

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MAY 25, 2006

VOL. 354 NO. 21

Pulmonary-Artery versus Central Venous Catheter to Guide Treatment of Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome
(ARDS) Clinical Trials Network*

ABSTRACT

BACKGROUND

The balance between the benefits and the risks of pulmonary-artery catheters (PACs) has not been established.

METHODS

We evaluated the relationship of benefits and risks of PACs in 1000 patients with established acute lung injury in a randomized trial comparing hemodynamic management guided by a PAC with hemodynamic management guided by a central venous catheter (CVC) using an explicit management protocol. Mortality during the first 60 days before discharge home was the primary outcome.

RESULTS

The groups had similar baseline characteristics. The rates of death during the first 60 days before discharge home were similar in the PAC and CVC groups (27.4 percent and 26.3 percent, respectively; $P=0.69$; absolute difference, 1.1 percent; 95 percent confidence interval, -4.4 to 6.6 percent), as were the mean (\pm SE) numbers of both ventilator-free days (13.2 ± 0.5 and 13.5 ± 0.5 ; $P=0.58$) and days not spent in the intensive care unit (12.0 ± 0.4 and 12.5 ± 0.5 ; $P=0.40$) to day 28. PAC-guided therapy did not improve these measures for patients in shock at the time of enrollment. There were no significant differences between groups in lung or kidney function, rates of hypotension, ventilator settings, or use of dialysis or vasopressors. Approximately 90 percent of protocol instructions were followed in both groups, with a 1 percent rate of crossover from CVC- to PAC-guided therapy. Fluid balance was similar in the two groups, as was the proportion of instructions given for fluid and diuretics. Dobutamine use was uncommon. The PAC group had approximately twice as many catheter-related complications (predominantly arrhythmias).

CONCLUSIONS

PAC-guided therapy did not improve survival or organ function but was associated with more complications than CVC-guided therapy. These results, when considered with those of previous studies, suggest that the PAC should not be routinely used for the management of acute lung injury. (ClinicalTrials.gov number, NCT00281268.)

The members of the Writing Committee (Arthur P. Wheeler, M.D., and Gordon R. Bernard, M.D., Vanderbilt University, Nashville; B. Taylor Thompson, M.D., and David Schoenfeld, Ph.D., Massachusetts General Hospital, Boston; Herbert P. Wiedemann, M.D., Cleveland Clinic, Cleveland; Ben deBoisblanc, M.D., Louisiana State University Health Sciences Center, New Orleans; Alfred F. Connors, Jr., M.D., Case Western Reserve University at MetroHealth Medical Center, Cleveland; R. Duncan Hite, M.D., Wake Forest University Health Sciences, Winston-Salem, N.C.; and Andrea L. Harabin, Ph.D., National Institutes of Health, Heart, Lung, and Blood Institute, Bethesda, Md.) assume responsibility for the integrity of the article. Address reprint requests to Dr. Wheeler at T-1217 MCN, Vanderbilt Medical Center, Nashville, TN 37232-2650, or at art.wheeler@vanderbilt.edu.

*Participants are listed in the Appendix.

This article was published at www.nejm.org on May 21, 2006.

N Engl J Med 2006;354:2213-24.

Copyright © 2006 Massachusetts Medical Society.

THE PULMONARY-ARTERY CATHETER (PAC) provides unique hemodynamic data, including the cardiac index and pulmonary-artery–occlusion pressure. People who advocate the use of the PAC note that the clinician’s ability to predict intravascular pressure with the use of this catheter is poor¹⁻³; central venous pressure, as obtained by means of the PAC, correlates imperfectly with pulmonary-artery–occlusion pressure⁴⁻⁶; and the insertion of a PAC often changes therapy.⁶⁻⁸ Although many critically ill patients receive PACs,⁹ no clear clinical benefit has been associated with their use.¹⁰⁻¹²

Practitioners often misinterpret the information obtained by means of a PAC or act incorrectly even when the data obtained with the use of this catheter are unambiguous, raising questions about the catheter’s value in usual practice.¹³⁻¹⁸ A number of retrospective, prospective uncontrolled, and cohort studies^{6,19-25} have raised questions about the safety of PACs, but because of their nonrandomized design, the results were not conclusive. Fears that the PAC could be harmful prompted calls for educational initiatives and even for a moratorium on its use until randomized trials were conducted.²⁶⁻²⁹ The results of randomized studies also cast doubt on the value of the PAC,³⁰⁻³⁵ but even these were regarded as inconclusive because of the studies’ small size, population selection, lack of a comparison group randomly assigned to central venous catheter (CVC)–guided therapy, or most important, lack of an explicit management protocol.³⁶⁻⁴⁰ To address these uncertainties, we conducted a randomized trial of the management of acute lung injury using an explicit hemodynamic protocol guided by blood pressure, urinary output, and the results of a physical examination plus data obtained with either a PAC (i.e., cardiac index and pulmonary-artery–occlusion pressure) or a CVC (i.e., central venous pressure). Oxygen delivery and central or mixed venous oxygen saturation were not used in the management protocol.

METHODS

STUDY DESIGN

The protocol for this multicenter factorial study, known as the Fluid and Catheter Treatment Trial (FACTT), can be found in the Supplementary Appendix, available with the full text of this article at www.nejm.org. Patients who had had acute lung

injury for 48 hours or less were randomly assigned in permuted blocks of eight to receive a PAC or a CVC with the use of an automated system. Hemodynamic data obtained from the catheter were combined with clinical measures for use in a standardized management protocol. Patients were simultaneously randomly assigned to a strategy of either liberal or conservative use of fluids guided by an explicit protocol (described in the Supplementary Appendix). Randomization was stratified according to hospital and the type of fluid therapy.

INCLUSION CRITERIA

Eligible patients were receiving positive-pressure ventilation by tracheal tube and had a ratio of the partial pressure of arterial oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) below 300 (adjusted if the altitude exceeded 1000 m) and bilateral infiltrates on chest radiography consistent with the presence of pulmonary edema not due to left atrial hypertension.⁴¹ If a potential participant did not have a CVC, the primary physician’s intent to insert one was required.

