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CLINICAL RESEARCH STUDY

Pulmonary artery catheterization in acute coronary syndromes: Insights from the GUSTO IIb and GUSTO III trials

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ABSTRACT

PURPOSE: To correlate pulmonary artery catheterization (PAC) use and 30-day outcomes and to characterize the use of pulmonary artery catheters among patients with acute coronary syndromes (ACS).

SUBJECTS AND METHODS: We retrospectively studied 26 437 ACS patients from two large multicenter, international randomized clinical trials. Multivariable and causal inference analyses were applied to adjust for differences in baseline risk.

RESULTS: PAC was performed in 735 patients (2.8%), with a median time to insertion of 24 hours. Patients undergoing PAC were older (median, 67 vs. 64 years), more often diabetic (25.7% vs.16.2%), and more likely to present with ST-segment elevation (81.6% vs. 70.2%) or Killip class III or IV (7.9% vs. 1.4%). US patients were 3.8 times more likely than non–US patients to undergo PAC. Patients managed with PAC also underwent more procedures, including percutaneous intervention (40.7% vs. 18.1%), coronary artery bypass grafting (12.5% vs. 7.7%), and endotracheal intubation (29.3% vs. 2.2%). Mortality at 30 days was substantially higher among patients with PAC for both unadjusted (odds ratio [OR] 8.7; 95% confidence interval [CI] 7.3–10.2) and adjusted analyses (OR 6.4; 95% CI 5.4–7.6) in all groups except in patients with cardiogenic shock (OR 0.99; 95% CI 0.80–1.23).

CONCLUSIONS: PAC was associated with increased mortality, both before and after adjustment for baseline patient differences and subsequent events that may have led to PAC use, except in patients with cardiogenic shock. The definitive role of PAC in managing patients with ACS is still to be determined.

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Continuous bedside hemodynamic monitoring with flow-directed, balloon-tipped pulmonary artery catheters was introduced in the 1970s.[1] Subsets of patients with myocardial infarction (MI) were recognized,[2] and, soon thereafter, pulmonary artery catheters began to be routinely used in the management of critically ill patients, particularly those with MI, cardiogenic shock, hypotension, and congestive heart failure (CHF).[2] For these unstable patients, pulmonary artery catheterization (PAC) is considered essential for monitoring hemodynamics, understanding the cardiopulmonary pathophysiology underlying the patient's condition, and guiding therapy.[3–7] Contrary to prevailing clinical opinion, in the 1990s, some investigators questioned the routine use of PAC, believing that it could lead to worse outcomes in critically ill patients.[8–10]

Few data support the concept that PAC improves outcomes in critically ill patients. In observational studies, there has been an increased adjusted risk for mortality in patients who have had PAC.[11–13] However, the interpretation of these studies is hampered by both selection and survival bias. Early randomized trials of PAC have been unsuccessful; one study was abandoned because physicians believed it unethical to withhold PAC from critically ill patients.[14] More recently, a randomized trial showed a neutral effect of PAC-guided management in patients with advanced heart failure.[15]

Current treatment guidelines for ST-segment elevation myocardial infarction recommend PAC in cases of cardiogenic shock and hypotension of uncertain etiology.[16] The adverse publicity attributed to PAC, the universal availability of echocardiography, and advances in noninvasive hemodynamic monitoring appear to have decreased the use of PAC in the intensive care setting.[8,10] Therefore, we believe a gauge is indicated for the baseline use of PAC, clinical characteristics, and outcomes. We used data from two clinical trials, the Global Use of Strategies to Open occluded coronary arteries in acute coronary syndromes (GUSTO IIb) and Global Use of Strategies to Open occluded coronary arteries (GUSTO III), to evaluate usage patterns of PAC in a large cohort of patients with acute coronary syndromes (ACS). Despite inherent limitations, we compared patient characteristics and clinical outcomes for patents with and without PAC for descriptive purposes.

Methods

Patient population

The GUSTO IIb and GUSTO III trials have been previously described.[17,18] In both trials, patient data were prospectively recorded on similar case report forms, which captured baseline clinical characteristics, medications, procedures including PAC, and clinical events at 30 days. No standardized criteria for use of PAC were defined for either trial.

