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A Randomized, Controlled Trial of the Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients

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ABSTRACT

BACKGROUND

Some observational studies suggest that the use of pulmonary-artery catheters to guide therapy is associated with increased mortality.

METHODS

We performed a randomized trial comparing goal-directed therapy guided by a pulmonary-artery catheter with standard care without the use of a pulmonary-artery catheter. The subjects were high-risk patients 60 years of age or older, with American Society of Anesthesiologists (ASA) class III or IV risk, who were scheduled for urgent or elective major surgery, followed by a stay in an intensive care unit. Outcomes were adjudicated by observers who were unaware of the treatment-group assignments. The primary outcome was in-hospital mortality from any cause.

RESULTS

Of 3803 eligible patients, 1994 (52.4 percent) underwent randomization. The baseline characteristics of the two treatment groups were similar. A total of 77 of 997 patients who underwent surgery without the use of a pulmonary-artery catheter (7.7 percent) died in the hospital, as compared with 78 of 997 patients in whom a pulmonary-artery catheter was used (7.8 percent) — a difference of 0.1 percentage point (95 percent confidence interval, −2.3 to 2.5). There was a higher rate of pulmonary embolism in the catheter group than in the standard-care group (8 events vs. 0 events, P=0.004). The survival rates at 6 months among patients in the standard-care and catheter groups were 88.1 and 87.4 percent, respectively (difference, −0.7 percentage point [95 percent confidence interval, −3.6 to 2.2]; negative survival differences favor standard care); at 12 months, the rates were 83.9 and 83.0 percent, respectively (difference, −0.9 percentage point [95 percent confidence interval, −4.3 to 2.4]). The median hospital stay was 10 days in each group.

CONCLUSIONS

We found no benefit to therapy directed by pulmonary-artery catheter over standard care in elderly, high-risk surgical patients requiring intensive care.

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THE CLINICAL VALUE OF DATA OBtained from pulmonary-artery catheters remains unproven. The light, flexible, balloon-tipped, flow-directed pulmonary-artery catheter was introduced clinically three decades ago,[1] and its use has continued without definitive evidence of decreased morbidity or mortality.[2] More than 1.5 million pulmonary-artery catheters are inserted into medical and surgical patients in North America annually,[3] despite calls for a moratorium[4,5] on the use of this invasive technology because observational studies have suggested an association with increased mortality.[6-8]

Proponents argue that physiological measurements provided by the use of a pulmonary-artery catheter permit refinements of treatment that improve patients' outcomes. This hypothesized benefit has driven the use of the pulmonary-artery catheter in the preoperative, perioperative, and postoperative treatment of patients in whom surgery is considered to entail a high risk because of coexisting conditions.[9] Studies to date of the use of pulmonary-artery catheters in populations of surgical patients have yielded inconsistent results, ranging from decreased mortality[10-14] to no effect[15,16] or increased morbidity or mortality.[17,18] Two systematic reviews[19,20] that analyzed the small, randomized clinical trials that included elderly surgical patients[9,10,17,21-33] showed no overall benefit. In a mixed population of surgical patients, medical patients, and patients with myocardial infarction,[6-8] investigators found that pulmonary-artery catheters may increase morbidity and mortality or be of no benefit.

A prospective cohort study by Connors et al.[8] that involved a mixed population of medical and surgical patients in intensive care units showed increased mortality, length of stay, and costs associated with use of a pulmonary-artery catheter. This study generated intense interest in the lay press[34] and professional publications. Subsequent consensus statements[35,36] recommended redoubled efforts at education regarding the use of pulmonary-artery catheters and randomized, controlled clinical trials of their use.

Trials to date have had methodologic problems, including selection bias, noncompliance by physicians, and crossover from standard care (without the use of a pulmonary-artery catheter) to use of a pulmonary-artery catheter.[28] To address these issues, we performed a multicenter, randomized, controlled clinical trial involving blinded assessment of outcomes to compare therapy guided by a pulmonary-artery catheter with standard therapy (not guided by a pulmonary-artery catheter) among high-risk elderly patients undergoing surgery followed by a stay in the intensive care unit (ICU).

METHODS

STUDY PARTICIPANTS

Eligible patients were 60 years of age or older with American Society of Anesthesiologists (ASA) class III or IV risk[37] and were scheduled for urgent or elective major abdominal, thoracic, vascular, or hip-fracture surgery. All patients provided written informed consent. Randomization was carried out by computer-generated sequence, stratified according to type of surgery (abdominal, thoracic, vascular, or orthopedic) and according to ASA class (III or IV) and blocked according to center; assignments were concealed in opaque, sealed envelopes that were numbered consecutively within each stratum. Local institutional review boards at each of the 19 participating centers, all in Canada, approved the study protocol. Abbott Laboratories had no role in the study design, data collection, analyses, or preparation of this article.

