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Hemodynamic Changes after Protamine Administration

Association with Mortality after Coronary Artery Bypass Surgery

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Background: **Protamine sulfate is standard therapy to reverse heparin anticoagulation. Hemodynamic responses to protamine are common, ranging from minor perturbations to cardiovascular collapse. Although severe fatal reactions occur, the relation of less extreme responses with postoperative mortality is unknown. Therefore, the authors tested the hypothesis that hemodynamic "protamine reactions" (systemic hypotension and pulmonary hypertension) are associated with mortality after cardiac surgery.**

Methods: **In a university hospital setting, the authors studied 6,921 coronary bypass patients using automated anesthesia record–keeping data and quality assurance databases. Degree/duration integrals of systemic hypotension (< 100 mmHg) and pulmonary hypertension (> 30 mmHg) for the 30-min after protamine administration were assessed for linear associations with mortality using multiple logistic regression models adjusting for risk factors.**

Results: **Overall mortality was 2%; greater hemodynamic responses were associated with increased mortality by odds ratios of 1.28 (systemic hypotension: 95% confidence interval, 1.14–1.43; $P < 0.001$) and 1.27 (pulmonary hypertension: 95% confidence interval, 1.06–1.48; $P < 0.001$) per 150-mmHg · min increment. Proximity of the response to protamine administration strengthened the relation, which persisted after exclusion of major hemodynamic disturbances. Tests for linearity confirmed an association even at the lowest range of values for both pressure effects.**

Conclusions: **Hemodynamic perturbations after protamine administration are independently related to in-hospital mortality after primary coronary artery bypass surgery; the relation is present even in the lowest observed range of values for both systemic hypotension and pulmonary hypertension. Although randomized trials are necessary to address causality, this evidence suggests that strategies that avoid or attenuate these reactions may improve patient care.**

PROTAMINE sulfate is standard therapy for reversing heparin anticoagulation during coronary artery bypass graft (CABG) surgery. However, the safety of protamine has been questioned because of adverse reactions ranging from minor hemodynamic instability to fatal cardiovascular collapse.[1–4] Although catastrophic events are rare, major adverse responses related to protamine administration occur during 2.6% of cardiac surgical procedures.[3] These "protamine reactions" are highly associated with adverse postoperative outcome[4] and are exaggerated in patients with impaired myocardial function.[5] Risk factors for protamine reaction are present in 39% of CABG surgery patients and include use of protamine-containing insulin, previous drug reaction, and allergy to protamine or fish.[6]

Protamine neutralization of heparin is often accompanied by small decreases in systemic blood pressure and increases in pulmonary artery pressure that are generally considered as benign and inevitable.[1,7,8] Although mechanistic understanding[2,9–11] has generated numerous preventive strategies,[7,12,13] none have been routinely adopted. Although major adverse events related to protamine administration are associated with in-hospital mortality,[4] the extent to which so-called minor hemodynamic responses to protamine are associated with outcome is not known. In a population of 2,069 patients undergoing cardiopulmonary bypass, Kimmel *et al.*[4] identified 53 patients who met the criteria for an adverse cardiorespiratory event temporally associated with protamine administration; mortality risk was increased more than fourfold in this group. Transient blood pressure changes around the time of protamine administration were specifically not included; however, there is no evidence to indicate that these transient perturbations are insignificant. Therefore, we tested the hypothesis that all degrees of systemic hypotension and pulmonary hypertension after protamine administration are associated with mortality after cardiac surgery.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

Patient Selection

With institutional review board approval (Duke University Medical Center, Durham, North Carolina), we retrospectively studied 6,921 consecutive patients undergoing primary elective CABG surgery at an institution between 1993 and 2000. Patients were excluded if the surgery was emergent, if the surgery involved additional procedures or circulatory arrest, or if protamine administration was not documented. Patient characteristics and other variables were obtained from the prospectively collected Duke Cardiovascular Database,[14] a quality assurance database from contemporaneous medical records,

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custom data sheets, and records of laboratory results. Quality assurance involves random chart review for data confirmation and assessment of data completeness.

Risk Stratification

Risk factors for in-hospital mortality after CABG surgery, identified by Hannan *et al.*[15] in the New York State population, were tested as a marker of preoperative mortality risk. These include age, sex, severity of presenting condition, preoperative intraaortic balloon counterpulsation, left main coronary artery disease, history of unstable angina, congestive cardiac failure, left ventricular ejection fraction, and comorbidities such as chronic obstructive pulmonary disease, diabetes, morbid obesity, and dialysis dependency. Cardiopulmonary bypass (CPB) duration was included for analysis as a marker of procedure complexity and risk because it is directly correlated with factors such as number of coronary grafts performed and is significantly associated with in-hospital mortality.[16] In addition, postoperative need for intraaortic balloon counterpulsation was recorded.

