The pulmonary artery catheter – a personal view

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Abstract

The pulmonary artery catheter (PAC) was introduced into critical care medicine without objective evidence of its efficacy. The direct risks from the PAC are around 1.5% for a serious complication and 0.2% for death.

The Connors study on 5,735 intensive care patients used case-matching techniques, and demonstrated a worse outcome in the PAC cohort. However, in this study the need for inotropes and the response to treatment were excluded from the regression analysis. Three further studies have failed to show an association between PAC placement and outcome after case-mix adjustment.

It has proved extremely difficult to recruit enough intensive care patients to exclude a clinically important mortality benefit of the PAC.

New techniques such as the oesophageal Doppler, pulse contour continuous cardiac output and lithium dilution cardiac output machines offer simpler, and perhaps better, alternatives to the PAC. Nonetheless, even if future trials are negative, the PAC should remain available for treatment of patients with unusual conditions or combinations of conditions.

Key words: pulmonary artery catheter, outcome, complications, survival benefit, randomised controlled trials, haemodynamic monitoring.

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Introduction

The pulmonary artery catheter (PAC) has been such an integral part of critical care medicine that it now seems surprising that there was no objective evidence of efficacy at the time of its introduction. For more than 20 years there was simply a prevailing assumption that the haemodynamic measurements offered by the PAC must benefit patients. A randomised trial of PAC efficacy would have been considered as unethical as a trial of pulse oximetry in anaesthetised patients.

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Since the 1980s, however, there has been increasing concern that the PAC might offer no therapeutic benefit, or might even be harmful in certain patient groups.[1,2] These early data came from retrospective observational studies of patients with acute myocardial infarction and were not immediately relevant to general critical care patients. Perhaps understandably, there still remained insufficient scepticism about the benefits of the PAC to allow a prospective randomised trial of efficacy.

In 1996, the PAC debate was given new impetus by a prospective cohort study of general critical care patients conducted by Connors and colleagues.[3] This paper used sophisticated case-mix matching techniques to demonstrate a worse outcome in the PAC cohort. Whatever the intrinsic merits of the Connors study, which is discussed in more detail below, there is no doubt that it changed the opinion of enough intensivists to enable successful recruitment of patients to randomised trials. In the last 18 months the earliest of several large randomised controlled trials which address the role of the PAC have finally been published.[4,5] This review is an attempt to place these new data in context and to address some of the key points in the debate concerning the PAC.

Direct complications from the PAC

Mechanical complications

The one certain fact facing the clinician considering placement of a PAC is that the patient will be at inevitable risk of a formidable list of direct complications (table 1). In the largest published

Table 1. Direct complications of pulmonary artery catheterisation

	Shah[6]	Sandham[4]	Richard[5]
Number of patients	6,245	941	335
Carotid artery puncture	120 (1.9%)	3 (0.3%)	17 (5%)
Pneumothorax	31 (0.5%)	8 (0.9%)	no data
Haemothorax	0	2 (0.2%)	1 (0.3%)
Pulmonary haemorrhage	4 (0.06%)	3 (0.3%)	no data
Pulmonary embolism	no data	8 (0.8%)	0
Combined rates from the three studies			
Carotid artery puncture	1.9%		
Serious (i.e. all other) complications	1.5%		

series of 6,245 patients given a PAC prior to surgery, mechanical complication rates were low: carotid puncture in 129 patients (1.9%), unintentional cannulation of the carotid artery in four (0.06%), pneumothorax in 31 (0.5%) and intra-pulmonary haemorrhage in four (0.06%).[6] In a more recent series, 0.8% of patients with a PAC developed pulmonary embolism, and the combined rate of serious complications from three large studies is 1.5%.[4-6]

The low complication rates reported in the first study may be explained by the fact that all PACs were placed or closely supervised by experienced attending anaesthetists. It is likely of course that for less skilled operators in day-to-day practice, complication rates will be higher. For example, a recent observational study of central venous cannula insertion from a respected US centre where most procedures were performed by residents, found an arterial puncture rate of 7%.[7]

Infection risk

Comparisons of infection data concerning intravascular catheters are complicated by non-uniformity of definitions, different conventions for quoting infection rates and the wide variation in infection rates between hospitals.[8] Recent data endorsed by the Center for Diseases Control (CDC) indicate that for heparin-bonded PACs the risk of catheter-related bloodstream infection is similar to that of central venous catheters, namely 2.6 *vs.* 2.3 per 1,000 catheter days.[9] There is, however, substantial variation in catheter-related bloodstream infection rates, with some UK hospitals reporting rates as high as 19 per 1,000 catheter days for intensive care patients.[10] As nearly all patients with a PAC will also require a central venous catheter, it is clear that whatever the nosocomial infection rates in a particular hospital, the risk of bloodstream infection is effectively doubled by the presence of a PAC. Using reasonable estimates of an average period of insertion of three days,[9] 20% as the attributable mortality for bloodstream infection[11] and taking the low CDC estimates for bloodstream infection rates, this is equivalent to a risk of death of only 0.1–0.2% per patient with a PAC.

