial infarction (MI) was made using Minnesota code criteria at a central analysis site by 2 blinded electrocardiographers with a third settling any lack of concordance.13,14

**Anesthetic and Monitoring Techniques**

Clinical management was at the discretion of each center and not prescribed by protocol; however, nearly all patients were managed with narcotic and sedative hypnotic anesthesia, and perioperatively monitored with multilead electrocardiography, arterial pressure, and central lines.

**Measurements and Outcome Variables**

Baseline serum potassium level was defined as the preoperative serum potassium level obtained as part of, or prior to, the preoperative physical examination. Patient demographics and clinical characteristics were recorded to identify which, if any, might predispose to variations in serum potassium level. Preoperative administration of potassium-wasting diuretics such as furosemide and hydrochlorothiazide was recorded.

Outcomes were defined as intermediate and final. Intermediate outcome included perioperative arrhythmias, which were defined as any occurrence of intraoperative or postoperative arrhythmia. Intraoperative arrhythmia was defined as the occurrence of an arrhythmia serious enough to warrant treatment in the precardio and postcardio pulmonary bypass periods. Postoperative arrhythmia events were identified by type, and further subdivided into ventricular arrhythmias (VAs) and atrial flutter or fibrillation (AFF). A subset of patients who experienced both VA and AFF was identified. The subset of patients requiring intraoperative treatment or having both ventricular and atrial arrhythmias in the postoperative period was arbitrarily defined as experiencing serious perioperative arrhythmias. We did not include first-degree heart block, left or right bundle-branch block, sinus bradycardia, or sinus tachycardia.

Final outcomes consisted of death, cardiac death, and the need for cardiopulmonary resuscitation (CPR). Death was defined as death prior to discharge from any cause. Cardiac death was defined as those patients whose death was considered to have been due to perioperative MI, cardiac failure, or cardiac arrhythmia. Cardiopulmonary resuscitation was defined as those patients who required closed chest cardiac massage or emergent electrical cardioversion in the postoperative period.

Patients were excluded from analysis if no preoperative serum potassium measurement was available, or if the value charted was less than 2.0 mmol/L or greater than 7.0 mmol/L, or if perioperative arrhythmia data were not available.

Descriptive statistics by potassium categories were generated for demographics, preoperative characteristics,
perioperative arrhythmias, and adverse outcomes. A histogram showing the distribution of preoperative serum potassium levels was also generated.

To define a discrete level of serum potassium associated with perioperative arrhythmias and adverse outcomes, we computed odds ratios (ORs) and 95% confidence intervals (CIs) for each of the perioperative adverse outcomes at serum potassium level thresholds of 3.2 to 3.6 mmol/L (by 0.1-mmol/L increments). Likewise, ORs and 95% CIs were computed at serum potassium level thresholds of 4.5 to 5.3 mmol/L (by 0.1-mmol/L increments).

These ORs were then recalculated, adjusting for several potential confounders of the association between preoperative serum potassium level thresholds and perioperative outcomes. The adjusted confounders were sex, age, and histories of arrhythmias, congestive heart failure, hypertension, and renal disease (including preoperative chronic renal failure and dialysis prior to admission). Although history of diuretic use was associated with both hypokalemia and arrhythmia, it could not be adjusted due to the causal relationship between diuretic use and development of hypokalemia.

The hypokalemic analysis was initially completed on all patients with preoperative serum potassium levels of less than 5.0 mmol/L, and the hyperkalemic analysis was completed on all patients with preoperative serum potassium levels of 3.5 mmol/L or more. These initial analyses were then confirmed using the entire patient set (n = 2402). No adjustments were made for multiple comparisons.

All analyses were performed using SAS computer programs (SAS Institute Inc, Cary, NC).

