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## The Arc of the Pulmonary Artery Catheter

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LONG-AWAITED ADVANCES IN THE TREATMENT OF CRITICALLY ill patients with shock and acute lung injury are evidenced by recent randomized trials of mortality-reducing interventions.<sup>1-5</sup> However, research that strives to change clinical practice is often met with a combination of celebration, skepticism, and controversy. One continuing controversy concerns the utility of the quintessential technology of the intensive care unit (ICU): the pulmonary artery catheter (PAC). The PAC is unique in its multipurpose role. Used for diagnosis, monitoring, and inexorably linked to goal-directed therapy, the PAC has shaped how generations of physicians define and treat critical illness. Indeed, according to a popular critical care textbook, the PAC is “not just important for the specialty of critical care, it is *responsible* for the specialty of critical care.”<sup>6</sup>

Pulmonary artery catheterization was initially performed in cardiac catheterization laboratories to aid in decision making about cardiothoracic surgery.<sup>7</sup> With the introduction of flow-directed balloon-tipped catheters in 1970, the PAC became accessible to many physicians and was soon adopted as a tool to guide cardiovascular therapy in perioperative and critical care medicine.<sup>8</sup> Consistent with the history of many new technologies in health care, especially in the ICU setting,<sup>9</sup> the effect of this technology on patient-centered outcomes was not initially tested in randomized trials. Benefit was assumed. For nearly 2 decades, the PAC provided enhanced understanding of cardiopulmonary pathophysiology through measures of cardiac output, right and left heart filling pressures, and systemic and pulmonary vascular resistance. Individualized pharmacotherapeutic interventions were thus possible, informed by real-time patient-specific data from the PAC.

In the 1980s, observational studies of patients with acute coronary syndromes distinctly challenged the utility and safety of this intervention, suggesting higher mortality for patients receiving a PAC.<sup>10,11</sup> In 1996, a retrospective observational study of 5735 critically ill patients suggested that the PAC was associated with increased mortality and increased costs of care, even after adjusting for the propensity to receive catheterization.<sup>12</sup> In 2000, a large retrospective observational study of

10217 patients showed that use of the PAC was independently associated with admission to a surgical ICU, care delivered by a nonintensivist, patient race, and private insurance coverage.<sup>13</sup> In 2001, a prospective observational study of 4059 patients undergoing major elective noncardiac surgery reported that those patients treated with a PAC had a 3-fold increase in major postoperative cardiac events.<sup>14</sup>

Together, these publications had important consequences. They generated debate about whether patients should be managed with a PAC and why. They raised awareness about how in nonexperimental studies potentially inadequately adjusted confounders could lead to spurious associations between the PAC and poor clinical outcomes. They challenged us to step back and critically evaluate the PAC in terms of patient populations mostly likely to benefit. It became better understood that a diagnostic and monitoring device cannot improve clinical end points unless the therapy based on data from that device is itself effective. It was no longer just about the information obtained from the PAC—what was done with the data matters. An editorial accompanying the provocative study by Connors et al<sup>12</sup> called (again) for a moratorium on the PAC or more randomized trials to test its effect on patient outcomes.<sup>15</sup>

The international critical care community embraced this research challenge, even though it was not new. Concurrent with the planning and conduct of other large trials, 2 systematic reviews of previous smaller randomized trials of elderly surgical patients found no overall benefit to the PAC, with or without goal-directed therapy.<sup>16,17</sup> An early attempt to conduct a randomized trial of the PAC in Ontario was limited by lack of equipoise and physician distress about the suitability of withholding the PAC from half of the patients.<sup>18</sup> Meanwhile, the Canadian Critical Care Trials group had been formed in recognition of the need to distinguish the clinical impression of benefit from unbiased evidence of benefit in large studies addressing several clinical issues.<sup>19</sup> Committed to answering research questions collaboratively in multicenter randomized trials, one of the group's first projects addressed the question of whether, among patients undergoing high-risk noncar-

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diac surgery, the PAC and protocol-guided therapy influenced 28-day mortality compared with a central venous catheter insertion and management at the discretion of the ICU team.<sup>20</sup> Among 1994 patients, Sandham et al<sup>20</sup> found no differences in mortality, length of hospital stay, or organ dysfunction; however, patients who received a PAC had a significantly higher rate of pulmonary embolism.

