Clinical Implications of Thrombocytopenia Among Patients Undergoing Intra-aortic Balloon Pump Counterpulsation in the Coronary Care Unit

Address for correspondence:
Howard A. Cooper, MD
Coronary Care Unit
Washington Hospital Center
110 Irving Street NW
Suite NA-1103
Washington, DC 20010
howard.a.cooper@medstar.net

Sion K. Roy, MD; Edward W. Howard, MBChB (Hons), PhD; Julio A. Panza, MD; Howard A. Cooper, MD
Department of Medicine, Georgetown University Hospital, Washington, DC (Roy, Howard);
Coronary Care Unit, Washington Hospital Center, Washington, DC (Panza, Cooper)

ABSTRACT

Background: Thrombocytopenia Hypothesis: intra-aortic balloon pump (IABP)-associated thrombocytopenia is not associated with an increased risk of major bleeding or in-hospital death. Thrombocytopenia is a common adverse effect of the IABP. However, the clinical implications of IABP-associated thrombocytopenia are unknown.

Methods: We assessed the incidence and predictors of thrombocytopenia, and the association between thrombocytopenia and relevant clinical end points, using prospectively collected data on 252 consecutive patients undergoing IABP in a single coronary care unit (CCU).

Results: Anticoagulation with intravenous heparin was administered to 182 patients (72%). Baseline platelet counts were 232 000 ± 96 000 mL, decreased to 154 000 ± 74 000 mL at day 3, and recovered to baseline by day 8. Thrombocytopenia (nadir <150 000 mL or >50% reduction from baseline) occurred in 109 patients (43%), with a similar incidence among patients who received heparin and those who did not (45% vs 40%, $P = 0.5$). Independent predictors of thrombocytopenia were lower body weight, cardiogenic shock, and duration of IABP support. The incidence of both major bleeding and in-hospital death were higher among patients who developed thrombocytopenia than among those who did not (13.8% vs 4.2%, $P = 0.01$ and 28% vs 16%, $P = 0.02$, respectively). However, after controlling for confounding variables, thrombocytopenia was not an independent predictor of either major bleeding (odds ratio [OR]: 2.2, 95% confidence interval [CI]: 0.8–6.4, $P = 0.1$) or in-hospital death (OR: 1.5, 95% CI: 0.8–2.9, $P = 0.3$).

Conclusions: Among patients undergoing IABP in the CCU, thrombocytopenia is generally mild, appears to be unrelated to concomitant heparin use, and is not associated with an increased risk of major bleeding or in-hospital death.

Introduction

Intra-aortic balloon pump (IABP) counterpulsation is used commonly for cardiac support in the coronary care unit (CCU). The most frequent adverse effect of IABP is thrombocytopenia, which has been reported to occur in 47% to 82% of patients.[1–3] Recently, a large multinational registry of patients with acute coronary syndromes reported that the development of thrombocytopenia, irrespective of cause, was associated with a substantial increase in the risk of major bleeding and in-hospital death.[4] However, there are few published data regarding the risk of bleeding and other clinical outcomes among patients with IABP-associated thrombocytopenia. Further, as previous reports have been limited to patients receiving adjunctive intravenous heparin, they have been unable to distinguish between IABP effects and heparin effects on the platelet count.[1–3,5]

This work was supported by the Cardiovascular Research Institute, Washington Hospital Center, Washington, DC. None of the authors has any conflict of interest with regard to the contents of this manuscript.

Based on these considerations, we examined the relationship between IABP-associated thrombocytopenia and the risk of major bleeding and in-hospital death in a well-characterized, prospective cohort of patients undergoing IABP in a single CCU. In addition, because our CCU policy allows for many patients undergoing IABP to forego heparin treatment, we analyzed whether IABP-associated thrombocytopenia was related to IABP alone, to treatment with intravenous heparin, or both.

Methods

Study Population and Treatment

The institutional review board for human research at the Washington Hospital Center approved the data analysis plan. Data were collected prospectively for consecutive CCU patients who underwent IABP between September 2006 and November 2007. For patients who underwent IABP on more than one occasion during this period, only the first treatment was analyzed. From September 2006 to March 2007, all patients undergoing IABP were treated with intravenous unfractionated heparin utilizing a standard weight-based dosing algorithm targeting

Clin. Cardiol. 33, 1, 30–35 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20694