Determination of Intraoperative Variables

Protamine and hemodynamic data were obtained by querying an automated anesthesia record–keeping system (Arkive; Arkive Inc., San Diego, CA). Drug administration is manually entered when it occurs[17]; hemodynamic data are automatically downloaded by this system at 1-min intervals.

To develop variables representing the range of hemodynamic perturbation, minute-by-minute accumulated "area under the line" for systolic arterial blood pressures less than 100 mmHg during the first 30 min after protamine administration was used as an index of systemic hypotension ($T_{sBP < 100}$); for all patients with a pulmonary artery catheter, an equivalent "over the line" metric was determined for pulmonary artery systolic pressures greater than 30 mmHg ($T_{sPAP > 30}$). For example, a systolic arterial blood pressure of 80 mmHg for 30 min would equal a $T_{sBP < 100}$ of 600 mmHg · min; a systolic pulmonary artery blood pressure of 40 mmHg for 30 min would equal a $T_{sPAP > 30}$ of 300 mmHg · min. These variables do not correspond with formal definitions of systemic hypotension and pulmonary hypertension but are indices that include almost all patients, providing sensitive continuous variables to assess the relation of hemodynamic perturbations and mortality.

In addition to linear analyses, we tested binary definitions for "severe" systemic hypotension (≥ 30 mmHg below baseline) and pulmonary hypertension (> 40 mmHg, including an increase of at least 10 mmHg above baseline). Baseline for each variable was the median value derived from the 5 min before protamine administration.

Intraoperative Management

Anesthesia included methadone or diazepam premedication, midazolam, fentanyl, thiopental, and isoflurane. Pancuronium was used for muscle relaxation. Nonpulsatile, hypothermic (28°–34°C) CPB was conducted using a membrane oxygenator (Cobe CML; Cobe Inc., Arvada, CO) after a crystalloid and mannitol prime and using an arterial line filter (Cobe). Porcine heparin was administered (300 U/kg) and supplemented during CPB to maintain an activated clotting time (Hemochron 801; International Technidyne Corp., Edison, NJ) of greater than 480 s. Protamine sulfate (Eli Lilly, Indianapolis, IN) was administered until the activated clotting time returned to baseline or a ratio of 1 mg:100 U heparin was reached. Although we do not have access to the specific rates of protamine administration for our study patients, a typical strategy would be to administer a 20-mg test dose that, if tolerated, is then followed by removal of the aortic cannula and the subsequent administration of 3–3.5 mg/kg as a slow, intermittent bolus over 10 min through a peripheral vein. This is a low dose (typically approximately 0.7–0.8 mg protamine/100 U heparin given), and further protamine in 25- to 50-mg increments is given as needed based on an activated clotting time test performed 5 min after the initial dose is completed. Occasionally, further optional protamine doses are given in the intensive care unit during the postoperative period, again based on activated clotting time testing.

After separation from CPB and in the intensive care unit, inotropic and vasoactive agents were used as necessary to maintain a cardiac index of greater than 2.0 $l \cdot min^{-1} \cdot m^{-2}$ and a mean arterial pressure of greater than 60 mmHg. A postoperative care pathway was followed with the aim of discharge from the intensive care unit on postoperative day 1 and from the hospital on postoperative day 5.

Statistical Analysis

The primary outcome measure was in-hospital mortality. Descriptive statistics are presented as mean and SD for continuous data and percentage for categorical data. The Hannan score was described by the median and 25th–75th percentile range. Thirty-minute postprotamine linear hemodynamic measures and the odds ratio and their 95% confidence intervals (CIs) were calculated. The relations between 30-min postprotamine linear hemodynamic measures and mortality was assessed using multiple logistic regression, adjusting for preoperative and intraoperative risk factors. Covariates were the components of the Hannan score. In addition, duration of CPB and number of grafts were included as markers of procedure complexity. Initially, all terms were included as predictors in a multivariable model, and terms not significant at $P < 0.05$ were eliminated from the model one at a time until only significant terms remained. A c-index, or area under the receiver operating character-

istic curve, was calculated to describe the predictive ability of the model. The Hosmer–Lemeshow goodness-of-fit statistic was calculated to assess how well the models fit the data. Tolerance and variance inflation diagnostics were performed on a model containing all significant covariates to determine whether the presence of multicollinearity among predictors. Predicted probabilities of death for each patient were generated from these models for graphing purposes, using mean values to control for preoperative and intraoperative risk factors.

The primary analyses were repeated for 15-min post-protamine intervals to assess the relation of proximity of hemodynamic responses to outcome. Equivalent analyses were repeated using the binary definitions of hemodynamic change as predictors in place of the continuous variables.