EXCLUSION CRITERIA

All reasons for exclusion are listed in Table 1 of the Supplementary Appendix. Major exclusion criteria were the presence of a PAC after the onset of acute lung injury; the presence of acute lung injury for more than 48 hours; an inability to obtain consent; the presence of chronic conditions that could independently influence survival, impair weaning, or compromise compliance with the protocol, such as dependence on dialysis or severe lung or neuromuscular disease; and irreversible conditions for which the estimated six-month mortality rate exceeded 50 percent, such as advanced cancer.

STUDY PROCEDURES

Ventilation according to the Acute Respiratory Distress Syndrome (ARDS) Network protocol of lower tidal volumes was begun within one hour after randomization and continued until day 28 or until the patient was breathing without assistance.⁴² The assigned catheter was inserted within four hours after randomization. A CVC inserted before randomization could be used to determine intravascular pressure in the CVC group. Hemodynamic management as dictated by the protocol was started within the next 2 hours and

continued for seven days or until 12 hours after the patient was able to breathe without assistance.⁴² The PAC could be replaced by a CVC if hemodynamic stability (defined by the absence of the need for protocol-directed interventions for more than 24 hours) was achieved after day 3. We recorded complications from all central catheters present during the hemodynamic-management period and for three days after their removal. For the purposes of tracking complications, each introducer, PAC, and CVC was considered a separate catheter. We monitored compliance with protocol instructions twice each day: once during a morning reference period and again at a randomly selected time. A 100 percent audit of all instructions conducted after the first 82 patients were enrolled showed rates of protocol compliance similar to those obtained during the random checks (data not shown).

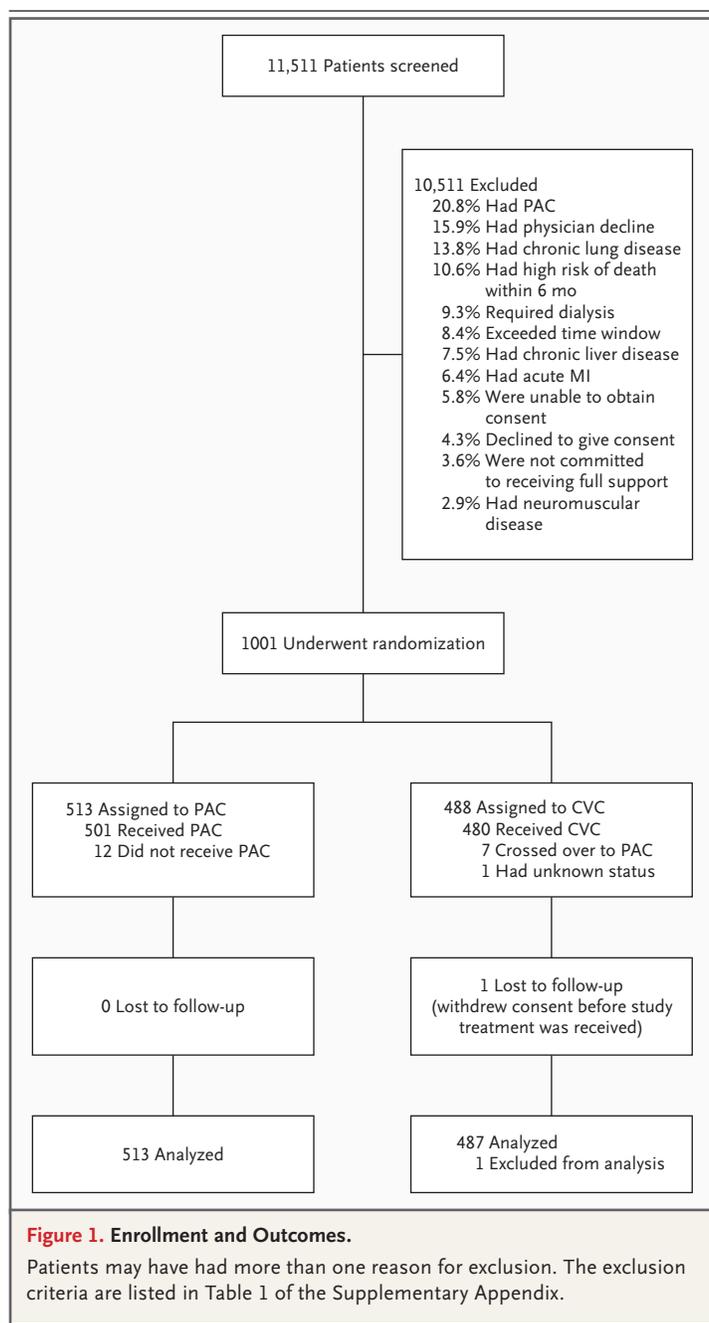
All study personnel underwent extensive training in the conduct of the protocol and the measurement of vascular pressure. They subsequently explained the study procedures to clinicians in the intensive care unit (ICU). Vascular pressures were measured in supine patients at end expiration; end expiration was identified with the use of an airway-pressure signal, but the vascular pressures used in the protocol were not adjusted for airway pressure.⁴³ Four main protocol variables were measured at least every four hours. Blood pressure and urinary output guided management in both groups. Pulmonary-artery-occlusion pressure and the cardiac index were included in the protocol in the PAC group, whereas central venous pressure and clinical assessment of circulatory effectiveness (i.e., skin temperature, appearance of the skin, and the rate of capillary refilling) were used in the CVC group. Lactate levels, the rate of oxygen delivery, and mixed venous and superior vena caval oxygen saturation were not used as protocol variables. Prompt reversal of hypotension, oliguria, and ineffective circulation was the overriding goal of the protocol. The treatment of patients in shock (defined by a mean systemic arterial pressure of less than 60 mm Hg or the need for vasopressors) was left to the judgment of the primary physician, with the exception that weaning from vasopressors was conducted according to the protocol after the patient's blood pressure had stabilized. Patients who were not in shock were prescribed fluids for oliguria and for ineffective circulation if central venous pressure or

pulmonary-artery-occlusion pressure was below the target range. Clinicians were free to select isotonic crystalloid, albumin, or blood products, although the protocol dictated the volume of each agent administered. Patients with ineffective circulation who were not in shock were given dobutamine with or without furosemide if their central venous pressure or pulmonary-artery-occlusion pressure exceeded the target range. Patients without hypotension who had adequate circulation and an intravascular pressure above the target range received furosemide. Patients who had a mean arterial pressure of at least 60 mm Hg without the use of vasopressors, a urinary output of at least 0.5 ml per kilogram of body weight per hour, and in the CVC group, adequate circulation on the basis of a physical examination or in the PAC group, a cardiac index of at least 2.5 liters per minute per square meter of body-surface area, received furosemide or fluids to return their intravascular pressure to the target range.

