Charles C. Reed Memorial Lecture

Perfusion: The Difficult Way From Empiricism To Validated Science

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Introduction

Recently, we celebrated fifty years of cardiopulmonary bypass (CPB). Looking back, we can only conclude that there has been a tremendous progression in CPB techniques over the years. As a result many perfusionists consider today's techniques the best ever. But can we really prove this statement? Do we really have hard evidence to convince other specialties in the cardiac treatment arena that our approach is the best available? According to the work of Bartels, who did a major review of the literature on CPB, we cannot.[1]

When his article was published in 2002, many people were surprised that a technique considered as the "gold standard" was not really based on validated science. Confusion grew even more when subsequently beating heart (OPCAB) surgery came up and showed, according to the author, better or equal outcomes.

Background

In order to understand this situation we have to go back to the early days, the days of Charles C. Reed. At that time surgical pioneers were looking for safe and effective ways to perform cardiac surgery. As a result the first CPB system was developed. Although the first CPB was rudimentary and it had many limitations compared to today's CPB, it made open heart surgery possible. However, further development of CPB was not easy, since every change in the system had to be tried out in the clinical arena. It is pretty sure that with the standards used by our ethical committees today, there would not have been any cardiac surgery at all. Nevertheless, although those early perfusion pioneers had only a fraction of the scientific knowledge and technology we have today at their disposal, they succeeded in making CPB much more effective and safe. They were also responsible for starting up the first perfusion societies and organizing the first conventions. Those pioneers were convinced that progress in perfusion technology could only be achieved by sharing knowledge. Because of this, they were able, in those challenging times, to comply with almost every demand of a surgeon. When we look back on what they could accomplish in this manner, it must make us humble.

Today, we live in a world of evidence-based medicine, meaning that every technique should have a proven added value before routinely used. Unfortunately, the perfusion community did not do very well in following this trend. For years there was no alternative to CPB, so no general attempt was done in obtaining the best possible perfusion technique for a given problem. Many perfusionists stuck to their historical grown CPB systems and did no longer make daily efforts to improve and validate it. The pioneering times, once defined by curiosity and enthusiasm, were gone and replaced by daily routine. When all of a sudden OPCAB appeared on the scene, the perfusion community had no answer on their claims. Although many people were skeptical in the beginning, OPCAB became rapidly a respected tool within the cardiac treatment arena. In Belgium, approximately 23% of all coronary artery bypass surgery is performed by OPCAB. In the beginning, many surgeons claimed that the major advantage of OPCAB was the avoidance of CPB. However, as the OPCAB series grew, it became clear that CPB was not the major cause of associated morbidity, since a lot of this associated morbidity, always attributed to CPB, was also observed in the OPCAB population. As a result of these new insights, we are now blessed with the ideal control group, and it is up to the perfusion community to document our techniques in a scientific way.

What do we need to do?

The first step would be a critical evaluation of our perfusion education programs. The curriculum should not only contain chapters on basic science but also focus on the basics of scientific research. The ideal situation might be an education associated to a university program, where the perfusion education merges with another existing scientific program. After passing a common limb, perfusion could be one of the choices students could make. This type of approach does already exist in the

Scandinavian region and is one of the possible approaches under consideration in Belgium.

Secondly, we need to generate more evidence-based data on CPB because we lack them today. Bartels[1] found in his paper the following results: "A total of 33,000 articles identified were retrieved. Of these, 1500 articles fulfilled the criteria for the first step of the selection procedure. The 225 articles with the best scientific evidence available were classified according to the level of their scientific evidence on the basis of their methodological rigor." He further concludes "Many studies showed methodological problems (e.g., imprecise study design or inappropriate statistical methods). As a result, most of the classified articles showed divergent results regarding individual principles of CPB performance. Thus, the scientific evidence regarding CPB principles could not be conclusive in these cases." Although one could discuss certain aspects of his approach the general lines are clear.

Action plan

In order to generate more scientific proof we need to establish the following points:

- Validation of our components
- Standardization of our techniques
- Meta-analysis of our results
- Generate mathematical models for validation and prediction of techniques
- Linking perfusion techniques to clearly defined patient populations
- Using and developing combined strategies of pharmacological and technical approaches for a given patient population

Validation of components and therapies

A validation of a technique means that we can actually prove and reproduce that a given procedure is better. A good example of a poorly validated technique is vascular access. There is evidence of a correlation between aorta manipulation and the occurrence of stroke and neurologic deficit.[2] A disadvantage of CPB is just the fact that one is obliged to manipulate the aorta for cannulation. Although, accepted as a cause of morbidity, there are very few papers that try to define critical thresholds for cannulas. For example what is the highest cannula outlet velocity one can tolerate before a plaque is "sandblasted" off of the aortic wall? What is the best design for reducing blood velocity without jeopardizing platelet function? Is there a place for compliant cannulas? This type of validation should be established for every component of our CPB system.

Standardization of techniques

"As many centers, as many techniques" is the general conclusion when visiting cardiac centers nationwide and worldwide. We should question if this is necessary, because it is a major cause why we cannot easily set-up large studies. Maybe we should go toward an integrated module as the heart of our CPB system. The module should be comprised of an oxygenator, a heat exchanger, a pumping system and eventually a reservoir and filter. This system could then be expanded according to the specific needs of a given procedure or of a given institution. As a result priming volume, surface area and the fluid dynamical aspects of CPB systems would be much more uniform all over the world. At the same time, because of the uniformity of the core of the system, a heart-lung machine would be capable to test in advance the integrity of the system and to detect even minor changes in performance before the start and during a clinical run.