In this issue of *THE JOURNAL*, Richard and colleagues<sup>21</sup> make a key contribution to this celebrated and much debated device, by studying the safety and clinical outcomes of patients frequently managed with PAC—those with early shock, with established acute respiratory distress syndrome (ARDS), or with both. These patients have a high morbidity, mortality, and cost, and are considered by many to be most likely to benefit from the PAC. In the United States, approximately 750 000 cases of sepsis occur each year, of which at least 225 000 are fatal.<sup>22</sup> Approximately 60 000 to 200 000 patients develop acute lung injury in the United States, which has a mortality rate of 40% to 60%.<sup>23-25</sup> Shock and ARDS are intrinsically linked; epidemiologic studies and clinical trials suggest that 30% to 43% of patients with severe sepsis develop ARDS.<sup>26,27</sup> More than 1.5 million patients per year receive PACs, many of which are for shock or ARDS, at an estimated cost of more than US \$2 billion.<sup>28</sup>

The trial by Richard et al<sup>21</sup> was conducted between January 30, 1999, and June 29, 2001, in 36 French ICU centers. Patients were stratified by site and randomized to insertion of a PAC. Concealed allocation was ensured by central telephone-in randomization. A total of 681 patients with shock or ARDS were assigned to receive a PAC or not; randomization resulted in 2 comparable groups at baseline. Post-randomization, the study was unblinded, as is common for many device trials. No patients were lost to follow-up and analysis was by intention-to-treat. Between patients receiving and not receiving the PAC, investigators found no difference in organ dysfunction, need for vasoactive agents, duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, or 28-day mortality.

In this trial, treatment based on data obtained from the PAC was at the discretion of individual physicians. Although therapeutic principles were established, such as “vasoactive support if necessary at a mean arterial pressure of at least 60 mm Hg when fluid balance was optimal,” strategies were neither detailed nor protocolized. The inability to blind caregivers and the lack of a goal-directed treatment protocol may be viewed by some as a design limitation, particularly because goal-directed therapy has recently been associated with lower mortality for patients with early severe sepsis and septic shock<sup>2</sup>; however, its impact in ARDS remains unproven. Furthermore, other trials of goal-directed therapy involving the PAC have found such targets difficult to achieve and not beneficial to patients.<sup>20,29</sup> This potential trade-off between the internal validity of a trial (were groups treated equally aside from the experimental intervention?) and the external validity of a trial (are results generalizable to other settings?) is both understandable and potentially optimal considering the clinical question posed by this study.

A design choice not to standardize treatment but to replicate day-to-day care in ICUs around the world may reflect the reality that there is nothing standard about “standard practice,” and there is no proven “best practice.” Thus, encoding only one treatment strategy into a trial protocol should not be viewed as the best or only approach—an issue among several that was hotly contested recently for the National Heart, Lung, and Blood Institute–funded ARDSNet studies.<sup>30</sup> Nevertheless, interpretation of the trial by Richard et al<sup>21</sup> would be enhanced by knowledge of the proportion of patients in each group that received interventions known to influence outcome during the period of study, such as red blood cell transfusions, low tidal volume ventilation, inotropes, and vasopressors.

Some questions about the safety of the PAC remain. Richard et al<sup>21</sup> reported 17 arterial punctures, 1 hemothorax, 60 patients with arrhythmias, 6 patients with catheter knots, 8 patients with signs of exit site infection and sepsis, and 2 with positive catheter cultures. However, it does not appear that systematic screening for complications was undertaken in both groups. Complications possible in both groups such as arterial punctures may not have been recorded as well in the control group vs the PAC group; therefore, reported complications may be underestimated overall and inflated in terms of their difference between the 2 groups. For all devices like the PAC, harm associated with catheter insertion and management may vary among physicians, underscoring how operator-dependent complications in device trials are the study outcomes least generalizable to other settings.