The study was approved by a protocol-review committee of the National Institutes of Health, National Heart, Lung, and Blood Institute, and the institutional review board at each participating location. Written consent was obtained from participants or legally authorized surrogates. An independent data and safety monitoring board conducted interim analyses after 82 patients had been enrolled and after each enrollment of approximately 200 patients. Sequential stopping rules for safety and efficacy used the method of O'Brien and Fleming.

STATISTICAL ANALYSIS

The study had a statistical power of 90 percent to detect a reduction by 10 percentage points in the primary end point, death before hospital discharge home during the first 60 days after randomization, with the planned enrollment of 1000 patients. We assumed patients who went home alive and without the use of a ventilator before day 60 were alive at 60 days. Data on patients who were receiving ventilation or in a hospital were censored on the last day of follow-up. The Kaplan-Meier method was used to estimate the mean (\pm SE) 60-day mortality rate, at the time of the last death occurring before 60 days. Differences in mortality between the groups were assessed by a *z* test. The primary analysis was conducted according to the intention to treat and on the basis of treatment-group assignment. Differences in continuous vari-



ables were assessed by analysis of variance. Differences in categorical variables were assessed by the Mantel–Haenszel test. Differences between continuous variables over time were assessed by repeated-measures analysis of variance. All analyses were stratified according to the fluid-therapy assignment. For continuous variables, means \pm SE are reported. Two-sided P values of 0.05 were considered to indicate statistical significance. Analy-

sis was conducted with the use of SAS software, version 8.2.

RESULTS

ENROLLMENT AND EXCLUSIONS

Screening for eligible patients was conducted at 20 North American centers between June 8, 2000, and October 3, 2005. The trial was halted on July 25, 2002, for a review by the Office of Human Research Protection and resumed unchanged except for the introduction of a modified consent form on July 23, 2003.⁴⁴⁻⁴⁶ Figure 1 shows the most common reasons for exclusion for the 10,511 patients who were screened but not enrolled and the follow-up for the 513 patients who were randomly assigned to PAC-guided therapy and the 488 who were assigned to CVC-guided therapy. All exclusions are listed in Table 1 of the Supplementary Appendix.

BASELINE CHARACTERISTICS

The two groups were similar with respect to demographic characteristics, ICU location, cause of lung injury, coexisting illnesses, and measures of the severity of illness at baseline (Table 1). Approximately 37 percent of patients in the PAC group and 32 percent of patients in the CVC group ($P=0.06$) met the criteria for shock, with 36 percent of patients in the PAC group receiving a vasopressor, as compared with 30 percent of patients in the CVC group ($P=0.05$) (Table 1). Tidal volume, $\text{PaO}_2:\text{FiO}_2$, pH, plateau pressure, oxygenation index, lung injury score, and hemoglobin levels were similar in the two groups. Similar percentages of each group were assigned to each fluid-therapy strategy (data not shown).

MAIN OUTCOMES

The rate of death during the first 60 days after randomization was similar in the PAC group and the CVC group (27.4 percent and 26.3 percent, respectively; $P=0.69$; absolute difference, 1.1 percent; 95 percent confidence interval, -4.4 to 6.6 percent), as were the number of ventilator-free days in the first 28 days (13.2 ± 0.5 and 13.5 ± 0.5 , respectively; $P=0.58$) (Fig. 2). CVC recipients had more ICU-free days during the first week of the study (0.88 day, vs. 0.66 day in the PAC group; $P=0.02$); however, these differences were small and not significant at day 28 (12.5 ± 0.5 vs. 12.0 ± 0.4 , $P=0.40$). The number of days without various

Table 1. Baseline and Postrandomization Characteristics.*

Characteristic	PAC Group (N=513)	CVC Group (N=487)	P Value
Age — yr	49.9±0.7	49.6±0.7	0.81
Female sex — %	46	47	0.89
Primary lung injury — %			0.81
Pneumonia	48	46	
Severe sepsis	23	24	
Aspiration	15	15	
Trauma	8	7	
Other	7	8	
Medical ICU — %	66	66	0.91
APACHE III score†	94.7±1.4	93.5±1.4	0.55
Coexisting conditions — no./total no. (%)			
Diabetes	89/500 (18)	84/467 (18)	0.94
HIV infection or AIDS	30/500 (6)	41/467 (9)	0.10
Cirrhosis	15/500 (3)	18/467 (4)	0.46
Solid tumors	7/500 (1)	8/467 (2)	0.71
Leukemia	14/500 (3)	8/467 (2)	0.27
Lymphoma	7/500 (1)	6/467 (1)	0.88
Immunosuppression	47/500 (9)	31/467 (7)	0.12
Hemodynamic variables			
Mean arterial pressure — mm Hg	77.5±0.7	76.8±0.6	0.41
Met shock criteria — %	37	32	0.06
Vasopressor use — %	36	30	0.05
Respiratory variables			
Tidal volume — ml/kg of PBW	7.4±0.1	7.4±0.1	0.88
Plateau pressure — cm of water	26.2±0.4	26.2±0.4	0.93
PEEP — cm of water	9.3±0.2	9.7±0.2	0.09
pH	7.36±0.0	7.36±0.0	0.79
PaO ₂ :FiO ₂	158.9±3.3	151.3±3.1	0.10
Bicarbonate — mmol/liter	22.3±0.2	22.3±0.2	0.93
Oxygenation index‡	12.8±0.4	13.3±0.5	0.48
Lung injury score§	2.7±0.0	2.8±0.0	0.05
Intervals — hr			
From ICU admission to first instruction	44.4±1.8	40.8±2.5	0.23
From qualification for acute lung injury to first instruction	25.2±0.7	23.0±0.6	0.02
From randomization to first protocol instruction	3.45±0.1	2.15±0.1	<0.001
Prerandomization fluids — ml			
24-Hr fluid intake	4919±171	4943±168	0.99
24-Hr fluid output	2233±82	2189±74	0.70

* Plus-minus values are means ±SE. HIV denotes human immunodeficiency virus, AIDS acquired immunodeficiency syndrome, PBW predicted body weight, and PEEP positive end-expiratory pressure.