STUDY DESIGN

Patients in the standard-care group were treated without use of a pulmonary-artery catheter. Measurement of central venous pressure (with the use of a central venous catheter) was allowed. The protocol approved by all centers specified that crossover of patients in the standard-care group to use of a pulmonary-artery catheter was not permitted; treating physicians considering crossover were advised to contact the principal investigator at the site. Patients in the catheter group had a pulmonary-artery catheter placed before surgery, and treatment was directed to physiological goals and treatment priorities defined by consensus among the investigators before the study began.

Goals in order of priority were an oxygen-delivery index of 550 to 600 ml per minute per square meter of body-surface area, a cardiac index of 3.5 to 4.5 liters per minute per square meter, a mean arterial pressure of 70 mm Hg, a pulmonary-capillary wedge pressure of 18 mm Hg, a heart rate of less than 120 beats per minute, and a hematocrit of more than 27 percent. Assessment of the achievement of these goals was based on the highest value obtained. Suggested therapy for the achievement of the goals

included, in order of priority, fluid loading, inotropic therapy, vasodilator therapy, vasopressors for hypotension, and blood transfusion for a hematocrit of less than 27 percent. Thromboprophylaxis using low-dose subcutaneous heparin was recommended for all patients both before and after surgery. A minimal postoperative ICU stay of 24 hours was required; the length of the ICU stay thereafter was at the discretion of the attending clinician.

Clinical data, including New York Heart Association[38] (NYHA) functional class, Goldman Cardiac Risk Index,[39] vital capacity, and forced expiratory volume in one second, were recorded at enrollment. Clinical and outcome data were obtained 24 hours after surgery and weekly during the ICU stay and the hospital stay, until death or hospital discharge. Vital status was ascertained 6 and 12 months after randomization by telephone contact with patients, family members, surgeons, or family physicians, or through hospital or provincial records. Base-line clinical and demographic data were collected on all patients who were eligible but not enrolled. A data safety and monitoring committee conducted a safety analysis after the enrollment of 800 patients and another after the enrollment of 1600 patients.

OUTCOME

The primary outcome was in-hospital mortality from any cause. Secondary outcomes were 6-month mortality, 12-month mortality, and in-hospital morbidity, which was defined a priori according to objective criteria as follows. Myocardial infarction was defined by the presence of a new Q-wave myocardial infarction on electrocardiography or the presence of compatible ST-T wave changes on electrocardiography plus an increase in either the creatine kinase MB fraction or troponin to abnormal levels. Left ventricular failure was assessed on the basis of adjudicated chest radiography. Arrhythmia was determined by electrocardiography or analysis of a rhythm strip. Pneumonia was defined according to the criteria of the Centers for Disease Control and Prevention.[40] Pulmonary embolism was documented by autopsy, positive pulmonary angiography, positive spiral computed tomography, high-probability ventilation–perfusion scanning, or positive noninvasive Doppler ultrasonography of the leg. Renal insufficiency was defined by a 50 percent increase in the creatinine concentration or the need for dialysis in a patient with preexisting non–dialysis-dependent renal failure. Liver insufficiency was defined by a serum bilirubin concentration higher than 34 mmol per liter and an increase of four seconds in the prothrombin time without the use of anticoagulant agents. Sepsis from the central venous or pulmonary-artery catheter was defined by inflammation at the insertion site and systemic sepsis plus a positive culture of blood or of material swabbed from the catheter tip that resolved with removal of the catheter.

AVOIDANCE OF BIAS

To avoid selective enrollment and crossover of patients, participating surgeons, anesthesiologists, and intensivists at 19 Canadian institutions agreed to refer all their eligible patients. At each site, a principal investigator was actively involved in enrollment and in the conduct of the study; a log was maintained to record information about all eligible patients. Random assignment to treatment groups and assessment of outcomes on the basis of a priori definitions was performed in a blinded manner. So that adjudicators of chest radiographs would remain unaware of treatment-group assignments when reading the radiographs, we placed opaque tape over the pulmonary-artery catheter in images and dummy tape on images from patients in the standard-care group. All outcomes except death were adjudicated by two observers who were unaware of the treatment-group assignments. Blinding of patients and clinicians was not considered to be feasible.

STATISTICAL ANALYSIS

The sample size of 1000 per group was chosen to provide the study with power exceeding 90 percent for distinguishing between mortality rates of 10 percent and 15 percent in the two groups, allowing a two-sided type I error rate of 5 percent. Additional calculations confirmed that there would be adequate power under varied assumptions — for example, 78 percent power to distinguish between mortality rates of 5 percent and 8 percent.