Of 27 201 patients enrolled in the two trials, 764 were referred for coronary artery bypass grafting (CABG) on the day of or before PAC; therefore, they were excluded from this analysis to avoid inclusion of patients for whom PAC was not indicated for a clinical condition. Thus, the total study population was 26 437 patients.

Statistical analysis

Data are presented as percentages for categorical variables and as medians (25th, 75th percentiles) for continuous variables. A chi-square test was used to evaluate the association between categorical factors and the use of PAC. Wilcoxon rank-sum tests were used for continuous measures.

To account for the bias of early death (no opportunity for PAC use), PAC was included in a Cox proportional hazards modeling with PAC as a time-dependent covariate. This same modeling process was used to examine the association of PAC with mortality within prespecified subgroups of patients: age <70 years, ST-segment elevation on admission electrocardiogram, US versus non–US patients, and shock prerandomization. These models included the significant prognostic baseline factors.

Stepwise and backwards variable-selection techniques were used to determine the baseline factors that remained significant predictors of 30-day death at the 0.05 level of significance. These factors were used as covariates for adjustment of possible confounding in all subsequent models.

Causal inference modeling

To adjust for baseline variables and complications that selected patients for the PAC procedure and to examine more closely the relation between PAC and mortality, we used a causal inference model[19–21] in which we evaluated the prognostic significance of PAC within distinct time units. We stepped through the first 5 days of patient information (days 1–5, where day 1 is the day of randomization). On day 1, all patients were included in a model that contained only baseline information and a variable of whether PAC was used on that day. Any patient who died on day 1 was excluded. For day 2, patients who survived through day 2 and did not have PAC on previous days (day 1 in this case) were included. The variables considered for adjustment now included the baseline characteristics as well as any complications that may have occurred on day 1. This process continued through day 5.

For all the models, adjustments were made for baseline factors. The post-baseline events of shock, stroke, and CHF were considered, along with arrhythmic events and mechanical complications.

All analyses were performed using SAS software (SAS Institute Inc., Cary, North Carolina). A P value of 0.05 was used for the test of statistical significance.

Table 1 Baseline characteristics (all patients)

	No PAC (n = 25 702)		PAC (n = 735)		*P* Value
Median age (years)	64 (59, 72)		67 (57, 74)		.0001
Female sex	7314	28.5%	244	33.2%	.005
Diabetes	4166	16.2%	189	25.7%	.001
Hypertension	10 729	41.8%	345	47.0%	.005
Hypercholesterolemia	9356	36.7%	251	34.5%	.24
Current smokers	9464	43.8%	268	44.8%	.58
Previous MI	5623	21.9%	177	24.1%	.16
Previous PCI	1683	6.6%	45	6.1%	.66
Previous CABG	1638	6.4%	56	7.6%	.17
Enrolled in the USA	7639	29.7%	428	58.2%	.001
Median heart rate (beats/min)	74 (63, 85)		80 (66, 96)		.0001
Median systolic blood pressure (mm Hg)	135 (120, 150)		122 (108, 144)		.0001
Median diastolic blood pressure (mm Hg)	80 (70, 90)		75 (60, 85)		.0001
ST elevation at enrollment	17 777	70.2%	600	81.6%	.001
Killip class III or IV	398	1.6%	58	7.9%	.001

Numbers are presented as percentages for categorical variables and as medians (25th, 75th percentiles) for continuous variables.
MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; USA = United States of America.

Results

Patient characteristics

In this study, 735 patients from the GUSTO IIb and GUSTO III trials who underwent PAC were compared with 25 702 patients managed without PAC. The median (interquartile range) time from hospitalization to PAC was 1 day (0, 3). Patients undergoing PAC were older, more likely to be female, diabetic, and to have hypertension (Table 1). Patients managed with PAC presented more frequently with ST-segment elevation MI and Killip class III or IV. PAC use was higher in the United States than other countries. For ST-segment elevation MI patients, PAC was performed in 382 of 5999 (6.4%) of U.S. patients and 241 of 12 944 (1.9%) of non-US patients ($P < .0001$). For non–ST-MI, PAC was performed in 68 of 2190 (3.1%) of US patients and 80 of 5720 (1.4%) of non-US patients ($P < .0001$).