Received: August 30, 2009
Accepted with revision: September 20, 2009

a partial thromboplastin time (PTT) of 1.5–2.5× normal while the IABP catheter was in place. From April 2007 onward, patients undergoing IABP were not given heparin unless another primary indication for systemic anticoagulation was present. These indications included unrevascularized acute coronary syndrome (ACS), large anterior myocardial infarction (MI), left ventricular thrombus, atrial fibrillation or flutter, mechanical prosthetic heart valve, and recent or current venous thromboembolism. We have previously reported the results of a comparison between these heparin strategies in this same patient cohort.[6]

Percutaneous IABP catheter insertion was performed by experienced interventional cardiologists in the catheterization laboratory under fluoroscopic guidance. All patients received either the Linear 7.5 French (Fr) intra-aortic balloon catheter (34 cc or 40 cc; Datascope, Farfield NJ) or the Fidelity 8 Fr intra-aortic balloon catheter (34 cc or 40 cc; Datascope) via the femoral artery through a compatible sheath. Catheter selection was determined by the interventional cardiologist based on patient size and clinical judgment. Patients were transferred to the CCU immediately after completion of the interventional procedure. Duration of IABP treatment was determined by the attending CCU physician based on the clinical and hemodynamic status of the patient.

Platelet Counts

Platelet counts were obtained at intervals determined by the treating physician, but at least once daily. The baseline platelet count (day 0) was defined as the last platelet count prior to initiation of IABP (all were within the preceding 24 h). Platelet counts were analyzed until the patient died or was discharged from the hospital, or until 9 days had elapsed since the initiation of IABP. Testing for heparin-induced thrombocytopenia (HIT) was performed based on clinical suspicion, using a solid phase enzyme-linked immunosorbent assay for the detection of platelet factor 4 heparin-dependent antibodies (GTI Diagnostics, Waukesha, WI).

Thrombocytopenia was defined as a platelet count <150 000 mL or a 50% or greater reduction in platelet count from baseline. Major bleeding was defined as intracranial hemorrhage or any clinically apparent bleeding that required blood transfusion or surgical intervention. In-hospital death from any cause was also assessed.

Statistical Analysis

Categorical variables are presented as percentages and continuous variables as mean ± standard deviation. Between-group comparisons were made using t tests, χ^2 tests, or Fisher exact tests, as appropriate. Separate multivariate logistic regression analyses were used to assess the independent relationship between baseline factors and the end points of thrombocytopenia, major bleeding, and in-hospital death. A 2-sided P value <0.05 was considered to represent statistical significance.

Results

Patient Characteristics and Treatment

There were 252 consecutive patients treated with IABP over the 15 month observation period (Table 1). The mean age was 63 years, 35% were female, and the mean ejection fraction (EF) was 35%. The primary diagnosis was ACS in 70% of patients (including ST-segment elevation myocardial infarction in 45%), refractory tachyarrhythmia (9%), acute or chronic cardiomyopathy (11%), stable coronary artery disease (2%), and other (8%). Indications for IABP were: support during catheterization/percutaneous coronary intervention (PCI; 49%), cardiogenic shock (45%), refractory ischemia (4%), mechanical complication of MI (1%), mechanical complication of infective endocarditis (1%), and other (<1%). Catheter size was 8 Fr in 34% of patients and 7.5 Fr in 66% of patients. The mean duration of IABP support was 1.8 ± 1.6 days (range, 0.1–10.9 d). Antiplatelet treatment included aspirin in 85% of patients, clopidogrel in 71% of patients, and eptifibatide in 18% of patients.

In keeping with the CCU policy in place during the early study period, the first 102 patients all received intravenous unfractionated heparin throughout their treatment with IABP. In the later study period, 80 patients had 1 or more primary indications for anticoagulation and received heparin and 70 patients received no heparin. Therefore, in the overall study cohort, 182 patients received heparin (72%) and 70 patients (28%) did not. Baseline characteristics, including duration of IABP support (1.9 ± 1.6 vs 1.6 ± 1.4 d, P = not significant), were similar among those who did and did not receive heparin, although as expected those treated with heparin were more likely to have a diagnosis of ACS (74% vs 60%, $P = 0.04$) and have a lower EF (34% ± 16% vs 40% ± 16%, $P = 0.005$).