All analyses were conducted on an intention-to-treat basis. Continuous variables such as age, vital capacity, and Goldman index[39] were compared with the use of the unpaired t-test or the Wilcoxon rank-sum test, depending on their distributional properties. Skewed variables were summarized as medians and interquartile ranges. Differences in proportions (in-hospital mortality rates, rates of medical conditions and complications, rates of interventions, and

Table 1. Characteristics of the Patients at Entry.*

Characteristic	Standard-Care Group (N=997)	Catheter Group (N=997)	Patients Who Were Eligible but Were Not Enrolled (N=1809)
Age — yr†	72.6±6.89	72.3±6.97	72.9±7.20
Male sex — no. (%)‡	702 (70.4)	716 (71.8)	1163 (62.5)
ASA risk class — no. (%)†§			
III	871 (87.4)	871 (87.4)	1624 (89.8)
IV	126 (12.6)	126 (12.6)	185 (10.2)
Type of surgery in patients with ASA class III risk — no. (%)			
Abdominal†	216 (21.7)	212 (21.3)	441 (24.5)
Thoracic†	50 (5.0)	52 (5.2)	127 (7.1)
Major vascular‡	538 (54.0)	527 (52.9)	797 (44.3)
Orthopedic‡	59 (5.9)	62 (6.2)	249 (13.8)
Surgery canceled‡	8 (0.8)	18 (1.8)	1 (0.1)
Type of surgery in patients with ASA class IV risk — no. (%)			
Abdominal†	69 (6.9)	64 (6.4)	82 (4.6)
Thoracic	8 (0.8)	13 (1.3)	12 (0.7)
Major vascular	21 (2.1)	22 (2.2)	45 (2.5)
Orthopedic	27 (2.7)	24 (2.4)	45 (2.5)
Surgery canceled	1 (0.1)	3 (0.3)	0
NYHA class — no. with data	916	912	1581
I — no. (%)	475 (51.9)	480 (52.6)	829 (52.4)
II — no. (%)	318 (34.7)	319 (35.0)	560 (35.4)
III — no. (%)	114 (12.4)	100 (11.0)	179 (11.3)
IV — no. (%)	9 (1.0)	13 (1.4)	13 (0.8)
Urgent status — no. (%)	62 (6.2)	74 (7.4)	142 (7.8)
Time from randomization to surgery — hr			
Median	16.5	16.5	—
Interquartile range	12.5–20.0	12.0–20.0	
History of angina — no. (%)†	367 (36.8)	381 (38.2)	608 (33.6)
History of myocardial infarction — no. (%)‡	414 (41.5)	386 (38.7)	630 (34.8)
History of congestive heart failure — no. (%)	162 (16.2)	161 (16.1)	286 (15.8)

rates of achievement of therapeutic goals) were compared with the use of Fisher's exact test (or the chi-square test, where appropriate), and confidence intervals were based on the normal approximation to the binomial distribution. Logistic regression was applied to in-hospital mortality in order to investigate the potential differences in treatment effects according to study center or base-line characteristics. Survival estimates were based on Turnbull's generalization of the Kaplan–Meier estimate, allowing for interval-censored data. Adjusted and unadjusted risk ratios were based on a parametric (Weibull) survival model. All reported P values are two-sided. No interim efficacy analysis was conducted.

RESULTS

STUDY POPULATION

Of the 3803 screened patients, 1994 patients (52.4 percent) underwent randomization — 997 patients each to the catheter group and the standard-care group — between March 9, 1990, and July 19, 1999. The remaining 1809 patients were not enrolled because they declined to participate (1074 patients), because no bed was available in the ICU (370 patients), or because their physicians did not refer them to the study (365 patients).

In the standard-care group, 945 patients (94.8 percent) received the planned therapy, and 52 did not; the reasons for not receiving the planned therapy were the lack of an available ICU bed (in 9 cases),

Table 1. (Continued.)

Characteristic	Standard-Care Group (N=997)	Catheter Group (N=997)	Patients Who Were Eligible but Were Not Enrolled (N=1809)
Goldman index¶			
Median	8	8	8
Interquartile range	3–10	3–11	3–8
Vital capacity — liters	2.78±0.94	2.80±0.99	—
Forced expiratory volume in one second — liters	1.92±0.74	1.93±0.75	—
Hemoglobin concentration — g/liter‖	132±20.0	130±20.8	130±23.1
Serum bilirubin concentration — mg/dl			
Median	0.5	0.5	—
Interquartile range	0.4–0.8	0.4–0.8	
Serum creatinine concentration — mg/dl			
Median	1.1	1.1	1.1
Interquartile range	0.9–1.4	0.9–1.4	0.9–1.4

* Plus–minus values are means ±SD. Abdominal surgery included cholecystectomy, bowel resection, gastric surgery, radical hysterectomy, radical cystectomy, nephrectomy, radical prostatectomy, and other types of abdominal surgery; thoracic surgery included lobectomy, pneumonectomy, esophageal surgery, decortication, and other types of thoracic surgery; major vascular surgery included repair of an abdominal aneurysm, aortofemoral bypass, and other types of major vascular surgery; and orthopedic surgery included total hip replacement, fracture fixation, and other types of orthopedic surgery. Among the patients who were eligible but were not enrolled, data on sex were missing for 40 patients, and data on type of surgery were missing for 9 patients with American Society of Anesthesiologists (ASA) class III risk and 1 patient with ASA class IV risk. To convert values for bilirubin to micromoles per liter, multiply by 17.1; to convert values for creatinine to micromoles per liter, multiply by 88.4. NYHA denotes New York Heart Association.

† P<0.05 for the comparison between the enrolled patients and the nonenrolled patients.

‡ P<0.001 for the comparison between the enrolled patients and the nonenrolled patients.