At hospital presentation, patients managed with PAC had lower blood pressure and higher median heart rate than did patients without PAC. Revascularization procedures, mechanical ventilators, temporary pacemakers, and intraaortic balloon pumps were used significantly more frequently in patients managed with PAC (Figure 1). Critical care length of stay was 5.5 days (3, 9) in patients with PAC and 3 days (2, 4.5) in patients without PAC ($P = .0001$). Total hospital length of stay was 9 days (6, 16) for patients with PAC and 8 days (5, 12) for patients without PAC ($P = .0001$).

Unadjusted outcomes

Mortality at 30 days was substantially higher in patients managed with PAC (OR 8.7; 95% CI 7.3–10.2). Other major adverse events, including bleeding, hypotension, and CHF, were also more frequent in patients managed with PAC (Figure 2).

Causal inference modeling analysis

The exact timing of in-hospital complications before PAC could not be determined for 57 patients; these patients were excluded from the causal inference analysis. Regardless of timing, PAC was associated with increased 30-day mortality. The analysis was performed after the first day (day 1) and each day thereafter through day 5. There was a trend toward increased mortality in patients undergoing PAC during days 1–2 compared with days 3–5. To identify potential sources of bias, we examined the association of PAC and 30-day mortality in patients enrolled in all sites and patients enrolled in sites that had performed at least one PAC. The analyses of all study sites and sites that performed PAC yielded similar results (Table 2).

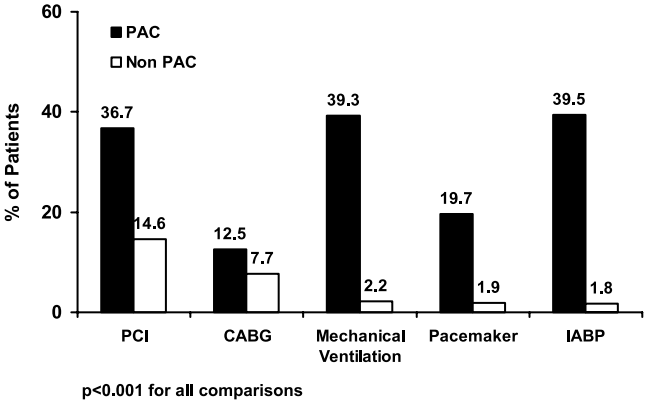

Figure 1 Resource utilization. PAC = pulmonary artery catheterization; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; IABP = intraaortic balloon pump.

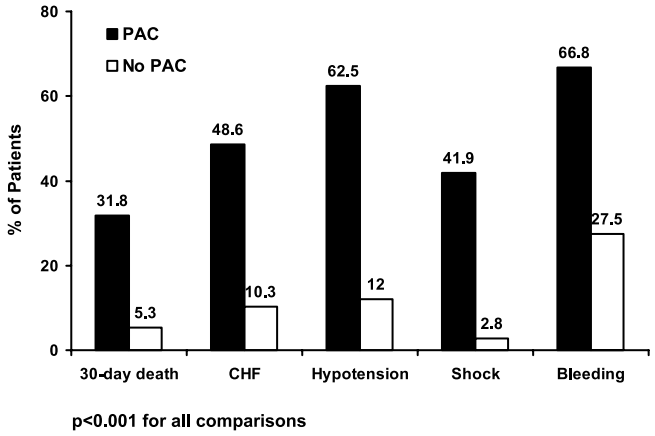

Figure 2 Unadjusted major adverse cardiac events. PAC = pulmonary artery catheterization; CHF = congestive heart failure.

Multivariable analysis of 30-day survival

The association of PAC with 30-day survival was assessed by adjusting for baseline characteristics and including PAC as a time-dependent covariate. With this model, we accounted for the time that each patient did not have PAC and the time beyond which PAC had been used. The probability of death at 30 days revealed an odds ratio of 6.42 (95% CI 5.42–7.59).