Because degree-duration integrals do not distinguish between large-brief and modest-sustained hemodynamic changes, we repeated the primary analysis, excluding patients who met our binary criteria as a marker for large "severe" hemodynamic changes.

After a logistic regression model was developed for the sample, further testing of our data included investigation of nonlinear terms and combinations of linear terms or splines. For example, if outliers were overly influential in determining the slope of the line, we might expect to see a deviation from linearity, or an "elbow," where the line was flat and then increased rapidly. By testing restricted cubic splines, typically used to describe smooth curves rather than elbows, we wanted to assess whether higher-order terms would contribute explanatory power to our model.

SAS version 8.02 (SAS Institute, Inc., Cary, NC) was used for all analyses; a P value of less than 0.05 was considered significant. All tests are two tailed.

Results

Of the 7,306 patients who met our inclusion criteria with clinical outcomes data, we were able to match 6,846 (93.7%) to our database containing intraoperative blood pressure data. Of the 6,846 patients included in the study, a subgroup of 5,649 (82.5%) also had pulmonary artery pressure monitoring. Seventy-five patients were excluded because no protamine dose was recorded; only one case of protamine allergy was documented in the anesthesia records. Patient characteristics and other variables are listed in table 1. Predicted in-hospital mortality (median Hannan score) was 2%; actual in-hospital mortality was 2%. The mean time between first and last dose of protamine in the operating room was 22 min (SD 18), and the mean protamine dose was 257 ± 95 mg.

Figure 1 illustrates the range of systolic arterial and pulmonary artery systolic blood pressures measured over the 30-min period after protamine administration. Hemodynamic perturbations occurred within 10 min of protamine administration for most patients (*e.g.*, 20% decrease in systemic blood pressure, 52% of patients; 20% increase in pulmonary artery pressure, 92% of patients).

Table 1. Patient Characteristics and Procedural and Outcome Variables

Characteristic (n = 6846)	Value
Preoperative	
Age, yr, mean ± SD	64 ± 11
Female	32%
African-American ethnicity	7%
Weight, kg, mean ± SD	83 ± 17
LVEF, %, mean ± SD	52 ± 14
Carotid bruit	10%
COPD	13%
CHF	17%
Diabetes	32%
Hypertension	68%
Hannan score (0.01 = 1% risk of death), median (25th–75th percentiles)	0.019 (0.011–0.035)
Procedural	
CPB duration, min, mean ± SD	106 ± 51
Number of proximal grafts	
1	4%
2	17%
3	49%
≥4	30%
Postoperative	
Inotropes	14%
IABP (new onset)	2%
Cardiac arrest	1%
Respiratory failure (tracheal reintubation or tracheostomy)	4%
Dialysis (new onset)	0.5%
Infection	4%
Extended postoperative stay (> 10 days)	7%
Mortality	2%

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; IABP = intraaortic balloon counterpulsation; LVEF = left ventricular ejection fraction.

Strong associations of both systemic hypotension and pulmonary artery hypertension related to protamine administration with mortality are present in our data (table 2). After accounting for comorbidities and markers of procedure complexity, the Hosmer–Lemeshow goodness-of-fit statistic, calculated for the systemic hypotension model (8 *df*, chi-square 2.56, $P = 0.96$) and the pulmonary hypertension model (8 *df*, chi-square 5.58, $P = 0.69$), did not support rejection of the null hypothesis that the models provide a good fit to the data. The c-index (area under the receiver operating characteristic curve) was 0.78 for both the systemic hypotension model and the pulmonary hypertension model. Tolerance values of the predictors range from 0.81 to 0.96 (corresponding to variance inflation values ranging from 1.03 to 1.24). Because the tolerance values are all greater than 0.4, we conclude that the model is appropriate statistically and no significant collinearity exists among

