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Exciting new ECMO technology awaits compelling scientific evidence for widespread use in adults with respiratory failure

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MacLaren et al. [1] discuss the exciting potential offered by extracorporeal support, including extracorporeal membrane oxygenation (ECMO). Many uses of ECMO have recently been discussed. These include a technically advanced means of transporting patients with severe respiratory failure [2] and a treatment for acute respiratory distress syndrome (ARDS) following novel H1N1 influenza infection [3]. Extracorporeal support remains an exciting domain of investigation, development and clinical application. Innovations, such as IVOX, abound among developers and practitioners of extracorporeal support [4]. Dr. Bartlett has been a consistent leader and innovator in this field.

MacLaren et al. [1] make impressive arguments, and their illustrations are clear and compelling. Their Fig. 6 is a striking example of the advances/changes in clinical care. The new extracorporeal circuits they nicely describe are clearly much simpler, easier to use, and appear more safe than those used in the past. Importantly, they appear safer than those used in the two past clinical trials that adhered to accepted experimental standards [5, 6]. This raises legitimate questions about the current value of the results of those two older clinical trials. These legitimate questions should be answered with new clinical trials that adhere to accepted experimental standards. The authors

clearly indicate that major advances in both extracorporeal circuitry and clinical care have taken place, since the technology of these two older clinical trials was introduced. I believe it is time for these advances to be matched by similar advances in extracorporeal clinical trials. Rigorous clinical trials with modern technology will likely provide results that answer crucial questions about “in whom, how, and when” extracorporeal support should be applied.

The experimental design of two-group randomized controlled clinical trials has not changed substantially since the older trials were completed [5, 6]. In the absence of credible new clinical trial results, we have no better information to guide decisions about widespread use of extracorporeal support than that provided by the two past clinical trials that adhered to accepted experimental standards [5, 6]. Some clinicians hold strong beliefs in the efficacy of ECMO support for patients with severe ARDS. Dr. MacLaren [7] articulately expressed these beliefs in a recent letter. Such strong beliefs are not new. In 1984 and 1985 Gattinoni et al. [8] reported a dramatic increase in survival with use of low frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO2R) (using veno-venous support). My colleagues and I conducted a randomized controlled clinical trial with the expectation that LFPPV-ECCO2R was likely to be a significant treatment advance (from our published discussion: “...we concluded from published reports that there was about a 0.5 prior probability that LFPPV-ECCO2R was a superior therapy for ARDS” [6]). However, we did not detect a survival advantage of LFPPV-ECCO2R. Gattinoni et al., in a letter to the editor, replied that the LFPPV-ECCO2R technique was not yet optimized and the technique not yet ready for a clinical trial (see letters to the editor in [6]). We asked, in a reply letter, how it could be known that the LFPPV-ECCO2R technique was beneficial (the conclusion of the strong believers) when the technique was not yet

adequately evolved to perform a clinical trial? I cite these published exchanges only to indicate that current uncertainty about the role of extracorporeal support is an old one. It will only be resolved by new and properly conducted randomized controlled clinical trials. Such a clinical trial has not yet been done. The recent clinical trial in the UK did not adhere to accepted experimental standards [9, 10]. The uncertainty might also be resolved by spectacular and compelling observational results, e.g., like those observed with the initial treatment of pneumococcal pneumonia with penicillin in the 1940s. However, this is unlikely. We will not likely encounter observational results more compelling than those of Gattinoni et al. [8] in 1984 and 1985 when they reported a 77% survival of patients meeting the 1970s ECMO criteria. Survival of such patients had to that point been consistently 10% in Boston and Salt Lake City centers, two of the original NIH ECMO clinical trial centers [5].

In response to previous publications [11, 12], Dr. MacLaren [7] raised three issues: ECMO must be correctly applied; ECMO must be applied to the appropriate patient; and finally that we need to define when, how, and in whom we can optimally use the technique. I believe MacLaren raised crucial issues that can only be defined with detailed methods for selection of patients, conduct of extracorporeal support, and management of important clinical interventions. Short of this, clinicians cannot know when, how, and in whom to optimally apply ECMO. For example, in the current publication, MacLaren et al. [1] indicate that patient complications continue to occur, uncertainties remain, and that “there are no effective means of confidently predicting recovery or death”.

The alternative to credible clinical trial results is to accept at face value the claim of experts that their experience “managing adult patients on ECMO for refractory respiratory failure,” or similar expressions, demonstrates,

documents, and validates the efficacy of ECMO [7]. Unfortunately, such beliefs, no matter how strongly and sincerely held, are frequently proven to be invalid when formally tested using scientifically rigorous methods [13]. Experience can easily mislead due to the selective emphasis or recollection that characterizes human cognition. Past treatments that were enthusiastically supported and widely disseminated but subsequently shown to be of no value—or even harmful—include avoiding beta blockers in heart failure treatment; insulin for schizophrenia; vitamin K for myocardial infarction; hormone replacement therapy to prevent cardiovascular disease; flecainide for ventricular tachycardia; and immobilization of scaphoid bone fractures [14]. More recently we have been exposed to a change in the management of sepsis. Sepsis therapy with drotrecogin alfa (Xigris[®]) was recently interrupted by withdrawal of the drug by the manufacturer [15].

Noah et al. [3] resumed the ECMO dialog in a recent publication describing retrieval of H1N1 respiratory failure patients for ECMO in the UK. This publication elicited an editorial that echoed arguments raised by others, calling for more compelling data to support the efficacy of ECMO before ECMO is widely propagated for management of severe ARDS [16]. Roger Bone, 25 years ago, discussed some of the issues that made observational studies of extracorporeal support difficult to interpret [17]. These issues are still a problem and they are central to the controversy surrounding extracorporeal support today. I believe extracorporeal support is an exciting and promising technique. I think its clinical applications require a more firm scientific foundation than currently exists. MacLaren et al. have compellingly described the new ECMO technology. I hope this is followed by new and compelling evidence that the new technology has enabled us to reap the promised benefits of extracorporeal support.

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