† Scores for the Acute Physiology and Chronic Health Evaluation (APACHE) III can range from 0 to 299, with higher scores indicating a higher probability of death.

‡ The oxygenation index was calculated as the (mean airway pressure × FiO₂:PaO₂) × 100.

§ Scores can range from 0 to 4, with higher scores indicating more severe lung injury.

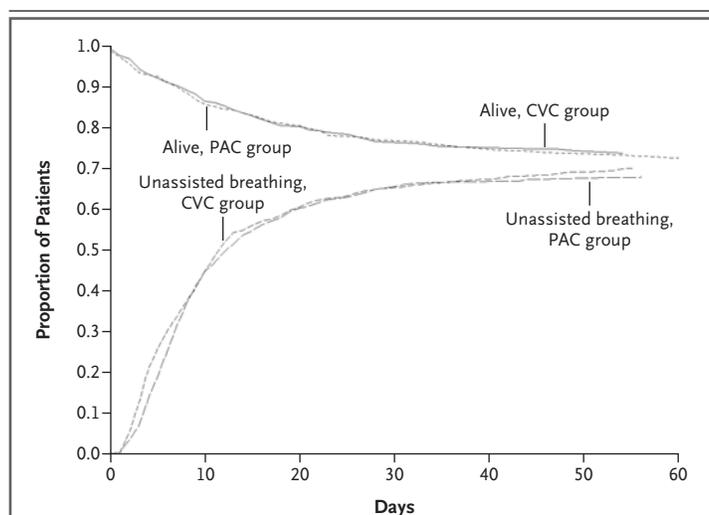


Figure 2. Kaplan–Meier Estimates of the Probability of Survival and of Survival without the Need for Assisted Ventilation during the First 60 Days after Randomization.

types of organ failure did not differ significantly between groups (Table 2 of the Supplementary Appendix). In the subgroup with shock at study entry, there were no significant differences between groups in the mortality rate or the number of organ-failure-free days (Table 3 of the Supplementary Appendix). There was no interaction between the type of catheter and the type of fluid therapy assigned.

ADVERSE EVENTS

Complications were uncommon and were reported at similar rates in each group: 0.08 ± 0.01 per catheter inserted in the PAC group and 0.06 ± 0.01 per catheter inserted in the CVC group ($P=0.35$). As compared with the CVC group, the PAC group had roughly 50 percent more catheters inserted (2.47 ± 0.05 vs. 1.64 ± 0.04 , $P<0.001$) and thus had a higher total number of complications, most of which were arrhythmias (Table 2). No deaths were related to the insertion of a catheter.

PROTOCOL CONDUCT AND INSTRUCTIONS

Patients in both groups had been in the ICU for approximately two days before beginning protocol-directed therapy (Table 1). The time from the documentation of acute lung injury to receipt of the first protocol instruction averaged about one day but was approximately two hours longer for the PAC group than the CVC group. This two-hour

difference was predominantly related to the longer time needed to insert the PAC after randomization (Table 1). Among patients assigned to receive PAC-guided therapy, 12 did not receive a PAC: 5 had exclusion criteria that were discovered after randomization, 5 withdrew consent, 1 died before a catheter could be placed, and 1 had complete heart block during insertion. All but one patient assigned to CVC-directed therapy received a CVC, but seven also had a PAC inserted (one on day 0, two on day 1, one on day 2, two on day 3, and one on day 6).

PAC recipients received more management instructions per day than did CVC recipients (4.8 ± 0.1 vs. 4.4 ± 0.2 , $P=0.03$). However, the PAC and CVC groups received similar proportions of protocol instructions for fluid (10 ± 1 percent and 12 ± 1 percent, respectively; $P=0.10$) and diuretic administration (27 ± 1 percent and 24 ± 1 percent, respectively; $P=0.16$). Dobutamine use was uncommon in both groups (7 percent in the PAC group and 2 percent in the CVC group, $P<0.001$). Instructions were followed at similar rates in the PAC and CVC groups (91 ± 1 percent and 88 ± 1 percent, respectively; $P=0.12$).

HEMODYNAMICS

The distribution of initial pulmonary-artery-occlusion pressures and central venous pressures is shown in Figure 3. Among patients in the PAC group, 29 percent had a pulmonary-artery-occlusion pressure of more than 18 mm Hg, 8 percent had a cardiac index below 2.5 liters per minute per square meter, and 3 percent had both values. Approximately half of all pulmonary-artery-occlusion pressures that exceeded 18 mm Hg were either 19 or 20 mm Hg. Figure 4 shows the mean arterial pressure, prevalence of vasopressor use, net fluid balance, mean pulmonary-artery-occlusion pressure, central venous pressure, heart rate, and cardiac index during the study. The proportion of patients in shock did not differ significantly between groups during the study. Among patients who were in shock at the time of enrollment, they met criteria for shock in 39 percent of reassessments in the PAC group and 40 percent of reassessments in the CVC group ($P=0.73$). Those who were not in shock at enrollment met the criteria for shock in only 6 percent of all reassessments in the PAC group and 7 percent of reassessments in the CVC group ($P=0.42$).

Table 2. Catheter-Related Complications.

Complication	PAC Group				CVC Group		
	Sheath	PAC	CVC	Total	Sheath	CVC	Total
	<i>number of patients</i>						
Technical and mechanical complications							
Difficult placement	1	8	1	10	0	2	2
Catheter malfunction	0	4	0	4	0	0	0
Pneumothorax	3	2	1	6	0	6	6
Air embolism	1	1	1	3	0	0	0
Arterial puncture	1	0	2	3	0	0	0
Arrhythmia							
Atrial	3	15	0	18	0	0	0
Ventricular	4	15	0	19	1	5	6
Conduction defect	1	4	0	5	1	0	1
Bleeding and clotting							
Hemothorax	2	1	0	3	1	0	1
Insertion-site bleeding	2	1	3	6	1	2	3
Thromboembolism	0	0	0	0	1	0	1
Local thrombosis	1	1	1	3	0	6	6
Infection							
Local	3	2	7	12	1	8	9
Bloodstream*	1	3	1	5	0	3	3
Other	0	2	1	3	0	3	3
Total	23	59	18	100	6	35	41

* Positive blood cultures were believed to be related to the presence of the catheter. Overall, 19 percent of patients in the PAC group and 18 percent of patients in the CVC group had one or more positive blood cultures (P=0.43).