If there is a clinically significant benefit from the PAC then this risk is clearly unimportant compared with, for example, a risk of death of 40% for sepsis. However, even with a 0.1% risk of death, given the figure of 1.2 million PAC insertions annually in the US,[12] around 1,200 patients will die from infectious complications of the PAC per year in the US alone.

In summary, combining all complications, the risk of direct harm from the PAC is small, perhaps 1.5% for a serious complication and less than 0.2% for death. Nevertheless, these direct risks alone are sufficiently high to require full investigation of the efficacy of the PAC.

The Connors observational study data

As mentioned previously, the Connors study has been so influential that it is worth describing in some detail.[3] Connors and colleagues performed logistic regression analysis, using variables selected by expert opinion, on a data set of 5,735 intensive care patients. They first calculated a propensity score for each patient, which reflected the patient's likelihood of receiving a PAC. Patients who actually received a PAC were then matched with patients who did not receive a PAC but who had a similar propensity score. Because, as would be expected, the patients in the PAC group tended to have higher propensity scores, only 2,016 of the original 5,735 could be paired. For these propensity-matched patients, however, the PA catheter group had a worse outcome than the non-PA catheter group (54.6% *vs.* 59.9% 60-day survival). Secondly, the authors analysed the whole data set by predicting mortality for all patients after adjustment by the propensity score and other predictors of death such as severity of illness). This mortality prediction model demonstrated that for patients with a PAC, the relative hazard of death at 30 days was 1.21.

As part of a robust statistical approach the authors performed a sensitivity analysis. This indicated that a missing variable would have to increase the risk of death and the estimated probability of PAC insertion by a factor of three to make the relative hazard of PAC placement 1.0 (equivalent to no change in risk of death).

Although the study was statistically thorough, the choice of variables has been criticised.[13] Intensive care clinicians will be surprised that a need for inotropes and the response to treatment were excluded from the regression analysis. These are counter-intuitive omissions. Clearly, two patients can have identical severity of illness scores while one is deteriorating despite aggressive treatment and the other is improving with relatively modest intervention. Although both patients would receive the same propensity score in the Connors study, the sicker one is in fact much more likely to receive a PAC.

Several recent studies support the hypothesis that response and level of treatment might be important missing variables in the Connors study. An observational study of 4,182 patients at a major UK university hospital applied a similar method to Connors and colleagues but included treatment with inotropes as a variable.[14] In this study, the propensity score for PAC did predict outcome, but the actual presence of a PAC did not.

A smaller French study of 119 acute respiratory distress syn-

drome (ARDS) patients examined the effect of treatment with vasoactive drugs on a mortality prediction model.[15] The investigators initially found that use of the PAC was predictive of death (odds ratio 4.26), but when treatment with vasoactive drugs was included in a second analysis, use of the PAC was no longer predictive. Significantly, in this second analysis, treatment with vasoactive drugs had a sufficiently large effect on risk of death (odds ratio 7.36) to suggest that it could be the missing variable suggested in the sensitivity analysis of the Connors study.

Three further studies have failed to demonstrate any association between PAC placement and outcome after case-mix adjustment.[16-18] Although these studies together enrolled only 345 patients with a PAC, they add to the doubts about the validity of the Connors study.

The finding by Connors and colleagues of a substantial risk of death from PAC placement now seems likely to be a statistical artefact. There has never been a satisfactory explanation for the reported 5% absolute increase in death rate, which is much larger than the risk of death from direct complications. In addition, more recent observational studies using different case-mix adjustment models have failed to find an association between PAC placement and increased mortality.

Pragmatic randomised controlled trials of the PAC

In 1991 an attempt to recruit patients to a randomised trial of the PAC failed because of reluctance by physicians to withhold the PAC from patients in the control arm.[19] It was therefore a considerable achievement for Rhodes and colleagues to complete the first prospective trial of the PAC in 200 intensive care patients.[20] This was a pragmatic trial which did not direct PAC-guided treatment by protocol. As a reflection of the influence of the Connors study, only one patient was withdrawn because of ethical concerns about non-placement of a PAC. Unfortunately, though, the Rhodes study was under-powered and no firm conclusion could be drawn from their finding of no mortality difference between the PAC and control groups.

In late 2003, Richard and colleagues published a multicentre pragmatic trial of the PAC in patients with shock or acute respiratory distress syndrome.[5] In total, 676 patients were randomised to PAC-guided or control treatment groups. On an intention-to-treat analysis there was no difference between the groups in mortality (59.4% *vs.* 61.0% 28-day mortality PAC *vs.* control) or in any secondary end point. However, this study too is underpowered to exclude a clinically significant mortality difference between the groups. The authors calculate that the absolute mortality difference between the groups is likely (95% confidence) to be less than 7.8%. It is clear therefore that neither of these published randomised controlled trials (RCTs) taken alone is large enough to rule out the 5% absolute increase in mortality of the Connors study.