A common argument against uniformity is that it takes away the freedom of choice. However, in reality it is the opposite because all components in such a core system would then be developed to achieve the lowest blood damage, the best hydrodynamic profile and low blood activation. To do this validation as an individual center for all used components is almost impossible due to a lack of means. So using standardized equipment will raise overall quality and allow the operator to focus 100% on occasional procedure or patient-related problems.

Meta-analysis of our results

Performing prospective randomized studies is an expensive and time consuming activity. Because of the high expense of many markers, a lot of those studies are statistically underpowered. In order to overcome this problem we can try to do a meta-analysis of the results of several publications on the same subject.

An interesting example of this, is the field of separation of pleuro-pericardial aspiration. All published studies find the same results and are thus amplifying one another.[3,4] A next step is to implement these techniques in our institutions in order to obtain larger groups that then can be analyzed based on clinical findings and routine laboratory results (e.g. blood loss, ventilation parameters, length of stay, etc.). This will help us to understand why a new technique is better and how we can use this

new knowledge in ameliorating other procedures.

Establish mathematical models for validation and prediction of techniques

In medicine in general as well as in perfusion, mathematical modeling is underused. Luckily there seems to be a slow increase in use over time. Mathematical models are useful tools for understanding complex mechanisms such as mass transfer in an artificial lung or the ideal fluid dynamic profile of an extracorporeal circulation as well as for understanding of pathophysiological phenomena such as deep hypothermic circulatory arrest (DHCA) or thrombin and fibrin generation during CPB.

From a technical perfusion standpoint they can be used in several ways. First as advisors, they can predict mass transfer of a given oxygenator under any given working condition. Based on which they can give early warnings to the operator regarding manufacturing/material related problems such as membrane plasma leakage or an out of specification oxygenator membrane mat. Secondly, they can help to analyze a non-routine situation in vitro. For example one could run a pediatric perfusion case, based on historical data, in order to define the best oxygenator size for a Jehovah's Witness' child, scheduled the next day. And last, they are very helpful for training purposes since one confront a student with the most exceptional situations before the student encounters them in reality.

Mathematical models also make it possible to understand better a non-physiological situation such as DHCA. Based on known physiological knowledge we can compare a model with existing historical data in order to validate it and when there is a good correlation we can feed the model with e.g. different acid-base strategies in order to establish the best approach. This approach is extremely meaningful for all procedures with a relatively low occurrence in the clinical practice.

Linking perfusion techniques to clearly defined patient populations

Today, there is almost no limit anymore on who can be operated on or not. As a result the average patient is older and sicker. In order to deal with this situation in an optimal way, we need to define subgroups such as geriatric patients; patients with impaired renal function or patients with previous neurological insults. In any patient scheduled for a cardiac operation we also need to check laboratory values and drug therapy. Since both may have a major impact on the conduct of CPB. For example, some drugs (e.g. Angiotensine Converting Enzyme Inhibiting (ACE) drugs) are known to have a major impact on arterial blood pressure during CPB and may ask for a specific approach. Based on this information and the existing knowledge in the literature, we then need to define the best possible strategy for a given subgroup and stick to that strategy for some time. During that time period we need to document all patients treated according to our set standards. Finally we need to analyze our data and subsequently to compare them against published data in order to refine our strategy. If insufficient data is available in the literature we need to set-up a prospective randomized study in order to compare what we consider the "best theoretical strategy", based on the available information, against an existing strategy.

Using a combined strategy of best pharmacological and technical approaches for a given patient population

Because of the sicker population and the tremendous progress in pharmacological treatment, it is quite obvious that we can no longer perform studies or make evaluations without linking our observations to the pharmacological approach used by the anesthetist. For example, there is evidence that inflammation is linked to the capability of the kidney in clearing inflammation markers[5] and that an impaired renal function is better preserved against hypoxia when methylprednisolone[6] is given. As a result inflammation might be less pronounced in a patient population with impaired renal function, when these patients receive methylprednisolone prior to CPB. So, two institutions using the same CPB technique can present different results on inflammation depending on whether they used methylprednisolone or not. Similar observations can be made for many other pharmacological treatments such as aprotinin, nitric oxide, etc.

As a consequence we need to combine the best technological approach with the best pharmacological treatment in order to obtain the best possible end result for a clearly defined population.

Conclusion

Cardiopulmonary bypass was and is a valuable tool in cardiac surgery but pro and

con need to be defined in a scientific way. In order to do so, we need standardization of our CPB and validation of our techniques. Based on this approach it will be possible to obtain evidence-based documentation. Every perfusionist has his or her role in this process by carefully documenting every performed case and by performing each case according to validated published knowledge. We have to step away from the single evaluation of components and go for evaluation of combined approaches of CPB techniques and pharmacological treatments. Survival of CPB will highly depend on the knowledge of the average perfusionist and on the capability of that same perfusionist to give valid scientific information to other health-care specialists in order to obtain the best possible treatment for a given patient.

References

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