LUNG FUNCTION

Ventilator settings and lung-function measures were similar in the two groups over time, with no significant differences in the respiratory rate, tidal volume, positive end-expiratory pressure, plateau pressure, PaO₂:FiO₂, pH, partial pressure of arterial carbon dioxide, oxygenation index, or lung injury score (Table 4 of the Supplementary Appendix).

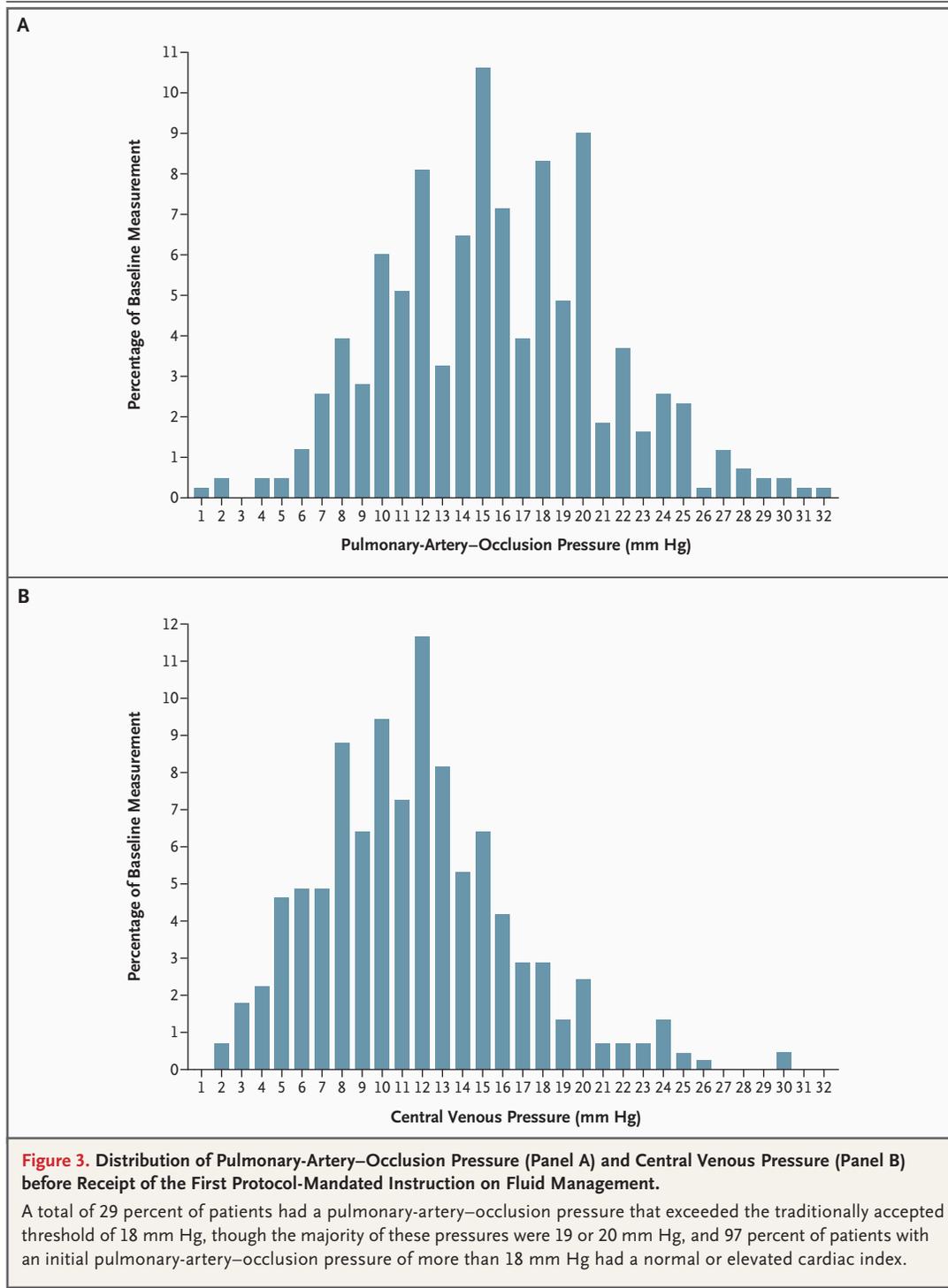
METABOLIC AND RENAL FUNCTION

While the hemodynamic management protocol was in use, there were no significant differences between groups in electrolyte, albumin, or hemoglobin levels (data not shown), although a higher percentage of patients in the PAC group than in the CVC group received erythrocyte transfusions

(38 percent vs. 30 percent, P=0.008). There were no significant differences between groups in the percentage of patients treated with kidney-replacement therapy (14 percent in the PAC group vs. 11 percent in the CVC group, P=0.15).