Goal-directed therapy and the PAC

Goal-directed therapy involves resuscitation by protocol to predefined end points. Protocols usually require generous fluid volumes and beta agonists to increase oxygen delivery to meet a version of the 'Shoemaker criteria'.[21] The majority of trials of goal-directed therapy have used protocols based on PAC-derived measurements. There have been several recent comprehensive reviews of goal-directed therapy but it is worth discussing briefly areas relevant to the PAC debate.[21-23]

Pragmatic versus goal-directed trials

Some commentators have suggested that pragmatic trials of the PAC are misguided since the treatments delivered to PAC and control groups are likely to be similar. By failing to direct therapy by protocol to particular end points pragmatic trials are 'missing the point', according to this view. However, it is worth considering the aim of each type of trial. Pragmatic trials address the question of whether the increased information available to clinicians improves management decisions and survival. Goal-directed trials address the efficacy of resuscitation to a specific end point monitored by the PAC. These are essentially independent questions and they require separate answers. There is, therefore, value in both types of trial. In fact, in one pragmatic trial there were significant differences in the volume of fluid administered to PAC and control groups in the first 24 hours.[20]

A current appraisal of goal-directed therapy

The evidence in favour of goal-directed therapy has until recently been largely based on small, and often methodologically flawed, trials.[22] A complicating factor has been apparently conflicting data suggesting that beta blockade improves outcome in high-risk vascular patients.[24] It has been suggested that attention should be focused on patients with early pathophysiology such as early sepsis or high-risk perioperative patients, but not patients with established multiorgan failure.[21]

There are now some encouraging data to support the hypothesis that goal-directed therapy works pre-emptively but cannot reverse established cellular dysfunction. Shoemaker has published a meta-analysis which demonstrated a positive effect for studies of early treatment, but no effect for studies of late treatment.[21] Rivers and colleagues recently demonstrated a reduction in mortality from 46.5% to 30.5%, in patients with early sepsis treated with goal-directed therapy guided by mixed venous oxygen saturation measurements from a central venous catheter.[25]

In the light of this evidence it is interesting to consider the RCT of the PAC in high-risk surgical patients by the Canadian Critical Care Clinical Trials Group.[4] This study randomised 1,994 elderly American Society of Anesthesiologists (ASA) class III or IV patients having high-risk surgery to goal-directed treatment with a PAC or standard care. The groups were well matched and, although there was a clear difference in treatment between groups, hospital mortality was 7.7% in the standard care group and 7.8% in the PAC group. The trial was large enough to exclude (with 95% confidence) an absolute mortality difference of 2.5% between the groups.

As this study included more than twice the total of 781 patients in the small trials of early goal-directed therapy, it is hard to underestimate its significance.[21] Furthermore, subgroup analy-

Table 2. Haemodynamic monitors

Monitor	Cardiac output	Pre-load index	Relative contraindications	Outcome data
Pulmonary artery catheter	Thermodilution	Pulmonary artery occlusion pressure	Tricuspid regurgitation Arrhythmias Clotting derangement	Meta-analysis of small studies showing mortality benefit in very high risk surgery[21]
Oesophageal Doppler	Doppler ultrasound	Corrected flow time (FT_C)	Awake patient Oesophageal varices Intra-aortic balloon pump	Few small studies with morbidity and length of stay as end point[28]
PiCCO	Trans-pulmonary thermodilution pulse-contour analysis	Global end-diastolic volume	Peripheral vascular disease Intra-aortic balloon pump	Small study in ARDS with length of stay as end point[29]
LidCO	Lithium dilution pulse-contour analysis	Stroke volume variability	First trimester of pregnancy Intra-aortic balloon pump	Nil
Svo_2-measuring central venous catheter	Nil	Central venous pressure	Nil	Evidence of mortality benefit in early sepsis from RCT[25]

Key: PiCCO = Pulse contour continuous cardiac output; LidCO = lithium dilution cardiac output; Svo_2 = mixed venous oxygen saturation

sis of the sickest patients in the Canadian study indicated no difference in mortality. This counts against the hypothesis that goal-directed therapy works only for patients with a peri-operative risk of death of greater than 20%.[21]

In summary, the PAC may yet be shown to benefit particular patient groups when treated with goal-directed therapy. However, additional small trials are unlikely to provide a clear answer and there is an urgent need for a large randomised trial directed at patients with a predicted peri-operative mortality of at least 20%.[21]

PAC and new technologies

When the PAC was introduced it was the only method of assessing cardiac output and left ventricular pre-load at the bedside. PAC-derived measurements are still often considered to be the gold standard. This is probably largely because the concept of pulmonary artery occlusion pressure (PAOP) as a pre-load index is physiologically transparent. Also, the complicated algorithms underlying cardiac output measurement by thermodilution are hidden from the clinician.