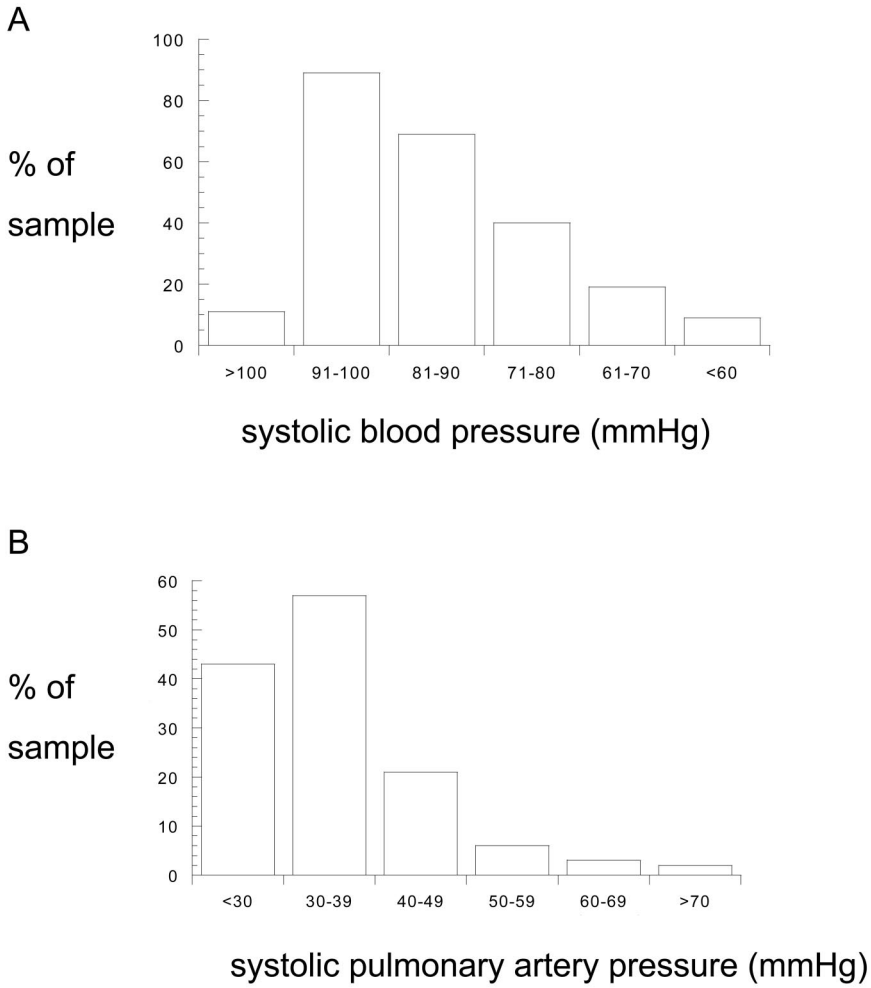

Fig. 1. The frequency of systolic arterial blood pressures (*A*) and systolic pulmonary artery pressures (*B*) observed during the 30 min after protamine administration are depicted. Blood pressure variables for all study patients are from an automated anesthesia record–keeping system, recorded at 1-min intervals.

our covariates. Other covariates associated with mortality risk are similar for both primary hemodynamic analyses and resemble those previously reported,[15] including advanced age, female sex, history of congestive heart failure, need for postoperative intraaortic balloon counterpulsation, extended duration of CPB, reduced left ventricular ejection fraction, and greater number of grafts. Figures 2A and B illustrate the probability of death

Table 2. Measures of Systemic Hypotension ($T_{sBP < 100}$) and Pulmonary Hypertension ($T_{sPAP > 30}$) (See Text) and Associated Mortality Odds Ratios, with and without Adjustment for Comorbidities and Surgery Complexity

	Hemodynamic Variable (mmHg · min): Survivors	Hemodynamic Variable (mmHg · min): Nonsurvivors	Mortality Odds Ratio (per 150-mmHg · min change) and 95% Confidence Interval	Adjusted Mortality Odds Ratio (per 150-mmHg · min change) and 95% Confidence Interval
Systemic hypotension (n = 6,846)				
Primary analysis				
$T_{sBP < 100}$ (30 min)	101.6 (145.0)	184.4 (272.6)	1.34 (1.21–1.46)	1.27 (1.08–1.39)
Secondary analyses				
$T_{sBP < 100}$ (first 15 min)	56.3 (86.0)	91.6 (139.8)	1.52 (1.25–1.81)	1.36 (1.04–1.73)
$T_{sBP < 100}$ (30 min, "severe" responses excluded)	95.1 (139.6)	153.8 (249.9)	1.28 (1.12–1.43)	1.22 (1.04–1.40)
Pulmonary hypertension (n = 5,649)				
Primary analysis				
$T_{sPAP > 30}$ (30 min)	46.1 (104.6)	104.3 (145.4)	1.50 (1.29–1.70)	1.37 (1.14–1.60)
Secondary analyses				
$T_{sPAP > 30}$ (first 15 min)	26.1 (58.0)	55.5 (78.8)	2.04 (1.55–2.62)	1.53 (1.03–1.39)
$T_{sPAP > 30}$ (30 min, "severe" responses excluded)	19.4 (55.5)	58.7 (108.0)	2.08 (1.60–2.64)	1.41 (1.02–1.88)

Hemodynamic changes during the 30 min after protamine are represented in the primary analysis; secondary analyses assess (1) the first 15 min after protamine administration and (2) analysis with exclusion of "severe" hemodynamic changes (see text).

