The ARCH Projects: design and rationale (IAASSG 001)


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Abstract

OBJECTIVE: A number of factors limit the effectiveness of current aortic arch studies in assessing optimal neuroprotection strategies, including insufficient patient numbers, heterogenous definitions of clinical variables, multiple technical strategies, inadequate reporting of surgical outcomes and a lack of collaborative effort. We have formed an international coalition of centres to provide more robust investigations into this topic.

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INTRODUCTION

Aortic arch surgery had been especially challenging for surgeons, largely because of the need to interrupt blood flow to the brain and to the downstream organs, mandated as part of the operative strategy. In 1954, DeBakey reported his first arch repair [1], but it was not until cardiopulmonary bypass was introduced that DeBakey et al. were able to replace the aortic arch successfully. Since then, surgical management of aortic arch pathologies has evolved significantly. Recognizing the importance of neuroprotection as the cornerstone of a successful surgical outcome, Gripp et al. [2] popularized hypothermic circulatory arrest (HCA) as an obligatory component of arch surgery in 1975. Although sufficient hypothermia can reduce systemic and cerebral metabolic demands, it is not possible to completely suspend metabolic activity. As a result, adjunctive measures, such as retrograde cerebral perfusion (RCP) and selective antegrade cerebral perfusion (SACP), have been utilized to support lingering cerebral metabolism, particularly during prolonged periods of circulatory arrest.

While modern pioneers continue to push the boundaries of surgery to refine operative techniques, such a rapid progress in surgical techniques has outpaced the availability of robust clinical evidence, despite voluminous observational studies. This inadequacy of data-driven literature has significantly curtailed the development of evidence-based guidelines. The International Aortic Arch Surgery Study Group (IAASSG) has been formed by 41 academic surgeons from 34 cardiac centres and 10 countries to address this issue. We aim to conduct the ARCH Projects, including establishing a multi-institutional retrospective database, randomized controlled trials (RCTs) and a prospective registry, that will provide robust clinical information with sufficient statistical power on patient management and prognostication. Furthermore, with the introduction of hybrid and endovascular arch repairs, traditional arch surgery is at a critical junction [3–5]. This collaborative endeavour will establish benchmarks for existing surgical and neuroprotective techniques, so as to provide a platform for directing future avenues of research.

THE INTERNATIONAL AORTIC ARCH SURGERY STUDY GROUP

The main objectives of the IAASSG are 4-fold: (i) to determine the optimal neuroprotection strategies and operative parameters for patients undergoing hemi-arch and total arch surgery; (ii) to assess perioperative mortality, morbidities and predictors for operative risk; (iii) to formulate a risk predictor model in arch surgery and (iv) to evaluate long-term survival outcomes and quality-of-life after aortic arch surgery.

IAASSG SCIENTIFIC COMMITTEE

The Scientific Committee consists of members of the Collaborative Research (CORE) Group, (www.coregroupinternational.org), which is composed of a highly experienced team of cardiothoracic surgeons, research fellows, systematic reviewers and biostatisticians from Australia, the USA and the UK (Table 1). The CORE Group is responsible for the concept, design and establishment and funding of the ARCH Projects, as well as performance of statistical analyses, coordination of research projects and management of administrative tasks.

IAASSG Research Steering Committee

The direction and progress of the ARCH Projects will be overseen by the Research Steering Committee, which consists of 19 academic surgeons from high-volume aortic centres (Table 1). The Research Committee will provide overall guidance and supervision of any research. The development of research projects and publications will be made by consensus with >50% concurrence.

IAASSG participating centres

Thirty-four tertiary institutions are partaking in this international project and are representative of high-volume aortic centres across the world. This should minimize variation in patient demographics and surgical skills, thus enabling broader acceptance and application of results. All participating centres are eligible to apply through the Research Steering Committee to perform research projects from the multi-institutional database.