DISCUSSION

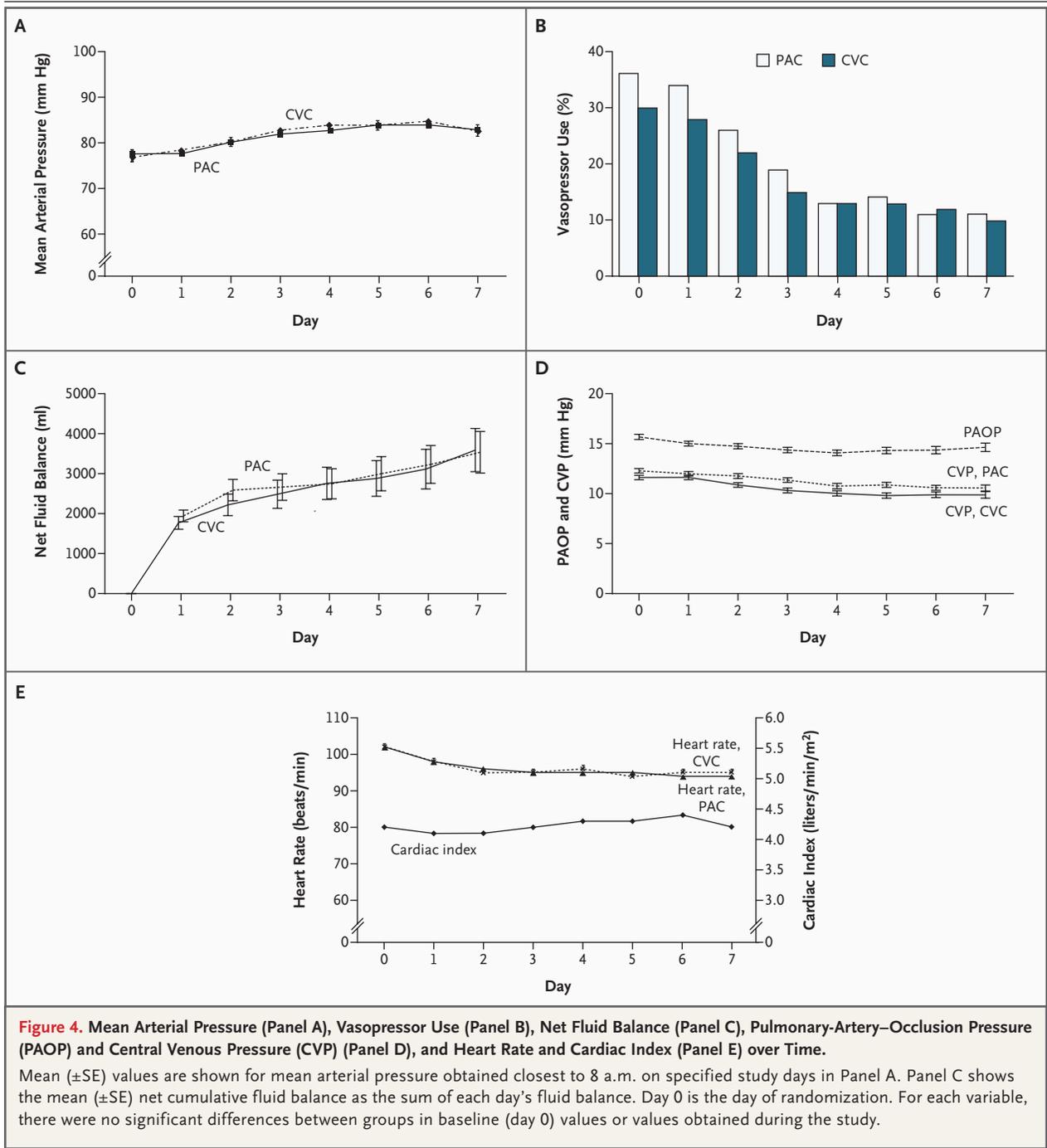
Because the PAC provides unique physiological information, it has been assumed that the use of this catheter would improve survival and decrease the duration of assisted ventilation and the rate of organ failure among patients with acute lung injury. Eroding this belief are observational and prospective trials indicating that such outcomes are not improved and may even be worsened by PAC use.¹⁹⁻²⁵ Since the initiation of this study, random-



ized trials of patients undergoing high-risk surgery,³¹ patients with the acute respiratory distress syndrome and sepsis,³² those with congestive heart failure,³⁴ and those with general critical illness^{33,35} have reported no benefit from PAC insertion. How-

ever, these studies were limited by the inclusion of relatively small numbers of patients and the lack of a strictly defined treatment protocol.

Prevention or reversal of organ failure is a common justification to insert a PAC, but we



were unable to identify any reduction in the incidence or the duration of any type of organ failure or the need for support (e.g., vasopressors, assisted ventilation, or kidney-replacement therapy) by using a PAC even in the subgroup of patients with shock at study entry. Likewise, PAC-guided therapy did not hasten discharge from the ICU; if

anything, CVC use was associated with more ICU-free time during the first seven days. However, the small differences seen could be artifactual. For example, patients with a CVC might be able to be transferred from the ICU sooner than patients with a PAC because CVCs are often allowed on regular medical–surgical floors.

The initial pulmonary-artery–occlusion pressure was greater than the traditional upper boundary of 18 mm Hg for acute lung injury in 29 percent of the patients. Since the cardiac index was normal in the vast majority of these patients (98 percent), cardiac failure is an unlikely explanation for the elevated pressure. On the basis of the results of protocols with a conservative approach to fluid administration and protocols with a liberal approach to fluid administration, as explained by Wiedemann et al. (available at www.nejm.org),⁴⁷ identification of an initially elevated pulmonary-artery–occlusion pressure did not translate into improved clinical outcomes, perhaps because both protocols mandated that diuretic therapy be given to lower the pulmonary-artery–occlusion pressure into a target range. Although uncommon, when the cardiac index was below 2.5 liters per minute per square meter, the protocol provided instructions for the administration of dobutamine, an inotropic and afterload-reducing agent.

Even though serious catheter-related complications were uncommon and there were no deaths related to insertion, more catheter-related complications occurred among patients given a PAC than among those given a CVC. These were predominantly arrhythmias: roughly half were atrial and half ventricular. Conduction block was also reported with the use of PACs but not CVCs. This observation is qualitatively similar to the increase in cardiac complications observed by Polanczyk et al. among patients undergoing noncardiac surgery.²⁴ Analysis of catheter-related complications is complex. Each catheter inserted in the PAC group appeared to carry a risk similar to that of a catheter inserted in the CVC group; however, almost one and a half times as many catheters were inserted in patients in the PAC group, a finding partly explained by the insertion of an introducer through which the PAC is typically passed. Ascertainment bias in arrhythmia reporting may also have occurred. Since we prohibited patients from having a PAC before entry, all PACs and many introducers were inserted under close observation during the study. In contrast, many CVCs were inserted before randomization; thus, arrhythmias occurring during insertion may not have been documented.

The strengths of this study include its size; randomized, multicenter design with concealed allocation; explicit methods; use of objective end points; and high rate of clinician compliance. Ex-

tensive pretrial training of study personnel in the conduct of the protocol and intravascular-pressure measurement, centralized review of pressure tracings, and use of airway-pressure signals to facilitate identification of end expiration most likely increased levels of accuracy and precision.⁴³ The use of explicit protocols for hemodynamic and ventilator management, rather than usual care or general guidelines as in previous studies, makes it clear how patients were treated.