§ The ASA risk classes range from I to V, with higher classes indicating greater risk; patients with class III risk have severe systemic disease, and patients with class IV risk have severe systemic disease that is a constant threat to life.

¶ The Goldman Cardiac Risk Index is a point system based on history, physical examination, electrocardiographic findings, general status, and type of operation. Higher classes indicate a higher predicted risk of cardiac events or death from cardiac causes. Class 1 is 0 to 5 points (risk of cardiac events, 0.7 percent; risk of death from cardiac causes, 0.2 percent); class 2 is 6 to 12 points (risk of cardiac events, 5.0 percent; risk of death from cardiac causes, 2.0 percent); class 3 is 13 to 25 points (risk of cardiac events, 15 percent; risk of death from cardiac causes, 2.0 percent); class 4 is more than 26 points (risk of cardiac events, 22 percent; risk of death from cardiac causes, 56 percent).

‖ P<0.05 for the comparison between the standard-care group and the catheter group.

the lack of an available operating room (in 9 cases), withdrawal of consent (in 7 cases), and other reasons (in 3 cases). In addition, crossover to use of a pulmonary-artery catheter occurred in 24 of the patients in the standard-care group (2.4 percent). In 11 cases, these crossovers represented inadvertent protocol violations; 12 pulmonary-artery catheters were deliberately placed by the treating physician; and in 1 case, the reason for placement was unknown. Twelve (50 percent) of the crossovers occurred on or after day 4. In the catheter group, 939 patients (94.2 percent) received the planned therapy, and 58 did not; the reasons were the lack of an available ICU bed (in 5 cases), the lack of an available operating room (in 20 cases), withdrawal of consent (in 23 cases), failure of the pulmonary-artery catheter (in 5 cases), and other reasons (in 5 cases).

The base-line characteristics of the patients in the standard-care group and the catheter group were similar (Table 1). The screened patients who were not enrolled were marginally older, were less likely to have ASA class IV risk, were more likely to be women, and had a lower incidence of angina and previous myocardial infarction than the patients who were enrolled.

MORTALITY

All subjects were followed until hospital discharge. The median length of the hospital stay from the time of enrollment was the same in the two groups (10 days [interquartile range, 7 to 15]). Six-month follow-up was complete for 963 patients in the standard-care group (96.6 percent) and 930 patients in the group assigned to pulmonary-artery catheters

Table 2. In-Hospital Mortality and Perioperative and Postoperative Morbidity.*

Variable	Standard-Care Group	Catheter Group	P Value
Length of hospital stay — days			
Median	10	10	0.41
Interquartile range	7–15	7–15	
In-hospital mortality — no. (%)	77 (7.7)	78 (7.8)	0.93
Myocardial infarction — no. (%)	33 (3.4)	40 (4.3)	0.41
Congestive heart failure — no. (%)	108 (11.2)	119 (12.6)	0.36
Supraventricular tachycardia — no. (%)	88 (9.1)	84 (8.9)	0.95
Ventricular tachycardia — no. (%)	2 (0.2)	2 (0.2)	1.00
Pulmonary embolism — no. (%)	0	8 (0.9)	0.004
Renal insufficiency — no. (%)	95 (9.8)	70 (7.4)	0.07
Hepatic insufficiency — no. (%)	26 (2.7)	23 (2.4)	0.84
Sepsis from central venous catheter or pulmonary-artery catheter — no. (%)	13 (1.3)	12 (1.3)	0.95
Wound infection — no. (%)	83 (8.6)	66 (7.0)	0.23
Pneumonia — no. (%)	70 (7.3)	63 (6.7)	0.70
Adverse events due to pulmonary-artery catheters or central venous catheters — no. (%)			
Pulmonary infarction	0	1 (0.1)	1.00
Hemothorax	0	2 (0.2)	0.24
Pulmonary hemorrhage	0	3 (0.3)	0.12
Pneumothorax	4 (0.4)	8 (0.9)	0.36
Arterial puncture	1 (0.1)	3 (0.3)	0.37

* There were 997 patients in each group, but because surgery was canceled for some patients for a variety of reasons, the total number of patients for all variables except length of hospital stay and in-hospital mortality was 965 for the standard-care group and 941 for the catheter group.

(93.3 percent), and 12-month follow-up was completed in 941 patients in the standard-care group (94.4 percent) and 910 patients in the catheter group (91.3 percent). In-hospital mortality was similar in the two groups (Table 2 and Fig. 1). In the standard-care group, 77 patients (7.7 percent [95 percent confidence interval, 6.1 to 9.6]) died without being discharged from the hospital, as compared with 78 patients in the catheter group (7.8 percent [95 percent confidence interval, 6.2 to 9.7]). The estimated absolute difference was 0.1 percentage point (95 percent confidence interval, −2.3 to 2.5).