In fact, thermodilution methods of cardiac output measurement are unreliable in patients with tricuspid regurgitation.[26] In addition, there are multiple influences on PAOP which make it a poor index of left ventricular pre-load in ventilated, inotrope-dependent patients.[27] Although the deficiencies of PAC-derived indices have been extensively reviewed, they often seem to be forgotten at the bedside.[27]

New technologies such as the oesophageal Doppler, pulse contour continuous cardiac output (PICCO) and lithium dilution cardiac output (LidCO) machines and central venous lines adapted to measure venous oxygen saturation, offer simpler and perhaps better alternatives to the PAC (table 2). For example, global end-diastolic volume, the index of pre-load derived from PICCO, may be superior to the PAOP.[30] The oesophageal Doppler offers near 100% safety and takes a few minutes to use. Several of these methods have already been used in trials of goal-directed therapy.[25,29] While there are still insufficient data for any of the devices to supplant the need for the PAC completely, the clinician now has a choice of methods for assessing pre-load and cardiac output. Crucially, the PAC is no longer the *sine qua non* of goal-directed therapy.

Clinical trials in progress

There are two multicentre clinical trials in progress.[31,32] The PAC-Man study is a pragmatic UK study which had recruited 1,046 patients by June 2004.[31] Patients are randomised to PAC or standard care with (stratum A) or without (stratum B) an alternative flow measurement technique. Because of a lower recruitment rate than predicted, the study will be less powerful than planned. If there is no difference between the results in the two strata, then the study will have 90% power to detect a 10% difference in absolute mortality between PAC and non-PAC guided care.

The ARDSNet is running a protocol-guided study of 1,000 patients to examine the effect of PAC versus central venous catheter management in patients with ARDS.[32] Using a 2 x 2 factorial design the study will also compare a 'wet' and 'dry' fluid regimen. The study has a similar power to the PAC-Man study.

Summary

This review began with the observation that the PAC was introduced with no assessment of its safety or efficacy. It is, therefore, curious to reflect that it was eventually a flawed study which spurred the intensive care community to organise randomised controlled trials of the PAC.[3] Large RCTs, one of standard management in patients with sepsis and ARDS, the other of goal-directed therapy in high-risk surgical patients, have now failed to demonstrate survival benefit from the PAC.[4,5] The larger of these

Key messages

- For 20 years there was an assumption that the PAC was beneficial
- Despite flaws, the Connors study changed opinion in the intensive care community
- The risk of direct complications of the PAC is low and does not explain the Connors study result
- Recent data from observational studies and a RCT have confirmed that the PAC is unlikely to be harmful
- Goal-directed therapy with the PAC in high-risk surgical patients (control mortality 7%) does not alter mortality
- Very large trials are needed for adequate statistical power. It now seems impossible to recruit adequate numbers of patients to exclude a small but clinically important benefit from the PAC
- Even if future trials are negative, the PAC should remain available. Its use should then be limited to patients selected carefully on an individual basis

studies was able to exclude an absolute mortality difference of 2.5% between PAC-guided and non-PAC-guided treatment.[4] At the risk of pre-empting the results of the two ongoing trials, it is interesting to speculate what the reaction might be to further negative results. In my opinion it would be a mistake if there were renewed calls for a moratorium on the PAC.[33]

First, the ongoing trials are only powered to exclude a 10% reduction in absolute mortality. Opinions will differ about the minimum reduction that is clinically important. However, even a reduction in absolute mortality of less than 2.5% will seem valuable to many, given the low cost of the PAC. Using similar assumptions to the PAC-Man trial, a study designed to have 90% power to exclude a 2.5% difference in mortality between groups would have to enrol more than 15 000 patients.

Unfortunately, both the ongoing and completed trials have demonstrated the great difficulty of recruiting large numbers of intensive care patients over a reasonable period of time. One of the lessons from the randomised controlled trials seems to be that it is impossible to recruit enough patients to exclude a clinically important mortality benefit of the PAC.

Secondly, even very large randomised controlled trials can never encompass the full range of patients in clinical practice. There will probably always be unusual patients with rare conditions (such as primary pulmonary hypertension) or rare combinations of conditions (such as pregnancy and congenital heart disease) who cannot be included in large clinical trials. For these patients it would be a matter of regret if clinicians were unable to exercise their judgement and use the PAC where they have good reason to believe it might help. In short, for all the benefits of evidence-based medicine there are limits to its scope. Common sense clinical decisions made at the bedside – the art of medicine – remain as important as ever.

Conflict of interest

None declared.

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