Our study had several weaknesses. One common to all such trials is the inability to mask catheter assignment; however, the selection of objective end points including death and organ-failure-free days reduces the impact of this shortcoming. The low rate of crossover to the other catheter group and the high rate of compliance with the protocol in both groups, as assessed by scheduled daily and additional random checks, suggest both that absence of blinding had little effect on the results and that clinical equipoise was maintained after randomization. Owing to the small number of patients and the lack of stratification, we were unable to exclude potentially beneficial effects of a PAC in subgroups of patients. Nevertheless, we saw no hint of improved outcomes in the PAC group, with the mortality rate nominally lower in the CVC group. Furthermore, because the majority of patients were enrolled in medical ICUs, the relevance of our results to other types of patients is unclear. In addition, among others, we excluded patients with congestive heart failure, patients with severe obstructive and restrictive lung disease, and those receiving dialysis, so our study does not provide information on the value of the PAC in those groups. Finally, it could be argued that despite extensive development by experts, iterative pilot testing, and high rates of compliance with the protocol, the hemodynamic-protocol rules used did not optimize the benefits of the PAC as compared with the CVC.

When considered with the results of previous randomized trials, our results suggest that the PAC is not useful for routine hemodynamic management in patients with established acute lung injury and is associated with more complications than the CVC. Our results do not address the safety or benefits of the PAC as a diagnostic tool or in other conditions, such as early resuscitation from septic shock. Similarly, our data do not address the safety or efficacy of PACs when they are

used with other protocols, in patients who have had acute lung injury for more than 48 hours, or in those with concomitant diseases who were excluded from our study.

Supported by contracts (NO1-HR-46054-64 and NO1-HR-16146-54) with the National Institutes of Health, National Heart, Lung, and Blood Institute.

No potential conflict of interest relevant to this article was reported.

APPENDIX

The following persons and institutions participated in the Fluid and Catheter Treatment trial: **Writing Committee** — A.P. Wheeler, H.P. Wiedemann, G.R. Bernard, B.T. Thompson, B. deBoisblanc, A.F. Connors, R.D. Hite, D.A. Schoenfeld, A.L. Harabin; **Steering Committee chair** — G.R. Bernard; **Clinical Coordinating Center** — D.A. Schoenfeld, B.T. Thompson, N. Ringwood, C. Oldmixon, F. Molay, A. Korpak, R. Morse, D. Hayden, M. Ancukiewicz, A. Minihan; **Protocol-Review Committee** — J.G.N. Garcia, R. Balk, S. Emerson, M. Shasby, W. Sibbald; **Data and Safety Monitoring Board** — R. Spragg, G. Corbie-Smith, J. Kelley, K. Leeper, A.S. Slutsky, B. Turnbull, C. Vreim; **National Heart, Lung, and Blood Institute** — A.L. Harabin, D. Gail, P. Lew, M. Waclawiw; **Clinical Centers** — *University of Washington, Harborview* — L. Hudson, K. Steinberg, M. Neff, R. Maier, K. Sims, C. Cooper, T. Berry-Bell, G. Carter, L. Andersson; *University of Michigan* — G.B. Toews, R.H. Bartlett, C. Watts, R. Hyzy, R. Arnoldi, R. Dechert, M. Purple; *University of Maryland* — H. Silverman, C. Shanholtz, A. Moore, L. Heinrich, W. Corral; *Johns Hopkins University* — R. Brower, D. Thompson, H. Fessler, S. Murray, A. Sculley; *Cleveland Clinic Foundation* — H.P. Wiedemann, A.C. Arroliga, J. Komara, T. Isabella, M. Ferrari; *University Hospitals of Cleveland* — J. Kern, R. Hejal, D. Haney; *MetroHealth Medical Center* — A.F. Connors; *University of Colorado Health Sciences Center* — E. Abraham, R. McIntyre, F. Piedalua; *Denver Veterans Affairs Medical Center* — C. Welch; *Denver Health Medical Center* — I. Douglas, R. Wolkin; *St. Anthony Hospital* — T. Bost, B. Sagel, A. Hawkes; *Duke University* — N. MacIntyre, J. Govert, W. Fulkerson, L. Mallatrat, L. Brown, S. Everett, E. VanDyne, N. Knudsen, M. Gentile; *University of North Carolina* — P. Rock, S. Carson, C. Schuler, L. Baker, V. Salo; *Vanderbilt University* — A.P. Wheeler, G.R. Bernard, T. Rice, B. Christman, S. Bozeman, T. Welch; *University of Pennsylvania* — P. Lancken, J. Christie, B. Fuchs, B. Finkel, S. Kaplan, V. Gracias, C.W. Hanson, P. Reilly, M.B. Shapiro, R. Burke, E. O'Connor, D. Wolfe; *Jefferson Medical College* — J. Gottlieb, P. Park, D.M. Dillon, A. Girod, J. Furlong; *LDS Hospital* — A. Morris, C. Grissom, L. Weaver, J. Orme, T. Clemmer, R. Davis, J. Gleed, S. Pies, T. Graydon, S. Anderson, K. Bennion, P. Skinner; *McKay-Dee Hospital* — C. Lawton, J. d'Hulst, D. Hanselman; *Utah Valley Regional Medical Center* — K. Sundar, T. Hill, K. Ludwig, D. Nielson; *University of California, San Francisco, San Francisco* — M.A. Matthay, M. Eisner, B. Daniel, O. Garcia; *San Francisco General* — J. Luce, R. Kallet; *University of California, San Francisco, Fresno* — M. Peterson, J. Lanford; *Baylor College of Medicine* — K. Guntupalli, V. Bandi, C. Pope; *Baystate Medical Center* — J. Steingrub, M. Tidswell, L. Kozikowski; *Louisiana State University* — B. deBoisblanc, J. Hunt, C. Glynn, P. Lauto, G. Meyaski, C. Romaine; *Louisiana State University—Earl K. Long* — S. Brierre, C. LeBlanc, K. Reed; *Alton-Ochsner Clinic Foundation* — D. Taylor, C. Thompson; *Tulane University Medical Center* — F. Simeone, M. Johnston, M. Wright; *University of Chicago* — G. Schmidt, J. Hall, S. Hemmann, B. Gehlbach, A. Vinayak, W. Schweickert; *Northwestern University* — J. Dematte D'Amico, H. Donnelly; *University of Texas Health Sciences Center* — A. Anzueto, J. McCarthy, S. Kucera, J. Peters, T. Houlihan, R. Steward, D. Vines; *University of Virginia* — J. Truwit, M. Marshall, W. Matsumura, R. Brett; *University of Pittsburgh* — M. Donahoe, P. Linden, J. Puyana, L. Lucht, A. Verno; *Wake Forest University* — R.D. Hite, P. Morris, A. Howard, A. Nesser, S. Perez; *Moses Cone Memorial Hospital* — P. Wright, C. Carter-Cole, J. McLean; *St. Paul's Hospital—Vancouver* — J. Russell, L. Lazowski, K. Foley; *Vancouver General Hospital* — D. Chittock, L. Grandolfo; *Mayo Foundation* — M. Murray.