Platelet Counts

The mean baseline platelet count was 232 000 ± 96 000 mL (range, 25 000–739 000). In the overall group, the platelet count began to decrease immediately after initiation of IABP, and continued to decline through day 3. The mean nadir platelet count was 154 000 ± 74 000 mL (range, 15 000–547 000), resulting in a mean reduction from baseline of 33% ± 24% (Figure 1). Thrombocytopenia developed in 109 patients (43%), among whom 101 patients (93%) had a nadir platelet count <150 000 mL. Thrombocytopenia was generally mild, with a nadir platelet count <100 000 mL in 78 patients (31%), <50 000 mL in 18 patients (7%), and <10 000 mL in 0 patients (0%). After day 3 the platelet count progressively increased, returning to baseline by day 8 and surpassing the baseline count on day 9 (Figure 1). With

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20694

Table 1. Baseline Characteristics

Characteristic	Overall (n = 252)	Thrombocytopenia (n = 109)	No Thrombocytopenia (n = 143)	*P* Value
Age (yrs)	63 ± 14	64 ± 15	61 ± 13	0.1
Female, (%)	35	46	27	0.002
White, (%)	58	59	57	0.8
Weight (kilograms)	86 ± 22	81 ± 18	91 ± 24	<0.001
Heart rate (beats per minute)	87 ± 20	90 ± 20	84 ± 19	0.04
Systolic blood pressure (mm Hg)	117 ± 26	115 ± 29	118 ± 23	0.5
Diastolic blood pressure (mm Hg)	68 ± 16	65 ± 15	70 ± 16	0.2
History of:				
Smoking, (%)	30	23	35	0.04
Hypertension (%)	60	60	59	1.0
Diabetes mellitus, (%)	22	26	20	0.2
End-stage renal disease, (%)	5	7	4	0.2
Coronary artery disease, (%)	34	28	39	0.1
CABG, (%)	8	9	8	0.7
PCI, (%)	21	15	25	0.04
PAD, (%)	7	9	5	0.2
Diagnosis:				
ACS, (%)	70	67	72	0.4
STEMI, (%)	45	46	45	0.9
Ejection fraction (%)	35 ± 16	33 ± 16	37 ± 16	0.09
Indication for IABP (%)				0.002
Support during catheterization/PCI	49	38	57	
Cardiogenic shock	45	59	35	
Refractory ischemia	4	3	5	
Mechanical complication of MI	1	0	1	
Mechanical complication of infective endocarditis	1	1	1	
Other	0	0	1	
IABP catheter diameter (%)				0.2
8 Fr	34	30	38	
7.5 Fr	66	70	62	

Abbreviations: CABG, Coronary artery bypass grafting; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; MI, myocardial infarction; IABP, intra-aortic balloon pump.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20694

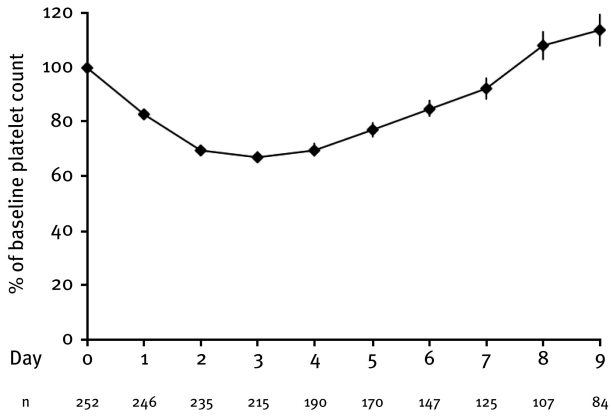

Figure 1. Platelet count as a percentage of baseline ± standard error.

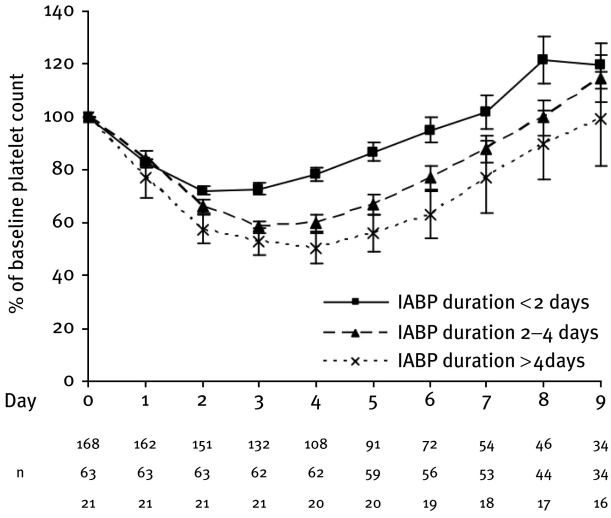

Figure 2. Platelet count as a percentage of baseline ± standard error according to intra-aortic baloon pump (IABP) duration.

increasing duration of IABP, the magnitude and duration of the reduction in platelet count increased (Figure 2).