RESULTS

Distribution of Potassium Levels and Patient Characteristics

Of the 2417 patients enrolled in the Multicenter Study of Perioperative Ischemia database, 2402 (99.3%) were eligible for inclusion in this analysis. In this study population, serum potassium levels appear normally distributed (FIGURE 1), with 70 (2.9%) having potassium levels below the traditional clinical threshold of 3.5 mmol/L. Patient characteristics within specific ranges of potassium values are

<table>
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<tr>
<th>Table 1. Association Between Preoperative Serum Potassium Levels and Preoperative Patient Characteristics*</th>
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<tr>
<td><strong>Preoperative Characteristics</strong></td>
</tr>
<tr>
<td>Sex, female</td>
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<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>History of arrhythmia</td>
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<tr>
<td>History of hypertension</td>
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<td>Preadmission use of diuretics</td>
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<td>*All data are presented as percentages with the exception of age.</td>
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<th>Table 2. Association Between Preoperative Serum Potassium Levels and Adverse Outcomes*</th>
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<tr>
<td><strong>Adverse Outcome</strong></td>
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<tr>
<td>Intraoperative arrhythmia</td>
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<tr>
<td>Postoperative fibrillation/flutter</td>
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<td>Perioperative arrhythmia</td>
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<td>CPR</td>
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<td>Death</td>
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<td>*All data are presented as percentages. CPR indicates cardiopulmonary resuscitation.</td>
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listed in Table 1. Female sex, history of arrhythmias, hypertension, and use of diuretics were more commonly found in patients with lower potassium levels. Patient characteristics not associated with decreased serum potassium levels were age, weight or height, history of congestive heart failure, ejection fraction, New York Heart Association class, race, and history of other medical conditions including renal dysfunction and diabetes. Elevated potassium levels were associated with a history of congestive heart failure, age, and history of renal disease, but not with history of arrhythmia or diabetes, preoperative diuretic or angiotensin-converting enzyme inhibitor use, or sex.

Preoperative Potassium Level and Perioperative Arrhythmia

Perioperative arrhythmias occurred in 53.7% of patients (1290/2402) with 238 patients (10.7%) having intraoperative arrhythmias, 329 (13.7%) having postoperative nonatrial arrhythmias, and 865 (36%) having postoperative AFF. Serious perioperative arrhythmias occurred in 498 patients (21%). Preoperative serum potassium values of less than 3.5 mmol/L were associated with a higher incidence of arrhythmias than preoperative levels above 3.5 mmol/L (Table 2). Accordingly, we defined hypokalemia as a serum potassium level of less than 3.5 mmol/L. As shown in Figures 2, 3, and 4, hypokalemia was a predictor of serious perioperative arrhythmia (OR, 2.2; 95% CI, 1.2-4.0), intraoperative arrhythmia (OR, 2.0; 95% CI, 1.0-3.6), and postoperative AFF (OR, 1.7; 95% CI, 1.0-2.7). Adjusting for age, sex, and history of arrhythmia did not alter this relationship. Although we found no association between use of digoxin and increased risk for arrhythmias, the number of patients with hypokalemia taking digoxin was too few to provide conclusive data.

Serum potassium levels above 5.5 mmol/L appear to be associated with development of postoperative AFF (50% incidence vs 36% overall), but the small sample size (n = 16) precludes definite conclusions (Table 2).
Preoperative Serum Potassium Level and Adverse Outcome

Overall, the incidence of adverse outcomes was 3.6% for death, 2.0% for cardiac death, and 3.5% for CPR. The adjusted OR and CIs for the occurrence of need for CPR and death are shown for each 0.1-mmol/L change in potassium level in Figure 5 and Figure 6. Univariate analyses yield a strong trend toward increased risk of death, cardiac death (data not shown), and CPR with both decreasing and increasing serum potassium level thresholds. It was also interesting to note a significant crude association between a potassium level threshold of less than 3.3 mmol/L and the need for CPR (OR, 3.3; 95% CI, 1.2-9.5). However, after adjusting for confounders, the significance of this association was lost. The small number of patients involved at this threshold affects the power to detect the existence of this association.

COMMENT

Our analysis of this large multicenter database is the first to identify a preoperative serum potassium level that is significantly associated with perioperative arrhythmia, and to validate an association between hypokalemia and risk of adverse outcomes in cardiac surgery patients. At preoperative levels between 3.5 and 5.0 mmol/L, we found no association between potassium level and the incidence of any type of perioperative arrhythmia. However, below this threshold, the association became progressively stronger and occurred at levels of hypokalemia often considered safe by anesthesiologists, surgeons, and other treating clinicians.