Survival to one year after randomization was similar in the two groups, with 155 deaths by one year in the standard-care group and 163 in the catheter group (relative risk in the catheter group, 1.1 [95 percent confidence interval, 0.9 to 1.4]), including 13 interval-censored deaths corresponding to 6 patients in the standard-care group and 7 patients in the catheter group for whom the date of death could not be obtained. In the standard-care group, the rate of survival was 88.1 percent (95 percent confidence interval, 86.0 to 90.1) at 6 months and 83.9 percent (95 percent confidence interval, 81.6 to 86.2) at 12 months; in the catheter group, the rate of survival was 87.4 percent (95 percent confidence interval, 85.3 to 89.5) at 6 months and 83.0 percent (95 percent confidence interval, 80.6 to 85.4) at 12 months. The estimated difference in survival was −0.7 percentage point (95 percent confidence interval, −3.6 to 2.2) at 6 months (with negative survival differences favoring standard care) and −0.9 percentage point (95 percent confidence interval, −4.3 to 2.4) at 12 months.

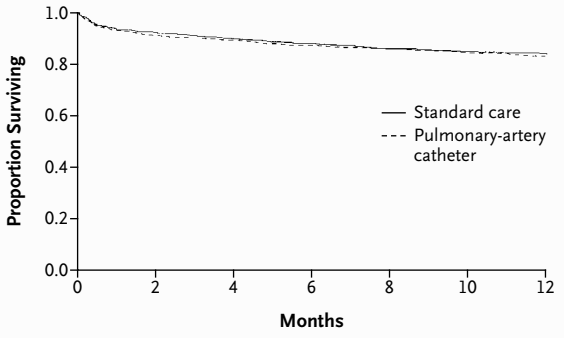
Regression-based adjustment for the base-line variables listed in Table 1 did not materially affect these findings. The adjusted risk ratio for death in the catheter group as compared with the standard-care group was 1.0 (95 percent confidence interval, 0.7 to 1.3) after adjustment for age, history of angina, type of surgery, preoperative ASA risk class,[37] Goldman index,[39] and hemoglobin level. We found no evidence of variation in treatment effect according to center or according to base-line characteristics; there were no significant interactions between treatment-group assignment and any covariate. Subgroup analyses of in-hospital mortality according to ASA risk class,[37] type of surgery, sex, age, and NYHA class[38] yielded results similar to those of the primary analysis (Fig. 2). Among patients with ASA class IV risk,[37] in-hospital mortality was 16.7 percent in the standard-care group and 20.6 percent in the catheter group; one-year mortality in this subgroup was 37.8 percent in the standard-care group and 38.2 percent in the catheter group. Among patients in NYHA class III or IV,[38] in-hospital mortality was 13.8 percent in the standard-care group and 18.6 percent in the catheter group, and one-year mortality was 29.3 percent and 35.3 percent, respectively.

MORBIDITY

Morbidity was similar in the two groups, except that there was a higher incidence of pulmonary embolism in the group assigned to pulmonary-artery catheters (0 events in the standard-care group vs. 8 events [0.8 percent] in the catheter group, P= 0.004). Thromboprophylaxis with unfractionated

or low-molecular-weight heparin was used in 906 patients in the standard-care group (90.9 percent) and 878 patients in the catheter group (88.1 percent, P=0.05). It was initiated within 24 hours after surgery in 52.1 percent of the patients in the standard-care group, as compared with 53.7 percent of those in the catheter group. Diagnostic testing for clinically suspected venous thromboembolism was performed in 69 patients in the standard-care group (6.9 percent) and 57 patients in the catheter group (5.7 percent, P=0.31). The types of testing used (including venography, Doppler ultrasonography, ventilation–perfusion lung scanning, and pulmonary angiography) were similar in the two groups.

The incidence of myocardial infarction, congestive heart failure, supraventricular tachycardia, ventricular tachycardia, hepatic insufficiency, sepsis from the central venous catheter or pulmonary-artery catheter, and pneumonia did not differ significantly between groups (Table 2). Fifteen patients in the catheter group (1.5 percent) had one or more adverse effects of the use of a pulmonary-artery catheter (two cases of hemothorax, three pulmonary hemorrhages, one pulmonary infarction, three inadvertent punctures of a major artery, and eight cases of pneumothorax). Central venous catheters were placed in 769 patients in the standard-care group (77.1 percent). Five of these patients (0.7 percent) had adverse effects of this catheter placement (an inadvertent puncture of a major artery in one patient and pneumothorax in four patients).



No. at Risk							
Standard care	997	885	861	844	803	794	786
Pulmonary-artery catheter	997	842	826	808	773	761	747

Figure 1. Kaplan–Meier Survival Curves to One Year.

Data for six patients in the standard-care group and seven patients in the catheter group for whom exact dates of death were unavailable are included in the number at risk up to the last follow-up contact when the patient was still alive.

ADHERENCE TO THE PROTOCOL

More patients in the catheter group than in the standard-care group received inotropic agents (48.9 percent vs. 32.8 percent, P<0.001), vasodilators (8.5 percent vs. 3.9 percent, P<0.001), antihypertensive medication (25.5 percent vs. 16.9 percent, P<0.001), packed red cells (56.6 percent vs. 47.0 percent, P<0.001), and colloid (54.8 percent vs. 47.7 percent, P=0.002).