Baseline characteristics of patients who did and did not develop thrombocytopenia are presented in Table 1. Patients who developed thrombocytopenia were more likely to be female, have a lower body weight, and have a higher heart rate, and were less likely to be smokers or have a history of PCI. Cardiogenic shock was significantly more likely to be the indication for IABP among patients who developed thrombocytopenia than among those that did not (59% vs 35%, $P < 0.001$). The mean duration of IABP was significantly greater among patients who developed thrombocytopenia than among those who did not (2.2 ± 1.7 days vs 1.5 ± 1.4 days, $P < 0.001$). On multivariate analysis, independent predictors of the development of

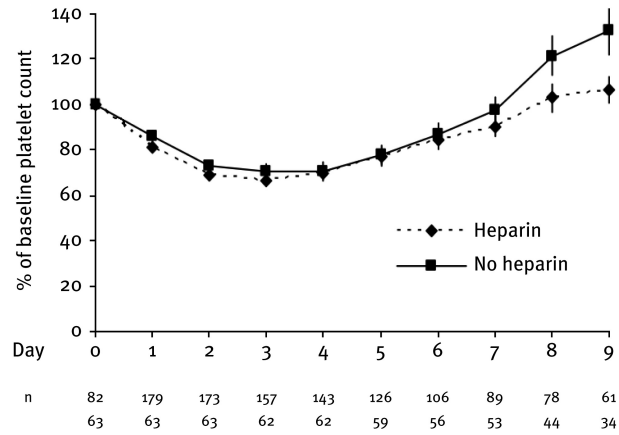

Figure 3. Platelet count as a percentage of baseline ± standard error according to heparin use.

thrombocytopenia were lower body weight, cardiogenic shock, and longer duration of IABP support (Table 2).

The mean nadir platelet count was similar among patients who were and were not treated with intravenous unfractionated heparin ($154\,000 \pm 78\,000$ mL vs $149\,000 \pm 68\,000$ mL, $P = 0.6$). In addition, the mean percent reduction in the platelet count from baseline was similar in the 2 groups ($34\% \pm 24\%$ vs $30\% \pm 24\%$, $P = 0.2$; Figure 3). The proportion of patients who developed thrombocytopenia was similar among those treated with heparin and those who were not (45% vs 40%, $P = 0.5$). When forced into the multivariate model, heparin use was not independently associated with the development of thrombocytopenia (odds ratio [OR]: 1.3, 95% confidence interval [CI]: 0.7–2.4, $P = 0.4$).

Testing for Heparin-induced thrombocytopenia (HIT) based on clinical suspicion was performed in 53 patients (21%) and laboratory evidence of HIT was detected in 11 patients (4%). The mean percent reduction in the platelet count from baseline was greater among patients with laboratory evidence of HIT than among those without ($53\% \pm 22\%$ vs $38\% \pm 22\%$, $P = 0.03$). In-hospital mortality was similar among patients with and without laboratory evidence of HIT (27% vs 21%, $P = 0.5$).

Clinical Outcomes

Major bleeding occurred in 21 patients (8.3%). The incidence of major bleeding was higher among patients who developed thrombocytopenia than among those who did not (13.8% vs 4.2%, $P = 0.01$). Furthermore, the risk of major bleeding tended to be highest among patients with the most severe degree of thrombocytopenia (Table 3). However, on multivariate analysis, thrombocytopenia was not independently associated with major bleeding (OR: 2.2, 95% CI: 0.8–6.4, $P = 0.1$). The only independent predictor of major bleeding was duration of IABP support (OR [per day]: 1.5, 95% CI: 1.2–1.9, $P = 0.001$).

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20694

Table 2. Multivariate Predictors of Thrombocytopenia

Characteristic	Odds Ratio	Lower 95% CI	Upper 95% CI	*P* Value
Weight (per kilogram)	0.98	0.97	1.00	0.01
Duration of IABP (per day)	1.3	1.0	1.5	0.02
Cardiogenic shock	2.0	1.1	4.0	0.04

IABP, Intra-aortic balloon pump.