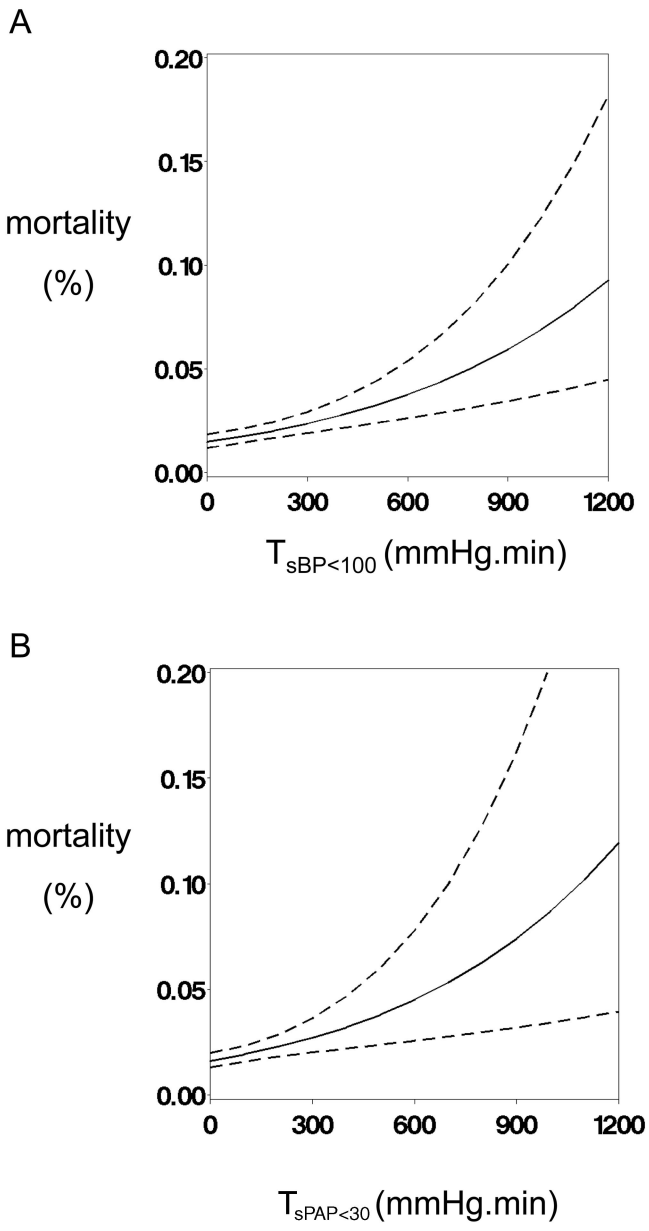

Fig. 2. Relation between protamine-related systemic hypotension (*A*; n = 6,846; $T_{sBP<100}$ [see text for definition]) and pulmonary hypertension (*B*; n = 5,649; $T_{sPAP>30}$ [see text for definition]), and in-hospital mortality (with 95% confidence intervals), after accounting for preoperative comorbidities and procedure complexity.

with increasing $T_{sBP < 100}$ and $T_{sPAP > 30}$, respectively, while controlling for preoperative and intraoperative risk factors set at mean values. For example, $T_{sBP < 100}$ values of 300, 600, and 900 mmHg · min are associated with mortality rates of 3.0, 5.0, and 8.7%, respectively (fig. 2A); the mean $T_{sBP < 100}$ is 100 ± 148 mmHg · min. Based on this SD, an increment of 150 mmHg · min was used for odds ratio calculations of the association of $T_{sBP < 100}$ (and $T_{sPAP > 30}$ for consistency). Similarly, $T_{sPAP > 30}$ values of 300, 600, and 900 mmHg · min are associated with in-hospital mortality rates of 2.6, 4.4, and 7.4%, respectively (fig. 2B); the mean $T_{sPAP > 30}$ is 56 ± 110 mmHg · min.

Proximity of hemodynamic response to protamine administration strengthens the relation between systemic hypotension and pulmonary hypertension and mortality. Analyses using 15- and 30-min observation periods after protamine administration demonstrate a greater adjusted odds ratio of mortality per 150 mmHg for the 15-min assessment for both systemic hypotension ($T_{sBP < 100}$: 1.40 [95% CI, 1.11–1.73] *vs.* 1.28 [95% CI, 1.14–1.43]) and pulmonary hypertension ($T_{sPAP > 30}$: 1.50 [95% CI, 1.07–2.04] *vs.* 1.27 [95% CI, 1.06–1.48]; table 2). To determine whether the associations of systemic blood pressure and pulmonary pressure are independent of each other, we constructed a model for the 30-min data in which both blood pressure indices were included as predictors, along with the previously described covariates. Both the systemic and pulmonary pressure variables retained their significance in the model ($T_{sBP < 100}$: odds ratio, 1.28 [95% CI, 1.13–1.42]; $P < 0.0001$; $T_{sPAP > 30}$: odds ratio, 1.26 [95% CI, 1.05–1.47]; $P = 0.007$), indicating that they have independent effects on mortality.