STUDY DESIGN

To achieve the outlined objectives, the IAASSG is conducting research projects in the following five coordinated steps. These are (i) systematically evaluating current literature; (ii) achieving clinical consensus; (iii) establishing the ARCH Project (I)—Multi-institutional Retrospective Database; (iv) conducting the ARCH Project (II)—Multi-institutional RCTs and (v) forming the ARCH Project (III)—Multi-institutional Prospective Registry. For more details, please visit the IAASSG website: www.archprojects.org.
Table 1: International Aortic Arch Surgery Study Group

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Step 1: systematically evaluating current literature

Meta-analyses and systematic reviews of the current literature have been performed by the IAASSG through May 2013, using electronic databases such as Ovid Medline, EMBASE, ACP Journal Club, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Database of Abstracts of Review of Effectiveness. The keywords and MeSH terms included: ‘aortic arch surgery’ or ‘aneurysm, dissecting’, or ‘aorta, thoracic’, or ‘aortic aneurysm’ and ‘circulatory arrest’ or ‘circulatory arrest, deep hypothermia induced’. Of 1127 references identified, 178 studies reported outcomes for patient series of ≥100. A summary of four primary neuroprotection strategies of interest, including deep hypothermic circulatory arrest (DHCA) alone, DHCA + RCP, DHCA + SACP or moderate hypothermic circulatory arrest (MHCA) + SACP, is presented below, as these represent the most widely practised and established techniques.

Deep hypothermic circulatory arrest. Since first introduced in 1975 [2], DHCA has underpinned the practice of arch surgery. In shorter operations, DHCA sufficiently reduces cerebral metabolic demand to enable circulatory arrest without significant deleterious neurological outcomes. Mortality for DHCA has been reported to be between 2 and 11%, with stroke rates between 4 and 14% [6, 7].

Patients operated on using deep hypothermic conditions can tolerate ~20–30 min of circulatory arrest, which in general is long enough for hemi-arch repairs, while 22–98% of these patients also achieved electrocerebral silence [8, 9]. However, it has been noted, mostly through laboratory studies, that hypothermia predisposes to enzyme and organ dysfunction, exacerbates bleeding, lengthens duration of bypass and aggravates systemic inflammatory responses [6]. Furthermore, low temperatures increase blood viscosity and impair the release of O2 to the tissues due to left-shift of the oxygen-dissociation curve. The relative paucity of clinical data on the impact of deep hypothermia in visceral organs requires further investigation.

Deep hypothermic circulatory arrest + retrograde cerebral perfusion. DHCA + RCP in arch surgery was first described by Ueda and associates in 1990 [10], with the belief that retrograde perfusion would enable metabolic sustenance to the brain and prevent neurological embolic events [11]. However, its acceptance as an effective neuroprotection strategy has diminished significantly in recent years, particularly after Ehrlich et al. [12] demonstrated in a porcine model that only 0.01% of retrograde perfusate through the superior vena cava traverses the brain capillaries, therefore disproving the raison d’être of RCP. Nevertheless, prior studies demonstrated mortality rates of 3.9–13.6% and stroke rates of 2.6–11.8% [11, 13, 14], and this technique is still rarely practised by some [14].

Deep hypothermic circulatory arrest + selective antegrade cerebral perfusion. DHCA + SACP has gained recent prominence as a preferred neuroprotection strategy for complex arch surgeries, as the ability to perfuse the brain during circulatory arrest supports any lingering cerebral metabolism not moderated by deep hypothermia. Reported mortality ranges from 3.9 to 16% and stroke ranges between 5.6 and 14% [6, 15]. However, concerns have been raised regarding the time required to rewarm the patient, the risk of introducing emboli due to cannulation of supra-aortic vessels and the potential deleterious effects of deep hypothermia on other organs.

A meta-analysis by IAASSG comparing DHCA with DHCA + SACP showed that adjunctive SACP reduces mortality rates (8.5 vs 15.2%; P = 0.008); other outcomes, such as neurologic deficit, were either comparable or inadequately reported [16].

Moderate hypothermic circulatory arrest + selective antegrade cerebral perfusion. The closer proximity of MHCA + SACP to normal physiology is now considered an attractive option for many surgeons. By using moderate hypothermia, some of the risks of deep hypothermia may be obviated, while sufficient cerebral metabolic supply is maintained [17, 18].