Subgroup analysis

Through the same analytical approach as above, PAC was associated with increased 30-day mortality after adjusting for baseline variables across all subgroups, except in patients with shock (Table 3). The confidence intervals did not overlap in the subgroups with ST-segment elevation and non–ST-segment elevation, indicating statistical interaction. A similar interaction was observed in patients with and without cardiogenic shock.

Discussion

We found important differences in baseline characteristics between patients who underwent PAC and those who did not. This underscores the difficulty in adjusting for bias in treatment selection when analyzing observational data, even when complex statistical methods are used. The results of our analysis are consistent with previous studies in which PAC was associated with increased unadjusted and adjusted 30-day mortality in all ACS patients, except in those with cardiogenic shock.[11,12] In addition, the mortality risk related to PAC is higher in the first 48 hours after hospital admission.

In the Worcester Heart Attack Study, PAC was used in 14% of 3263 MI patients in 16 hospitals. Use of PAC significantly increased over a 9-year period—from 7% in 1975 to 20% in 1984. For patients managed with PAC, unadjusted in-hospital mortality rates and length of stay increased, regardless of the development of acute complications. After adjusting for baseline variables, PAC was associated with a 2.6-fold increase in hospital mortality. However, for patients in whom cardiogenic shock developed, the mortality outcomes were similar between those with and without PAC.[11] An analysis of 5841 MI patients from the SPRINT registry showed similar results. In the 371 (6.4%) patients who were managed with PAC, hospital mortality increased (OR 2.98). Outcomes were similar between patients with sustained hypotension and those with cardiogenic shock, regardless of the use of PAC.[12] In 1996,

Table 2 Causal inference analysis of PAC and 30-day mortality

		OR (95% CI)	
Day analyzed	Covariates	All sites (n = 26 774)	Sites with ≥1 PAC (n = 12 740)
0	Baseline variables	4.89 (3.51, 6.82)	5.11 (3.62, 7.21)
1	Baseline variables, arrhythmic and nonarrhythmic heart events, shock, stroke and CHF	6.84 (4.52, 10.37)	7.66 (5.02, 11.70)
2	Baseline variables, arrhythmic and nonarrhythmic heart events, shock, stroke and CHF	2.29 (1.22, 4.31)	3.01 (1.61, 5.63)
3	Baseline variables, arrhythmic and nonarrhythmic heart events, shock, stroke and CHF	3.04 (1.43, 6.46)	3.76 (1.78, 7.96)
4	Baseline variables, arrhythmic and nonarrhythmic heart events, shock, stroke and CHF	3.57 (1.50, 8.45)	3.79 (1.57, 9.17)

Baseline variables: age, weight, systolic blood pressure, baseline Killip class, location of myocardial infarction (MI), previous MI, smoking status, diabetes mellitus, previous coronary artery bypass grafting, previous cardiovascular disease, hypertension, enrollment in the US vs. other countries, sex, and electrocardiographic category (ST-segment elevation vs. non–ST-segment elevation).

Arrhythmic events: 2nd or 3rd degree atrioventricular block, asystole, atrial fibrillation, sustained ventricular tachycardia, or ventricular fibrillation.

Nonarrhythmic events: sustained hypotension, acute mitral regurgitation, acute ventricular septal defect, or tamponade.

CHF = congestive heart failure.

Table 3 Subgroup analysis: Adjusted risk of 30-day mortality

	30-day hazard ratios (95% CI)		
Variable	GUSTO IIb	GUSTO III	Combined
Overall	7.43 (5.77, 9.56)	6.23 (4.96, 7.83)	6.42 (5.42, 7.59)
Age, years			
<70	7.65 (5.02, 11.66)	6.10 (4.22, 8.83)	6.43 (4.88, 8.46)
≥70	7.38 (5.38, 10.11)	6.19 (4.62, 8.28)	6.31 (5.10, 7.80)
Admission electrocardiogram*			
ST ↑	4.14 (2.83, 6.04)	. . .	. . .
Non-ST ↑	14.59 (10.31, 20.65)	. . .	. . .
Country			
Non-US	9.63 (6.85, 13.54)	6.92 (4.99, 9.60)	7.43 (5.88, 9.38)
US	5.89 (3.94, 8.81)	6.36 (4.52, 8.96)	6.10 (4.72, 7.89)
Shock			
Nonshock	5.56 (3.56, 8.68)	4.80 (3.23, 7.15)	4.80 (3.56, 6.47)
Shock	1.15 (0.84, 1.58)	0.91 (0.68, 1.23)	0.99 (0.80, 1.23)