REFERENCES

- Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. *Crit Care Med* 1984;12:549-53.
- Steingrub JS, Celoria G, Vickers-Lahti M, Teres D, Bria W. Therapeutic impact of pulmonary artery catheterization in a medical/surgical ICU. *Chest* 1991;99:1451-5.
- Ferguson ND, Meade MO, Hallett DC, Stewart TE. High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome. *Intensive Care Med* 2002;28:1073-7.
- Civetta JM, Gabel JC. Flow directed-pulmonary artery catheterization in surgical patients: indications and modifications of technic. *Ann Surg* 1972;176:753-6.
- Forrester JS, Diamond G, McHugh TJ, Swan HJC. Filling pressures in the right and left sides of the heart in acute myocardial infarction: a reappraisal of central-venous-pressure monitoring. *N Engl J Med* 1971;285:190-3.
- Marinelli WA, Weinert CR, Gross CR, et al. Right heart catheterization in acute lung injury: an observational study. *Am J Respir Crit Care Med* 1999;160:69-76.
- Mimoz O, Rauss A, Rekiq N, Brun-Buisson C, Lemaire F, Brochard L. Pulmonary artery catheterization in critically ill patients: a prospective analysis of outcome changes associated with catheter-prompted changes in therapy. *Crit Care Med* 1994;22:573-9.
- Connors AF Jr, McCaffree DR, Gray BA. Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. *N Engl J Med* 1983;308:263-7.
- Chalfin DB. The pulmonary artery catheter: economic aspects. *New Horiz* 1997;5:292-6.
- 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.
- Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;94:1176-86.
- Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA* 2005;294:1664-70.
- Gnaegi A, Feihl F, Perret C. Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act? *Crit Care Med* 1997;25:213-20.
- Iberti TJ, Fischer EP, Leibowitz AB, Panacek EA, Silverstein JH, Albertson TE. A multicenter study of physicians' knowledge of the pulmonary artery catheter. *JAMA* 1990;264:2928-32.
- Jacka MJ, Cohen MM, To T, Devitt JH, Byrick R. Pulmonary artery occlusion pressure estimation: how confident are anesthesiologists? *Crit Care Med* 2002;30:1197-203.
- Burns D, Burns D, Shively M. Critical care nurses' knowledge of pulmonary artery catheters. *Am J Crit Care* 1996;5:49-54.
- Jain M, Canham M, Upadhyay D, Corbridge T. Variability in interventions with pulmonary artery catheter data. *Intensive Care Med* 2003;29:2059-62.
- Ontario Intensive Care Study Group.

- Evaluation of right heart catheterization in critically ill patients. *Crit Care Med* 1992; 20:928-33.
19. Afessa B, Spencer S, Khan W, LaGatta M, Bridges L, Freire AX. Association of pulmonary artery catheter use with in-hospital mortality. *Crit Care Med* 2001;29:1145-8.
 20. 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.
 21. Zion MM, Balkin J, Rosenmann D, et al. Use of pulmonary catheters in patients with acute myocardial infarction: analysis of experience in 5,841 patients in the SPRINT Registry. *Chest* 1990;98:1331-5.
 22. Sakr Y, Vincent JL, Reinhart K, et al. Use of the pulmonary artery catheter is not associated with worse outcome in the ICU. *Chest* 2005;128:2722-31.
 23. Cohen MG, Kelly RV, Kong DF, et al. Pulmonary artery catheterization in acute coronary syndromes: insights from the GUSTO IIb and GUSTO III trials. *Am J Med* 2005;118:482-8.
 24. 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.
 25. 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.
 26. 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.
 27. Robin ED. The cult of the Swan-Ganz catheter: overuse and abuse of pulmonary flow catheters. *Ann Intern Med* 1985;103:445-9.
 28. Dalen JE, Bone RC. Is it time to pull the pulmonary artery catheter? *JAMA* 1996; 276:916-8.
 29. Dalen JE. The pulmonary artery catheter — friend, foe, or accomplice? *JAMA* 2001;286:348-50.
 30. Guyatt G. A randomized control trial of right-heart catheterization in critically ill patients. *J Intensive Care Med* 1991; 6:91-5.
 31. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5-14.
 32. Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2003; 290:2713-20.
 33. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005;366:472-7.
 34. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 2005;294:1625-33.
 35. Rhodes A, Cusack RJ, Newman PJ, Grounds RM, Bennett ED. A randomized, controlled trial of the pulmonary artery catheter in critically ill patients. *Intensive Care Med* 2002;28:256-64.
 36. Morris AH. Developing and implementing computerized protocols for standardization of clinical decisions. *Ann Intern Med* 2000;132:373-83.
 37. *Idem*. Treatment algorithms and protocolized care. *Curr Opin Crit Care* 2003; 9:236-40.
 38. 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.
 39. Walker MB, Waldmann CS. The use of pulmonary artery catheters in intensive care: time for reappraisal? *Clin Intensive Care* 1994;5:15-9.
 40. Angus D, Black N. Wider lessons of the pulmonary artery catheter trial. *BMJ* 2001;322:446.
 41. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.
 42. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
 43. Rizvi K, Deboisblanc BP, Truwi JD, et al. Effect of airway pressure display on interobserver agreement in the assessment of vascular pressures in patients with acute lung injury and acute respiratory distress syndrome. *Crit Care Med* 2005;33:98-103.
 44. Drazen JM. Controlling research trials. *N Engl J Med* 2003;348:1377-80.
 45. Steinbrook R. How best to ventilate? Trial design and patient safety in studies of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:1393-401.
 46. Steinbrook R. Trial design and patient safety — the debate continues. *N Engl J Med* 2003;349:629-30.
 47. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Comparison of two fluid management strategies in acute lung injury. (Available at www.nejm.org)

Copyright © 2006 Massachusetts Medical Society.

CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see *N Engl J Med* 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.