A separate meta-analysis conducted by IAASSG assessing the existing evidence for neuroprotection strategies in aortic arch surgery showed that MHCA + SACP is more advantageous in reducing stroke rates compared with DHCA alone (7.3 vs 12.8%; P = 0.0007) [19]. A key finding from this study is the paucity and inconsistency of the reporting of systemic outcomes. Indeed, only renal failure and bleeding were reported reliably to enable statistical analysis.
Limitation of existing studies. Despite the apparent wealth of information, these observational studies and meta-analyses are not adequate for addressing our objectives outlined above. Furthermore, the current literature is limited by a number of factors, including:

(i) Heterogeneous definitions of clinical variables.
(ii) Confounding factors that cannot be controlled or adjusted without original data.
(iii) Insufficient reporting of postoperative outcomes.
(iv) Low patient numbers and inadequately powered individual studies.

In addition to the perfunctory status of the literature, several obstacles inherent to the nature of aortic arch surgery have hindered robust evaluation of operative techniques:

(i) Low prevalence of patients that require surgery in a single centre; accumulating large number of patients will take a prolonged period, during which time the surgical strategies may have evolved and the 'best approach' at the time may become out-dated.
(ii) Variations in surgical techniques that confound statistical analysis—this includes arrest temperature, perfusate temperature, cannulation site, neuroprotection adjuncts, etc. As none of the small-scale case series provided definitive answers for neuroprotection, the same questions are likely to continue to be debated in the coming decade.
(iii) Aortic arch surgery is a highly complex operation and usually performed at specialized aortic centres; small single-centre cohorts do not ensure study quality and applicability.

Step 2: achieving clinical consensus

A further limitation of the existing literature is the lack of standardized definitions and reporting criteria for several critical variables. For example, despite its ubiquitous application, no consistent definition exists for the varying ranges of hypothermia during circulatory arrest. Such inconsistencies hinder the validity of comparisons between institutional reports, thus curtailing the evidence-based evolution of surgical practice. Consensus needs to be reached to standardize reporting formats in order to improve the validity of future institutional studies.

Consensus on hypothermia classification. The IAASSG has already achieved two important Consensuses among international aortic arch surgeons. A Consensus Statement published by members of the IAASSG Research Steering Committee has standardized the definitions of hypothermia to include profound (≥14°C), deep (14.1–20°C), moderate (20.1–28°C) or mild hypothermia (≥28°C), to be measured at the nasopharynx [8].

Consensus on clinical endpoints. Additionally, a key finding of the above literature review is the deficient reporting of systemic clinical outcomes. While the majority of studies focused on mortality and neurological adverse events, morbidities such as renal, respiratory and cardiovascular outcomes were poorly reported. To overcome this, a Consensus Survey of important clinical endpoints that must be reported after arch surgery, along with their grading system, has been conducted by the IAASSG. A consensus has been achieved by 45 aortic surgeons from 40 high-volume aortic arch institutions and 12 countries. This report is in preparation for publication and will ensure uniformity and consistency between future documentations of clinical outcomes.

Step 3: the ARCH Project (I)—Retrospective Database

Presently, only a few studies with sufficient patient numbers have been conducted to compare surgical techniques and outcomes. While the literature is replete with observational studies, demographic and technique heterogeneities between institutions preclude robust examination of critical variables and endpoints.

Existing RCTs comparing neuroprotective techniques in adult aortic arch surgery are insufficiently powered to determine survival outcomes [20–22]. Based on the results of a RCT investigating neurocognitive functions after arch surgery with HCA, HCA + SACP or HCA + RCP, Svensson et al. [22] concluded that 650 patients are required for a study to be sufficiently powered just to evaluate the role of RCP in reducing stroke rate. Existing multi-institutional databases, such as the International Registry for Aortic Dissection (IRAD) and German Registry for Acute Aortic Dissection Type A (GERAADA), have been unable to conclusively evaluate variations in surgical techniques. For example, a major shortcoming of IRAD is its lack of detailed technical surgical data [23]. By the same token, while >50 institutions are partaking in GERAADA, they are all from the same geographic area and lack long-term follow-up [24]; such geographic bias may introduce confounding population health and epidemiological factors, as well as potentially limiting the generalizability of surgical techniques and outcomes. Results from these two registries are further limited by the lack of risk stratification and the focus on aortic dissection, which overlooks other aetiologies.