In addition, preoperative serum potassium levels below 3.3 mmol/L and above 5.2 mmol/L showed a univariate association with the need for CPR.

Figure 5. Adjusted Odds Ratios and 95% Confidence Intervals for Cardiopulmonary Resuscitation

Odds ratios and confidence intervals are presented from near normal through increasing abnormal serum potassium levels. Among normokalemic patients the incidence of need for cardiopulmonary resuscitation is about constant at 3.2%.

Figure 6. Adjusted Odds Ratios and 95% Confidence Intervals for Outcome of Death

Odds ratios and confidence intervals are presented from near normal through increasing abnormal serum potassium levels. Among normokalemic patients the incidence of death is about constant at 3.5%.

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Although we cannot draw any conclusions regarding a causal relationship between preoperative serum potassium level and adverse outcomes, the presence of an abnormal serum potassium level prior to surgery can identify those patients at particular risk.

These results establish a definitive criterion standard for preoperative hyperkalemia as a serum potassium level of less than 3.5 mmol/L. Our results further identify preoperative hyperkalemia as an independent, potentially reversible risk factor for development of serious perioperative arrhythmias.

**Hyperkalemia and Cardiac Arrhythmias**

Significant elevations of extracellular potassium, generally thought to be above 7.0 mmol/L, reduce the resting potential across the cell membrane and lead to an inability to conduct an electrical charge. Milder elevations of potassium levels have infrequently been found to be associated with development of arrhythmias. In laboratory investigation, Logic found that regional hyperkalemia, produced by intracoronary infusion of potassium, enhanced the likelihood of development of ventricular tachycardia and fibrillation. There is also a known, albeit rare (5 case reports) association between hyperkalemic periodic paralysis, a genetically inherited condition, and the development of cardiac arrhythmias. Eventually, Cooper et al reported that hyperkalemia as well as hyperkalemia was significantly associated with the development of ventricular fibrillation and tachycardia in patients admitted to a coronary care unit with the diagnosis of MI. Our data are inconclusive due to small sample size and confounding patient characteristics, but the potential association between hyperkalemia and the outcomes of death, cardiac death, and CPR deserves further investigation.

Decreases in extracellular potassium increase the duration of the action potential (increased phase 3 depolarization duration), increase automaticity (increased slope of diastolic depolarization), and decrease conduction velocity. These mechanisms, in part, may account for the relationship of hyperkalemia to cardiac arrhythmias. For example, hyperkalemia in laboratory models precipitates reentrant cardiac arrhythmias by decreasing conduction, increasing refractoriness, and unidirectional block. Dogs with hyperkalemia have an abrupt lowering of the ventricular fibrillation threshold and experience frequent runs of ventricular tachycardia. More severe reductions in potassium levels result in spontaneous ventricular fibrillation in isolated, perfused rabbit hearts. However, the latter effect can be reversed by infusion of potassium, suggesting that reversal of hyperkalemia may help to avert an adverse outcome.

**Clinical Studies**

The ischemic heart appears to be particularly vulnerable to hyperkalemia and is therefore at greater risk for malignant arrhythmias. In the early 1980s, the Multiple Risk Factor Intervention Trial suggested an association between the use of thiazide (potassium-wasting) diuretics and the risk of sudden death. These findings were substantiated in a series of meta-analyses of clinical trials assessing treatment of hypertensive patients. In 1994, Siscovick et al demonstrated that the risk of primary cardiac arrest progressively increased in a dose-related manner in patients undergoing thiazide treatment for hypertension. In addition, the incidence of VAs and sudden deaths increased markedly in patients with baseline electrocardiographic abnormalities, including left ventricular hypertrophy.

Perhaps the most convincing data are derived from patients experiencing acute MI. In 1315 patients admitted to the coronary care unit with the diagnosis of MI, the incidence of ventricular fibrillation was 3.5%, increasing to 8% in patients with hyperkalemia (<3.5 mmol/L). No episodes of ventricular fibrillation occurred when the serum potassium level was greater than 4.6 mmol/L, but levels less than 3.9 mmol/L were associated with a 5-fold increase in the risk of ventricular tachycardia (P<.01). Solomon and Cole also found an increase (5% vs 25%) in the incidence of ventricular fibrillation in patients with potassium levels greater than 4.5 vs those less than 3.0 mmol/L. Similar increases in risk have been found in numerous other studies. Friedensohn et al found a significant difference in serum potassium levels between those patients who did or did not develop malignant arrhythmias, but the difference could not be detected clinically (4.10 vs 4.19 mmol/L with vs without arrhythmias).