Table 3 illustrates binary definitions of systemic hypotension (≥ 30 mmHg below baseline) and pulmonary hypertension (> 40 mmHg, including an increase of at least 10 mmHg above baseline) with mortality, adjusted for preoperative and intraoperative risk factors; odds ratios were calculated after controlling for preoperative and intraoperative risk factors in a logistic regression model. Overall, "severe" hemodynamic responses related to protamine were common; 23.6% of patients met the definition of either systemic hypotension or pulmonary hypertension, and mortality in this group was 3.4%,

Table 3. Multivariate Associations of Binary Definitions of Systemic Hypotension and Pulmonary Hypertension with Mortality

	Incidence, %	Adjusted Mortality Odds Ratio (95% confidence interval)	*P* value
Systemic hypotension (n = 6,846)	12.4	1.8 (1.1–2.8)	0.01
Pulmonary hypertension (n = 5,649)	15.8	1.50 (1.0–2.32)	0.04
Either of above (n = 5,649)	26.8	1.7 (1.2–2.5)	0.003
Both of above (n = 5,649)	1.4	2.8 (1.2–6.8)	0.005
Neither of above (n = 5,649)	73.2	0.57 (0.39–0.83)	0.003

Odds ratios (95% confidence intervals) were obtained after adjusting for Hannan score and cardiopulmonary bypass duration.

Pulmonary hypertension = systolic pulmonary artery pressure increase to > 40 mmHg, including an increase of at least 10 mmHg above baseline, systemic hypotension = a reduction in systolic arterial blood pressure by ≥ 30 mmHg below baseline.

compared with 1.8% for the remainder. All typical hemodynamic responses were associated with increased mortality risk (table 3). To assess smaller sustained hemodynamic changes, we performed a secondary analysis excluding patients meeting our criteria for severe hemodynamic responses outlined above; a strong relation persisted with mortality for both systemic hypotension ($P = 0.008$) and pulmonary hypertension ($P = 0.03$).

To further assess the association of hemodynamic responses with mortality, we tested the possibility that our data were not well described by linear models by investigating nonlinear terms and combinations of linear terms or splines. We found no point in our data at which a significant deviation from linearity could be detected. In addition, a test of restricted cubic splines, which fit smooth curves, determined that higher-order terms did not add explanatory power to our model. These findings indicate that a logistic regression model (which is linear in the logit) is an appropriate description of the relations. This linearity supports an association between hemodynamic responses and mortality throughout the observed range of values.

Discussion

In our study, we found an independent relation between hemodynamic changes after protamine administration and in-hospital mortality after primary CABG surgery. Even after accounting for comorbidities and procedure complexity, systemic hypotension and pulmonary hypertension during the 30 min after protamine administration are both independently associated with in-hospital mortality. The relations are continuous over the range of hemodynamic response and persist even when severe reactions are removed from analysis. Tests for linearity confirm associations even in the lowest observed range of values for both pressure effects. Although our findings suggest that common "minor" protamine reactions may not be benign and may even contribute to adverse outcome, because no equivalent drug devoid of adverse effects is available for comparison in a randomized trial, it is only possible to speculate that a direct causal link exists between protamine and mortality risk.

In a retrospective chart review of 2,159 cardiac surgical patients, Kimmel *et al.*[4] reported an increased mortality rate in the 2.6% of patients with major complications, including hemodynamic instability, temporally related to protamine. We have extended this concept using continuous variables that document the full range of hemodynamic changes. Our findings indicate that indices of hemodynamic change reflecting the degree and duration of systemic hypotension and pulmonary hypertension during the minutes after protamine administration can be used to predict mortality risk.

One of the limitations of a retrospective investigation is the risk of incomplete or biased data. We used hemodynamic data from an automated anesthesia record–keeping system that should not be prone to error. Outcomes for our study were taken from a prospectively gathered quality-assurance database entered within several days of hospital discharge that should be more accurate and less biased than a traditional chart review. A timing bias with regard to the charting of protamine dosing is possible; however, it is standard at our institution to document drugs through the touch-screen format located on the anesthesia machine as they are given. The relation of hemodynamic responses to protamine dosing in our study is supported by the strengthening of the relation with increasing proximity to recorded time of drug administration.

The relation of pulmonary artery hypertension after protamine administration with adverse outcome in our study may reflect the responses of patients with poor myocardial function and increased baseline pulmonary artery pressure. However, our secondary analysis using a more stringent definition to assess acute pulmonary hypertensive response still identifies an association of hemodynamic response with mortality, even after controlling for markers of preoperative and intraoperative risk, including left ventricular ejection fraction.