Table 3. Clinical End Points According to Nadir Platelet Count

End Point	Nadir Platelet Count (1000 mL)				*P* Value for Trend
	<50 (n = 18)	50–<100 (n = 60)	100–<150 (n = 81)	>150 (n = 93)	
Major bleeding (n,%)	4 (22)	6 (10)	4 (5)	7 (8)	0.1
In-hospital death (n,%)	9 (50)	17 (28)	14 (17)	14 (15)	0.004

In-hospital death occurred in 54 patients (21%). In-hospital death was more common among patients who developed thrombocytopenia than among those who did not (28% vs 16%, $P = 0.02$). Furthermore, the risk of in-hospital death was higher among patients exhibiting the most severe degree of thrombocytopenia (Table 3). However, on multivariate analysis, thrombocytopenia was not independently associated with in-hospital death (OR: 1.5, 95% CI: 0.8–2.9, $P = 0.3$). Independent predictors of in-hospital death were a history of end-stage renal disease (OR: 3.6, 95% CI: 1.0–12.9, $P = 0.049$) and diabetes mellitus (OR: 2.5, 95% CI: 1.2–5.2, $P = 0.01$).

Discussion

IABP was developed in 1962,[7] and clinical use of this device was first reported in 1968.[8] Percutaneous insertion was described by Bregman et al in 1980, allowing for widespread use.[9] Thrombocytopenia has long been known to be an adverse effect of IABP, but the published literature on this topic is quite limited.[1–3,5] The 2 most recently published studies, reported 10 years apart, yielded remarkably similar results using the same definition of thrombocytopenia as the present analysis. Vonderheide et al performed a prospective study of 58 CCU patients treated with IABP and 51 control patients without IABP. Thrombocytopenia developed in 47% of IABP patients compared with 12% of non-IABP patients ($P < 0.01$). In the IABP group, the mean reduction from baseline was 37% and the nadir platelet count was reached on day 4.[2] Bream-Rouwenhorst et al, in a retrospective cohort study involving 107 CCU patients undergoing IABP, reported the development of thrombocytopenia in 58% of patients. The mean reduction from baseline was 40% and the nadir count was reached on day 3.[1] Our study confirms these findings in a significantly larger patient population. Among 252 consecutive CCU patients undergoing IABP, we found that platelet counts began to fall immediately after IABP insertion, continued to fall through day 3, and thereafter increased until at day 9 the platelet count exceeded the baseline count. The mean maximum percent reduction in platelet count from baseline was 33% and the incidence of thrombocytopenia was 43%.

Also similar to previous data, we detected HIT in a small percentage of IABP patients who were receiving heparin.[1,10] As in the study by Bream-Rouwenhorst et al, we found that the degree of platelet count reduction was greater among patients with HIT than among those without HIT.[1] Because of the important clinical implications of this diagnosis, this finding suggests that IABP patients who are receiving heparin and who have a marked reduction in platelet count (>50%) should be considered for HIT testing.

Beyond confirming the results of prior studies in a larger patient cohort, the present study provides important new insights with respect to IABP-associated thrombocytopenia. First, since the introduction of IABP, systemic anticoagulation with intravenous heparin has been considered standard adjunctive therapy in patients undergoing IABP with the intent of reducing the incidence of limb ischemia.[11] In each of the prior studies, therefore, all patients were treated with heparin while undergoing IABP treatment. As heparin can lead to thrombocytopenia via both immunogenic and non-immunogenic mechanisms,[12] it was not possible for these studies to distinguish between heparin effects and IABP effects. To our knowledge, ours is the first study to report on the effect of IABP on platelet counts in a substantial cohort of patients who were not treated with heparin. Among 70 patients undergoing IABP without heparin anticoagulation, the tempo and degree of platelet count reduction was similar

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20694

to that seen among patients receiving heparin anticoagulation. Further, on multivariate modeling, heparin use was not an independent predictor of thrombocytopenia. In conjunction with previous data demonstrating that the reduction in platelet count among patients undergoing IABP is independent of the use of clopidogrel and glycoprotein IIb/IIIa inhibitors,[1] it becomes clear that this phenomenon is largely a result of the mechanical effects of IABP.

More importantly, no previous study has systematically investigated the clinical implications of IABP-associated thrombocytopenia. In our study, we prospectively collected data with respect to the key end points of major bleeding and in-hospital death. Although the incidence of major bleeding was substantially greater among patients who developed thrombocytopenia (13.8% vs 4.2%), after controlling for patient differences—particularly the duration of IABP support—thrombocytopenia was not significantly associated with this end point. Although this might be considered a surprising negative finding, it likely relates to the relatively mild degree of thrombocytopenia seen in this patient population. That the duration of IABP support was an independent predictor of both thrombocytopenia and major bleeding likely relates to the correlation between duration of IABP support and both the severity of illness and the duration of heparin treatment. Similarly, although in-hospital death was more common among IABP patients who developed thrombocytopenia than among those who did not (28% vs 16%), thrombocytopenia was not an independent predictor of in-hospital death. Taken together, these findings suggest that IABP-associated thrombocytopenia is not a major clinical problem and should not necessarily prompt discontinuation of IABP support or important adjunctive medications.