Richard et al<sup>21</sup> appropriately caution that a lower than expected enrollment and smaller sample size than originally planned may have limited the power to detect a difference in effectiveness or safety end points between the PAC and control groups. However, taking into account the observed difference in mortality, they conclude at the risk of 5% that the absolute difference in mortality between groups is no more than 7.8%. Although this trial does not indicate harm with PAC use, harm cannot be definitely ruled out. The potential risk of an absolute difference in mortality of 7.8% is still important but a randomized trial may need to recruit 3000 to 4000 patients to exclude an increased absolute risk of death of 5% suggested by a previous observational study.<sup>12</sup>

In terms of trial management, this study has 3 unique features. Investigators report that a single institution's research ethics board approved the protocol rather than each participating center; in North America, the latter is more typical in today's era of heightened research oversight. Second, as is usual for studies in the critically ill, informed consent was requested of patients but was more commonly obtained from their next of kin. When patients could understand, they were given the right to withdraw their participation; 5 of 681 randomized patients denied inclusion of their data. Although these omissions do not influence the trial's interpretation, this phenomenon suggests that how clinical research is experienced by and best explained to those individuals with resolving critical illness could itself be an informative field of research. Third, this trial was managed by the French Pulmonary Artery Catheter

Study Steering Committee, in collaboration with a data and safety monitoring board. The admirably honest and all too familiar patient recruitment challenges are reported, leading the steering committee to target trial completion with 80% rather than 90% power to detect a 10% difference in 28-day mortality between the 2 groups. When the planned study duration extended from 18 months to 30 months, it is plausible that concerns about shifts in practice patterns led the steering committee to stop the trial after accrual of 681 (out of a revised target of 754) patients. As reported, the data and safety monitoring board approved this decision, perhaps in part on the grounds that temporal changes in treatment (based on data from the PAC or not) could modify the treatment effect and create trial results that may be difficult to interpret. This issue raises questions about precisely which treatments, if powerful and unequally applied between the 2 groups, could influence the trial results, because it is possible and the benefits of low tidal volume ventilation,<sup>1</sup> early goal-directed therapy,<sup>2</sup> activated protein C,<sup>3</sup> and corticosteroids<sup>5</sup> for severe sepsis might have been informally disseminated during the conduct of this trial. However, this seems very unlikely. The transparent management decisions reported by Richard et al<sup>21</sup> are refreshing to read. Trialists may speculate about the fate of this study under similar circumstances but in different jurisdictions, given that some research environments create arms-length organizational structures and separate decisional responsibilities for trial policies regarding power, sample size, and stopping rules.

The results of this multicenter randomized controlled clinical trial of the PAC in patients with shock, ARDS, or both may lead to more than one interpretation. The PAC was not associated with increased mortality or morbidity; however, neither was it associated with improved clinical outcomes. This trial and other studies provide reassurance that further investigation into the role of the PAC is feasible, likely safe, and should proceed forthwith. Even larger trials may be needed to more definitively evaluate this technology. A complementary approach is selection of specific patient populations to test protocolized treatment schedules based on data obtained from the PAC. Intensivists eagerly await the completion of 2 ongoing studies that champion these different designs: the UK National Health Service sponsored study Pulmonary Artery Catheters in Patient Management in Intensive Care (PAC-Man)<sup>31</sup> and the recently resumed National Heart, Lung, and Blood Institute-sponsored Fluids and Catheters Treatment Trial (FACTT) of the ARDSNet.<sup>32</sup>

Critical care medicine is well poised to build on its solid foundation of pathophysiological research and technology development with collaborative multicenter clinical investigations. These complementary approaches to inquiry are needed to help physicians better understand the risk:benefit, effort:yield, and cost:benefit of the PAC, as well as other old and new interventions used to care for the most seriously ill hospitalized patients in the ICU.<sup>33</sup>

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