To overcome these limitations, and to provide convincing evidence for different surgical techniques, a multicentre database for operations involving the aortic arch is required to better compare overall survival outcomes. The collaborative pooling of data will generate hypotheses, identify prognostic factors, assess optimal operative strategies and aid in the formulation of evidence-based surgical guidelines. Furthermore, this will enable an evaluation of the influence that cerebral perfusion strategy, temperature and the location of cannulation have on patient outcomes such as mortality and neurological dysfunction.

Participating centres. Institutions that have published series between 2000 and 2013 with >100 aortic arch operations have been contacted and invited to submit their prospectively collected data. Expert advice was sought from the Research Steering Committee regarding recruitment of other centres. Thirty-four institutions from 10 countries have already agreed to participate (Fig. 1), with recruitment of additional centres anticipated.

Patients and methods. Ethics approval is obtained from participating institutions through their institutional review boards or through the chairperson of the ethics committee, who will waive the need for patient consent for the study as individual patients will not be identified. The study population is defined as patients who were considered for hemi-arch or total arch replacement surgery between 2000 and 2013 from the participating international institutions. The inclusion criteria are aortic arch pathologies (elective or emergent) and treatment strategies that utilized hemi-arch replacement, total arch replacement or an endovascular approach. Paediatric patients will
be excluded. Standardized clinical data on consecutive patients from each of the participating institutions will be entered into a central database. Follow-up data from most recent reviews will also be included. Each institution must confirm that the pooled data represent consecutive operative procedures performed in the study period by participating surgeons.

**Standardized data form.** A data list of variables of interest will be created to retrieve relevant information. The variables included in this list have been found to have significant prognostic values in other studies or because they may have potential clinical implications for future patient management. These blinded data will be collected electronically.
Step 4: the Arch Project (II)—Randomized Controlled Trials

Results from the retrospective database will guide the next phase of aortic arch surgical research, involving the design of multi-institutional RCTs (Fig. 2). Indeed, several authors have concluded that RCTs are required to convincingly assess optimal surgical practice [6, 25]. The RCTs should be conducted separately in patients undergoing hemi-arch and total arch replacements. For hemi-arch cases, treatment arms favoured include DHCA alone, DHCA + RCP, DHCA + SACP and MHCA + SACP. For total arch replacement, patients are randomized to DHCA + SACP vs MHCA + SACP. This will provide the highest level of evidence for neuroprotection in aortic arch surgery. Consensus needs to be reached on the details of surgical strategies for each treatment arm.

Step 5: the ARCH Project (III)—prospective registry

Participation in RCTs is entirely voluntary. Patients not eligible for randomization or from centres where randomization is not possible or deemed unnecessary will be entered into a prospective registry. This open-ended registry will serve as a platform for ongoing evaluation of evolving surgical practice.

In addition, the IAASSG will formulate an acceptable standardized methodological protocol for the collection, preservation and storage of plasma and aortic tissue material in order to homogenize and facilitate large-scale collaborative and integrated biomarkers and omics research into aortic arch pathologies. Protocol details will include complete proband phenotype characterization and collection, and processing and storage methods of biological samples for downstream application.

CONCLUSION

The establishment of the ARCH projects will promote closer collaboration among all centres and allow sufficiently powered statistical analyses for risk factor prediction, longitudinal assessment and propensity-scored analysis. By amalgamating multi-institutional clinical data and matching patients with similar risk factors and confounding variables who underwent different treatment strategies, it will be possible to test for hypotheses regarding optimal neuroprotection strategies for hemi-arch and total arch replacements. Ultimately, definitive answers will be provided through prospective RCTs. Such a collective effort will herald a turning point in the surgical management of aortic arch pathologies.

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REFERENCES