Our findings in patients undergoing IABP should also be considered in light of previous reports regarding thrombocytopenia in patient populations with acute cardiac disease but without IABP. For example, among a very large cohort of patients with ACS the Global Registry of Acute Coronary Events (GRACE) investigators found that thrombocytopenia was independently associated with a large increase in the risk of both major bleeding (OR: 3.39) and in-hospital death (OR: 2.10). Findings were similar after exclusion of patients with diagnosed HIT or glycoprotein-associated thrombocytopenia.[4] Importantly, however, thrombocytopenia in the GRACE study population was due to a variety of etiologies and fewer than 3% of patients underwent IABP. Furthermore, the definition of thrombocytopenia used in the GRACE analysis was a nadir platelet count $<100\,000$ mL, as compared with the more liberal definition used in the present study. Therefore, it appears that severe thrombocytopenia related to systemic factors indicates a much higher risk of adverse outcomes, whereas relatively modest thrombocytopenia related to a mechanical factor (ie, IABP) does not.

Our analysis has certain limitations that require consideration. First, although larger than previous studies, the number of patients analyzed was relatively small. This limited our statistical power and resulted in relatively wide confidence intervals around the point estimates in our multivariate analyses. Second, HIT testing was not performed routinely; therefore we cannot exclude the possibility that this condition was responsible for thrombocytopenia in additional patients. Finally, we studied only patients undergoing IABP in the CCU setting. Further research is required to confirm our results among patients undergoing IABP in other patient populations such as those undergoing cardiac surgery, where the implications of thrombocytopenia might be more pronounced.

Conclusions

Thrombocytopenia is a common adverse effect of IABP that appears to be primarily related to mechanical factors and not to concomitant treatment with heparin. Thrombocytopenia occurring in the setting of IABP is generally mild and is not significantly associated with major bleeding or in-hospital death. These findings suggest that IABP-associated thrombocytopenia should not necessarily prompt discontinuation of IABP support or important adjunctive medications.

References

1. Bream-Rouwenhorst HR, Hobbs RA, Horwitz PA. Thrombocytopenia in patients treated with heparin, combination antiplatelet therapy, and intra-aortic balloon pump counterpulsation. *J Interv Cardiol*. 2008;21(4):350–356.
2. Vonderheide RH, Thadhani R, Kuter DJ. Association of thrombocytopenia with the use of intra-aortic balloon pumps. *Am J Med*. 1998;105(1):27–32.
3. McCabe JC, Abel RM, Subramanian VA, et al. Complications of intra-aortic balloon insertion and counterpulsation. *Circulation*. 1978;57(4):769–773.
4. Gore JM, Spencer FA, Gurfinkel EP, et al. Thrombocytopenia in patients with an acute coronary syndrome (from the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol*. 2009;103(2):175–180.
5. Leinbach RC, Nyilas E, Caulfield JB, et al. Evaluation of hematologic effects of intra-aortic balloon assistance in man. *Trans Am Soc Artif Intern Organs*. 1972;18(0):493–500, 512.
6. Cooper HA, Thompson E, Panza JA. The role of heparin anticoagulation during intra-aortic balloon counterpulsation in the coronary care unit. *Acute Card Care*. 2008;10(4):214–220.
7. Moulopoulos SD, Topaz S, Kolff WJ. Diastolic balloon pumping (with carbon dioxide) in the aorta—a mechanical assistance to the failing circulation. *Am Heart J*. 1962;63:669–675.
8. Kantrowitz A, Tjonneland S, Freed PS, et al. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA*. 1968;203(2):113–118.
9. Bregman D, Nichols AB, Weiss MB, et al. Percutaneous intra-aortic balloon insertion. *Am J Cardiol*. 1980;46(2):261–264.
10. Laish-Farkash A, Hod H, Matetzky S, et al. Safety of intra-aortic balloon pump using glycoprotein IIb/IIIa antagonists. *Clin Cardiol*. 2009;32(2):99–103.
11. Trost JC, Hillis LD. Intra-aortic balloon counterpulsation. *Am J Cardiol*. 2006;97(9):1391–1398.
12. Jang IK, Hursting MJ. When heparins promote thrombosis: review of heparin-induced thrombocytopenia. *Circulation*. 2005;111(20):2671–2683.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20694