Shah et al studied 688 consecutive patients with cardiac disease who were older than 70 years and undergoing noncardiac surgery. They found hyperkalemia to be an independent predictor of mortality, but had a much higher mortality rate among patients with hyperkalemia than we did (Shah et al, 2/7 [28%] vs this study, 3/70 [4.3%]). The small sample size of the study by Shah et al caused concern regarding the statistical validity of the results.

In 1985, Vitez et al reported that hyperkalemia (<3.5 mmol/L) did not increase the incidence of electronically identified intraoperative arrhythmias in 150 relatively healthy patients undergoing mostly noncardiac surgery (Holter monitoring [n = 88]; observation of electrocardiograph monitor [n = 69]) between normokalemic patients (48%) or patients with hyperkalemia (35%, P = .80). The only identified risk factor for malignant arrhythmias intraoperatively was the presence of cardiovascular disease with concurrent digoxin therapy. Hyperkalemia (<3.5
Hypokalemia, therefore, is independently associated with the risk of perioperative arrhythmias and may predict the need for CPR. It is also reversible in contrast to virtually all other known risk factors for poor outcome, such as age, sex, poor ejection fraction, diabetes, repeat surgery, or the urgency of surgery.

Although we did not study the effect of potassium repletion on outcome, such treatment is relatively simple and inexpensive. Some 500 000 cardiac surgical procedures are performed each year in the United States, with 13 500 performed in patients with hypokalemia based on these data. A therapy as simple and inexpensive as potassium repletion may mitigate an adverse outcome in a large number of patients.

Limitations of This Study
The focus of our study was to examine the association between preoperative serum potassium level and outcome. We did not attempt to control for or track the electrolyte therapy that patients may have received. In addition, magnesium levels were not determined in these patients and we did not examine fluctuations of potassium levels or interactions with other electrolytes during hospitalization. We further cannot address whether either hypokalemia or hyperkalemia has a causative relationship in addition to the associative relationship we report. Nor can we determine whether potassium correction alters risk; such a determination requires a prospective, randomized trial. We found only 1 such attempted study by Zehender et al.27 This prospective, double-blind trial randomly assigned normokalemic patients with frequent VAs to either placebo or potassium and magnesium therapy and found that active therapy reduced ventricular premature beats by 17%. This study, however, only enrolled patients with normal serum potassium levels, so our question remains to be addressed.

Given the low incidence of hypokalemia (2.9%) and death (3.6%) in this population, this study is underpowered to demonstrate a statistically significant association between hypokalemia and death. Using a 2-sided type I error rate of .05 and a type II error rate of .20, we project that a sample size of approximately 10 000 patients would be required to detect a statistically significant association between hypokalemia and death. Despite this limitation, this group of 70 surgical patients with hypokalemia and 146 surgical patients with hyperkalemia with cardiac disease represents the largest group of patients in whom perioperative outcomes have been studied. While lacking statistical significance in this small study, the trend toward increasing OR for both the need for CPR and death at successive levels of serum potassium below 3.5 mmol/L warrants further attention.

In summary, we found a significant association between preoperative serum
potassium levels of less than 3.5 mmol/L and perioperative arrhythmias in patients undergoing elective coronary artery bypass graft surgery. The association between hypokalemia and arrhythmias was independent of other patient characteristics. Of the previously identified risk factors for adverse outcomes during cardiac surgery, such as age, sex, or urgency of procedure, hypokalemia may represent the only potentially reversible risk factor. A larger, controlled study of the potential benefit of preoperative potassium repletion should be undertaken. However, until such a study is completed, preoperative potassium screening and repletion should be considered for patients scheduled for elective cardiac surgery. Both screening and therapy represent low-risk, low-cost prophylaxis.

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