A criticism of our study is that we do not account for clinical interventions to treat hemodynamic perturbations. However, the majority of these would obscure the hemodynamic perturbations and therefore reduce the likelihood of identifying statistical association between these responses and adverse outcome.

Other factors may be related to hemodynamic instability after CPB involving surgical complexity or underlying premorbid conditions that increase the risk of adverse outcome. We designed our analysis to include markers of preoperative mortality risk and intraoperative complexity described in the literature[15] and tested to confirm association with mortality in our population; we still found hemodynamic instability after protamine administration to be independently associated with mortality.

Cause and effect cannot be conclusively demonstrated in a retrospective study, because uncontrolled confounding may persist despite adjustments. However, it is important to explore potential pathophysiological mechanisms. A direct link between catastrophic hemodynamic collapse after protamine and mortality is easy to comprehend, but mechanistic links between the common, modest hemodynamic changes and excess mortality in our study have not been investigated. Complement activation and other related components of the inflammatory response are linked to outcomes after cardiac surgery, providing a plausible interpretation for our findings. Heparin–protamine complexes are known to activate the classic complement pathway[9] and trigger release of inflammatory mediators.[2,11] Complement fragments C3a

and C5a (anaphylotoxins) degranulate basophils and mast cells, releasing histamine, leukotrienes, and thromboxanes. C5a activates macrophages, monocytes, and neutrophils, resulting in proteolytic enzyme and interleukin-1 release, free radical generation, margination, chemotaxis, and increased vascular permeability.[18] Histamine contributes to cause the peripheral vasodilation and systemic hypotension,[19] consistently observed after protamine reversal of heparin,[8] whereas C5a and thromboxane, released after protamine, can precipitate pulmonary hypertension and bronchospasm,[11] thereby linking our observations to pathophysiologic changes associated with protamine. Complement activation after CABG surgery is related to outcome, including postoperative arrhythmias[20] and pulmonary dysfunction.[21] Similarly, inhibition of the complement cascade reduces leukocyte and platelet activation[22] and improves outcome after CABG surgery.[23] Although proinflammatory mediators are activated during heparin reversal by protamine, a direct link between these factors and adverse outcome, including mortality risk, is unconfirmed and speculative only.

Because the full range of blood pressure responses related to protamine are associated with mortality risk after cardiac surgery, hemodynamic "protamine reactions" may be a useful metric to evaluate future therapies aimed at avoiding associated adverse outcome.[24,25] In addition, investigations are necessary to assess whether equivalent associations between protamine and outcome exist in other procedures and settings where protamine is used.

In summary, hemodynamic responses in the 30 min after protamine administration for heparin neutralization during CABG surgery are associated with in-hospital mortality after controlling for preoperative and intraoperative risk factors, even in the lowest observed range of values for both systemic hypotension and pulmonary hypertension. This is consistent with and extends previous findings that major adverse events, temporally related to protamine administration, are associated with increased mortality risk.[4] Future randomized trials are necessary to differentiate association from causality in the relation between hemodynamic "protamine reactions" and adverse outcome. These trials may also identify therapeutic strategies that reduce such hemodynamic perturbations and improve patient outcome after cardiac surgery.

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References

1. Weiss ME, Nyhan D, Peng ZK, Horrow JC, Lowenstein E, Hirshman C, Adkinson NF Jr: Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. N Engl J Med 1989; 320:886–92

2. Weiler JM, Gellhaus MA, Carter JG, Meng RL, Benson PM, Hottel RA, Schillig KB, Vegh AB, Clarke WR: A prospective study of the risk of an immediate adverse reaction to protamine sulfate during cardiopulmonary bypass surgery. J Allergy Clin Immunol 1990; 85:713–9

3. Kimmel SE, Sekeres MA, Berlin JA, Goldberg LR, Strom BL: Adverse events after protamine administration in patients undergoing cardiopulmonary bypass: Risks and predictors of under-reporting. J Clin Epidemiol 1998; 51:1–10

4. Kimmel SE, Sekeres M, Berlin JA, Ellison N: Mortality and adverse events after protamine administration in patients undergoing cardiopulmonary bypass. Anesth Analg 2002; 94:1402–8

5. Michaels IA, Barash PG: Hemodynamic changes during protamine administration. Anesth Analg 1983; 62:831–5

6. Kimmel SE, Sekeres MA, Berlin JA, Ellison N, DiSesa VJ, Strom BL: Risk factors for clinically important adverse events after protamine administration following cardiopulmonary bypass. J Am Coll Cardiol 1998; 32:1916–22