In the catheter group, the goals for the cardiac index (3.5 to 4.5 ml per minute per square meter) and the oxygen-delivery index (550 ml per minute per square meter) were met in 18.6 percent and 21.0 percent of patients, respectively, at entry and in 79.0 percent and 62.9 percent of patients, respectively, after surgery (Fig. 3). Central venous pressure did not differ significantly between the patients in the catheter group and the 769 patients in the standard-care group in whom central venous catheters were placed. The mean central venous pressure for the preoperative, intraoperative, and postoperative periods were 6.5, 10.4, and 9.1 mm Hg, respectively, in the standard-care group, as compared with 6.7, 10.1, and 9.3 mm Hg, respectively, in the catheter group.

DISCUSSION

In this large, multicenter, randomized, single-blind clinical trial, we observed no evidence of a benefit of treatment guided by a pulmonary-artery catheter, as compared with standard care. On the other hand, the results of our study indicate that in this population of surgical patients, the insertion of a pulmonary-artery catheter is not linked to excess mortality, as has been reported previously. The confidence interval for the difference in mortality excludes an absolute difference of more than 2.5 percent favoring either strategy, and no difference emerged at the one-year follow-up. The length of the hospital stay was similar in the two groups.

In our study, treatment guided by a pulmonary-artery catheter was coupled with defined physiological goals and treatment strategies designed to optimize treatment. Our findings and the findings of others[10,17,24] demonstrate that it is difficult to achieve such physiological goals — a practical reality of therapy guided by a pulmonary-artery catheter. Nevertheless, such therapy was associated with a significantly different treatment effect from standard care. The a priori goals for the oxygen-delivery

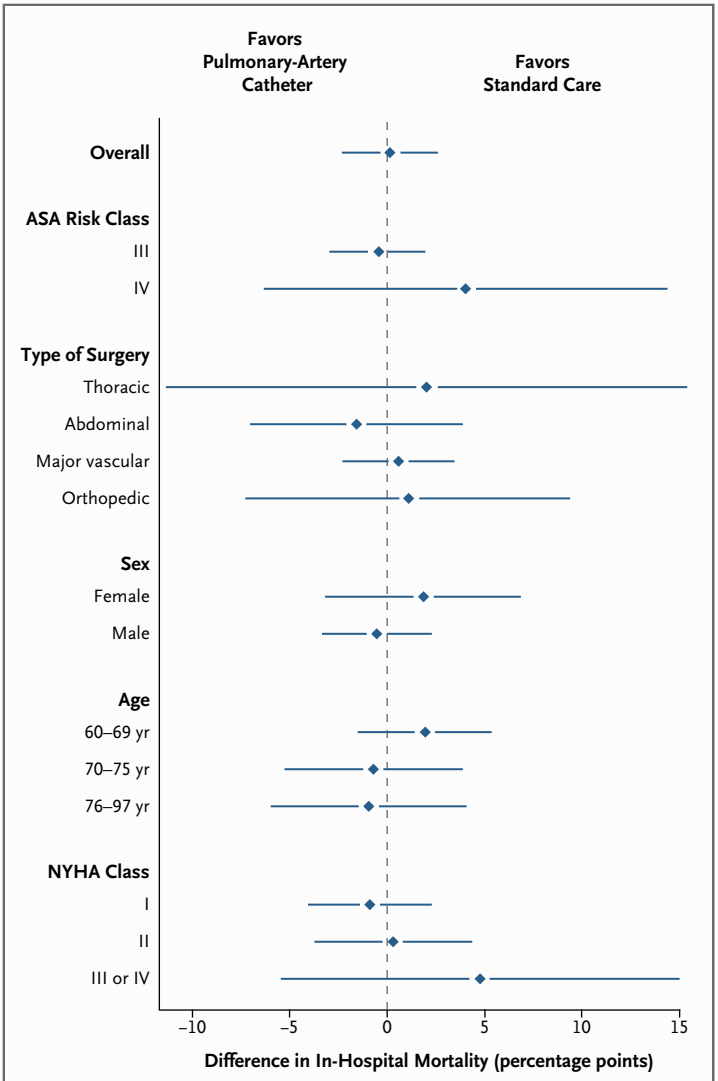


Figure 2. Estimated Differences in In-Hospital Mortality in the Catheter Group as Compared with the Standard-Care Group, Overall and According to American Society of Anesthesiologists (ASA) Risk Class, Type of Surgery, Sex, Age, and New York Heart Association (NYHA) Class.

Positive differences indicate excess mortality in the catheter group as compared with the standard-care group, whereas negative differences indicate lower mortality in the catheter group. Bars represent 95 percent confidence intervals.

index and the cardiac index for treatment guided by a pulmonary-artery catheter were achieved in the majority of patients (62.9 percent and 79.0 percent, respectively) after surgery.

Our study evaluated patients for whom admission to the ICU is recommended. The relatively low numbers of patients with ASA class IV risk[37] and NYHA class III or IV symptoms[38] reflect the characteristics of the population of elderly patients undergoing elective or urgent surgery in Canada.