*MI analysis based on GUSTO IIb trial data only.

an analysis from the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT)[13] showed that critically ill patients who received a PAC were 24% more likely to die within 1 month of the procedure, required more intensive care, and had longer hospital stays. Adjustment for selection bias was performed by using a case-matched analysis and a propensity score. Interestingly, patients with CHF were not affected by the use of PAC.[13] An editorial accompanying that report called for a moratorium on the use of PAC until the results of well-conducted, randomized clinical trials could be made available.[8] A more recent observational study in patients undergoing noncardiac surgery has shown similar results, with poorer outcomes in patients managed with PAC.[22]

There has been much speculation as to why mortality increases with the use of PAC.[23–32] Inconsistencies in the interpretation of PAC data by physicians and nurses may lead to incorrect clinical decision-making.[23–25] Complications may arise from the PAC procedure itself, such as infections, pneumothorax, ventricular ectopy, and venous thrombosis.[26–28] In addition, the aggressive style of care implemented in response to hemodynamic data may lead to a more frequent use of inotropic agents, resulting in higher mortality rates.[29–32]

In 1997, a government-sponsored PAC workshop recommended that randomized controlled clinical trials be undertaken for patients with advanced CHF, acute respiratory distress syndrome (ARDS), sepsis, and low-risk CABG.[33] Three randomized clinical trials conducted in Europe and Canada in critically ill intensive-care patients, high-risk surgical elderly patients, and ARDS patients showed no survival benefit associated with PAC-guided management over standard care.[34–36] The recently presented Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial was stopped for futility after enrolling 433 patients with advanced heart failure at 26 U.S. and Canadian sites. PAC did not significantly affect the primary endpoint (days alive and not hospitalized over 6 months) (hazard ratio: 1.00), nor the endpoints of time to death, death plus hospitalization, or days hospitalized. Use of inotropic agents was discouraged, and PAC was not associated with increased complication rates.[15] One ongoing trial is recruiting patients with ARDS.[37]

The Worcester Heart Attack Study and the SPRINT Registry were conducted almost two decades ago. Compared with these studies, a lower proportion of patients in the GUSTO IIb and GUSTO III trials underwent PAC; however, the unadjusted 30-day mortality rate of 31.8% in these trials was similar to that of the earlier studies.

The SUPPORT analysis has been criticized because temporal factors that may influence medical decision-making, such as trends over time and responses to treatment, were not included in the propensity score. The regression analyses used in SUPPORT estimated the likelihood of future events under static experimental conditions.[38] Therefore, we opted for a causal inference analysis to infer aspects of the data generation process, assisting in the prediction of the likelihood of events under static as well as changing conditions.[19] This included predicting the effects of spontaneous changes, such as life-threatening complications, and the effectuation of a procedure such as PAC. By using this analysis at different time-points, from day 1 to day 5, we considered a patient to be in the non-PAC group during the time interval before the procedure was performed. Patients who underwent PAC on a particular day were compared with those who had survived to that day and had not undergone PAC. Causal analysis considers survivor bias, as patients have to have survived long enough to be able to undergo PAC.[19,20]

Our observational study is subject to treatment selection bias. Even though exclusion criteria were minimal in the GUSTO trials, patients enrolled in clinical trials are at lower risk than those in general practice. This is reflected in the low proportion of patients who underwent PAC.

Substantial efforts were made to adjust for baseline variables and complications that may have led to PAC. However, factors not collected in the database may explain our study results.

We were unable to demonstrate evidence of benefit associated with PAC use in ACS. Because accurate adjustment for treatment selection bias is problematic within observational studies, randomized trials are needed to determine the benefit–risk ratio of PAC use in ACS. In the meantime, decisions on use of PAC must be weighed carefully on an individual case basis.

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