7. Abe K, Sakakibara T, Miyamoto Y, Ohnishi K: Effect of prostaglandin E1 on pulmonary hypertension after protamine injection during cardiac surgery. Eur J Clin Pharmacol 1998; 54:21–5

8. Shapira N, Schaff HV, Piehler JM, White RD, Still JC, Pluth JR: Cardiovascular effects of protamine sulfate in man. J Thorac Cardiovasc Surg 1982; 84:505–14

9. Bruins P, te Velthuis H, Eerenberg-Belmer AJ, Yazdanbakhsh AP, de Beaumont EM, Eijsman L, Trouwborst A, Hack CE: Heparin-protamine complexes and C-reactive protein induce activation of the classical complement pathway: Studies in patients undergoing cardiac surgery and in vitro. Thromb Haemost 2000; 84:237–43

10. Belboul A, al-Khaja N: The effect of protamine on the epicardial microflow and the graft flow in open-heart surgery. Perfusion 1997; 12:99–106

11. Morel DR, Zapol WM, Thomas SJ, Kitain EM, Robinson DR, Moss J, Chenoweth DE, Lowenstein E: C5a and thromboxane generation associated with pulmonary vaso- and broncho-constriction during protamine reversal of heparin. ANESTHESIOLOGY 1987; 66:597–604

12. Kanbak M, Kahraman S, Celebioglu B, Akpolat N, Ercan S, Erdem K: Prophylactic administration of histamine 1 and/or histamine 2 receptor blockers in the prevention of heparin- and protamine-related haemodynamic effects. Anaesth Intensive Care 1996; 24:559–63

13. Loubser PG: Effect of methylprednisolone on complement activation during heparin neutralization. J Cardiovasc Pharmacol 1997; 29:23–7

14. Jones RH, Kesler K, Phillips HRD, Mark DB, Smith PK, Nelson CL, Newman MF, Reves JG, Anderson RW, Califf RM: Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. J Thorac Cardiovasc Surg 1996; 111:1013–25

15. Hannan E, Kilburn H, Racz M, Shileds E, Chassin M: Improving the outcomes of coronary artery bypass surgery in New York State. JAMA 1994; 271:761–6

16. Hill SE, van Wermeskerken GK, Lardenoye JW, Phillips-Bute B, Smith PK, Reves JG, Newman MF: Intraoperative physiologic variables and outcome in cardiac surgery: I. In-hospital mortality. Ann Thorac Surg 2000; 69:1070–5

17. Coleman RL, Stanley T III, Gilbert WC, Sanderson IC, Moyer GA, Sibert KS, Reves JG: The implementation and acceptance of an intra-operative anesthesia information management system. J Clin Monit 1997; 13:121–8

18. Walport M: Complement, Immunology, 3rd edition. Edited by Roitt I, Brostoff J, Male D. London, Mosby-Europe, 1993, pp 1–16

19. Babe KS, Serafin WE: Histamine, bradykinin and their antagonists, Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th edition. Edited by Hardman JG, Limbird LE. New York, Pergamon Press, 1995, pp 585–6

20. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, Wildevuur CR, Eijsman L, Trouwborst A, Hack CE: Activation of the complement system during and after cardiopulmonary bypass surgery: Postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997; 96:3542–8

21. Shastri KA, Logue GL, Stern MP, Rehman S, Raza S: Complement activation by heparin-protamine complexes during cardiopulmonary bypass: Effect of C4A null allele. J Thorac Cardiovasc Surg 1997; 114:482–8

22. Rinder CS, Rinder HM, Smith BR, Fitch JC, Smith MJ, Tracey JB, Matis LA, Squinto SP, Rollins SA: Blockade of C5a and C5b-9 generation inhibits leukocyte and platelet activation during extracorporeal circulation. J Clin Invest 1995; 96:1564–72

23. Fitch JC, Rollins S, Matis L, Alford B, Aranki S, Collard CD, Dewar M, Elefteriades J, Hines R, Kopf G, Kraker P, Li L, O'Hara R, Rinder C, Rinder H, Shaw R, Smith B, Stahl G, Shernan SK: Pharmacology and biological efficacy of a recombinant, humanized, single-chain antibody C5 complement inhibitor in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass. Circulation 1999; 100:2499–506

24. Dehmer GJ, Lange RA, Tate DA, Pirwitz M, Daniel W, Fisher M, Bonnem EM: Randomized trial of recombinant platelet factor 4 versus protamine for the reversal of heparin anticoagulation in humans. Circulation 1996; 94: II347–52

25. Heres EK, Horrow JC, Gravlee GP, Tardiff BE, Luber J Jr, Schneider J, Barragry T, Broughton R: A dose-determining trial of heparinase-I (Neutralase) for heparin neutralization in coronary artery surgery. Anesth Analg 2001; 93:1446–52