The extent of excess morbidity due to pulmonary embolism in the group assigned to pulmonary-artery catheters was small. Nevertheless, such morbidity must be interpreted in the light of the 1.5 million patients who receive pulmonary-artery catheters in North America annually. If the incidence of pulmonary embolism is similar in all populations of patients who receive pulmonary-artery catheters, the use of these catheters could potentially translate into 12,000 additional pulmonary embolisms annually.

Our study, which evaluated high-risk surgical patients who commonly undergo monitoring by pulmonary-artery catheter and who were at risk for substantial illness and death, builds on the findings of previous studies. Much of the published literature to date reports clinical trials that were nonrandomized and most of which were retrospective; previously reported randomized trials[9,10,17,21-23] have been small and insufficiently powered to provide a definitive answer. It is important to reconcile our findings with those of the prospective cohort study reported by Connors et al.,[8] which showed increased mortality and length of stay with the use of pulmonary-artery catheters in a mixed population of medical and surgical patients in the ICU.[8] Although Connors et al. attempted to control for confounding by using a "propensity score," the lack of randomization leads to the possibility of many unknown sources of bias that may have influenced the findings of this observational study. In particular, the decision to use a pulmonary-artery catheter may have been a marker for greater severity of illness.

Our trial enrolled 52 percent of eligible patients, and our randomization strategy resulted in groups of patients that were similar at entry. The rate of crossover of patients in the standard-care group to the use of a pulmonary-artery catheter was low (2.4 percent). All outcomes were adjudicated by observers who were unaware of the treatment-group assignments.

In summary, in elderly, high-risk surgical patients who undergo elective or urgent major surgery followed by care in the ICU, we found no clinical advantage to therapy guided by a pulmonary-artery catheter as compared with standard care in the ICU. The results of this study cannot necessarily be generalized to other populations of patients in the ICU, such as those with acute lung injury or circulatory or septic shock. Our study also suggests that randomized

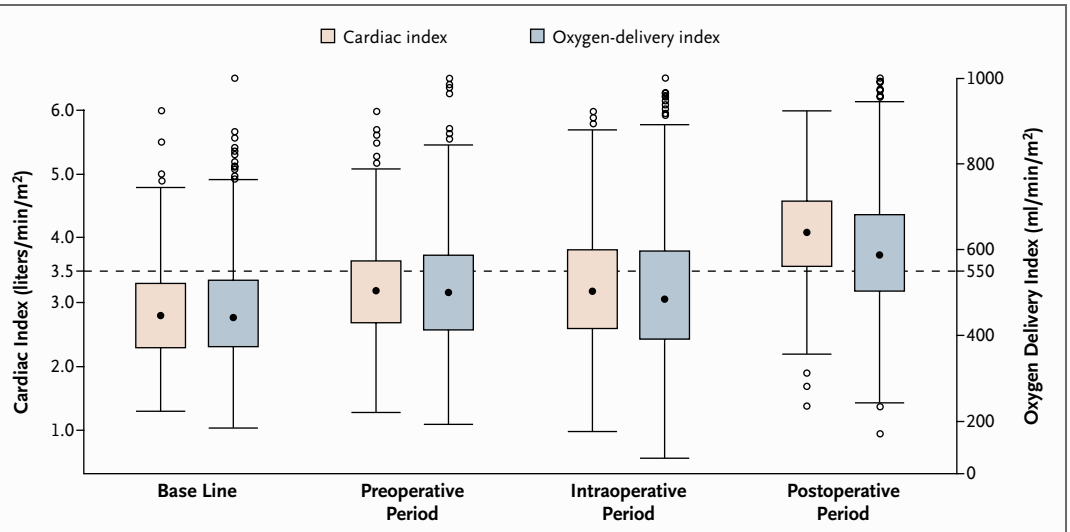


Figure 3. Box Plots of Maximal Attained Values for the Cardiac Index and the Oxygen-Delivery Index at Base Line and during the Preoperative, Intraoperative, and Postoperative Periods in Patients Assigned to Pulmonary-Artery Catheters.

Lower and upper limits of boxes indicate the 25th and 75th percentiles; dots within boxes indicate the median values. The lines extending from the boxes indicate the range of nonoutlying values. Outliers are plotted separately (open circles). The portion of the box plot above the broken line corresponds to the subgroup of patients in whom the defined goals were met.

clinical trials of the use of pulmonary-artery catheters in other populations of patients are feasible.

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APPENDIX

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REFERENCES

1. Swan HJC, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with the use of a flow-directed balloon-tipped catheter. N Engl J Med 1970;283:447-51.
2. Cooper AB, Doig GS, Sibbald WJ. Pulmonary artery catheters in the critically ill: an overview using the methodology of evidence-based medicine. Crit Care Clin 1996; 12:777-94.
3. Rapoport J, Teres D, Steingrub J, Higgins T, McGee W, Lemeshow S. Patient characteristics and ICU organizational factors that influence frequency of pulmonary artery catheterization. JAMA 2000;283:2559-67.
4. Robin ED. Death by pulmonary artery flow-directed catheter: time for a moratorium? Chest 1987;92:727-31.
5. Dalen JE, Bone RC. Is it time to pull the pulmonary artery catheter? JAMA 1996;276: 916-8.
6. Gore JM, Goldberg RJ, Spodick DH, Alpert JS, Dalen JE. A community-wide assessment of the use of pulmonary artery

catheters in patients with acute myocardial infarction. Chest 1987;92:721-7.
7. Zion MM, Balkin J, Rosenmann D, et al. Use of pulmonary artery catheters in patients with acute myocardial infarction: analysis of experience in 5,841 patients in the SPRINT Registry. Chest 1990;98:1331-5.
8. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996;276:889-97.
9. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee T-S. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94:1176-86.
10. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699-707.
11. Del Guercio LRM, Cohn JD. Monitoring operative risk in the elderly. JAMA 1980;243: 1350-5.
12. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 1983;59:499-505.
13. Savino JA, Del Guercio LRM. Preoperative assessment of high-risk surgical patients. Surg Clin North Am 1985;65:763-91.
14. Older P, Smith R. Experience with the preoperative invasive measurement of haemodynamic, respiratory and renal function in 100 elderly patients scheduled for major abdominal surgery. Anaesth Intensive Care 1988;16:389-95.
15. Wu AW, Rubin HR, Rosen MJ. Are elderly people less responsive to intensive care? J Am Geriatr Soc 1990;38:621-7.
16. Tuman KJ, McCarthy RJ, Spiess BD, et al. Effect of pulmonary artery catheterization on outcome in patients undergoing coronary artery surgery. Anesthesiology 1989; 70:199-206.
17. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330: 1717-22.
18. Polanczyk CA, Rohde LE, Goldman L, et al. Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: an observational study. JAMA 2001;286:309-14.
19. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 1996;24:517-24.
20. Ivanov RI, Allen J, Sandham JD, Calvin JE. Pulmonary artery catheterization: a narrative and systematic critique of randomized controlled trials and recommendations for the future. New Horiz 1997;5:268-76.
21. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992;102:216-20.
22. Yu M, Levy MM, Smith P, et al. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: a prospective, randomized, controlled study. Crit Care Med 1993;21:830-8.
23. Yu M, Takanishi D, Takiguchi S, et al. A prospective controlled randomized trial of supranormal O_2 consumption as measured by indirect calorimetry. Crit Care Med 1994; 22:Suppl:111a. abstract.
24. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995; 333:1025-32.
25. Schultz RJ, Whitfield GF, LaMura JJ, Raciti A, Krishnamurthy S. The role of physiologic monitoring in patients with fractures of the hip. J Trauma 1985;25:309-16.
26. Pearson KS, Gomez MN, Moyers JR, Carter JG, Tinker JH. A cost/benefit analysis of randomized invasive monitoring for patients undergoing cardiac surgery. Anesth Analg 1989;69:336-41.
27. Isaacson IJ, Lowdon JD, Berry AJ, et al. The value of pulmonary artery and central venous monitoring in patients undergoing abdominal aortic reconstructive surgery: a comparative study of two selected, randomized groups. J Vasc Surg 1990;12:754-60.
28. Guyatt G, Ontario Intensive Care Study Group. A randomized control trial of right-heart catheterization in critically ill patients. Intensive Care Med 1991;6:91-5.
29. Berlauk JF, Abrams JH, Gilmour IJ, O'Connor SR, Knighton DR, Cerra FB. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: a prospective, randomized clinical trial. Ann Surg 1991;214:289-99.
30. Fleming A, Bishop M, Shoemaker W, et al. Prospective trial of supranormal values as goals of resuscitation in severe trauma. Arch Surg 1992;127:1175-81.
31. Bishop M, Shoemaker W, Appel P, Kram H. Prospective trial of supranormal values in severely traumatized patients. Crit Care Med 1992;20:Suppl:S93. abstract.
32. Yu M, Takanishi D, Myers SA, et al. Frequency of mortality and myocardial infarction during maximizing oxygen delivery: a prospective, randomized trial. Crit Care Med 1995;23:1025-32.
33. Durham RM, Neunaber K, Mazuski J, Shapiro MJ, Baue AE. The use of oxygen consumption and delivery as endpoints for resuscitation in critically ill patients. J Trauma 1996;41:32-9.
34. Cowley G, Hager M. Deep in the heart: are catheters safe? Newsweek. September 30, 1996:71.
35. Pulmonary Artery Catheter Consensus conference: consensus statement. Crit Care Med 1997;25:910-25.
36. Bernard GR, Sopko G, Cerra F, et al. Pulmonary artery catheterization and clinical outcomes: National Heart, Lung, and Blood Institute and Food and Drug Administration Workshop Report: consensus statement. JAMA 2000;283:2568-72.
37. New classification of physical status. Anesthesiology 1963;24:111.
38. Fisher JD. New York Heart Association classification. Arch Intern Med 1972;129: 836.
39. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977;297:845-50.
40. CDC definitions for nosocomial infections, 1988. Am Rev Respir Dis 1989;139: 1058-9.