Prolonged Mechanical Ventilation After Aortic Arch Repair Requiring Deep Hypothermic Circulatory Arrest: Incidence, Effect on Outcome, and Clinical Predictors

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Abstract: *Objective*: To delineate the incidence, outcome impact, and clinical predictors of prolonged mechanical ventilation (PMV) after adult aortic arch repair requiring deep hypothermic circulatory arrest (AAR-DHCA)

Aims: (1) To determine the incidence of PMV after AAR–DHCA. (2) To determine whether PMV after AAR-DHCA is a multivariate predictor for mortality or length of stay in the intensive care unit. (3) To determine multivariate predictors for PMV after AAR-DHCA. (4) To determine whether aprotinin influences PMV after AAR-DHCA.

Study Design: Retrospective and observational. Prolonged mechanical ventilation was defined as mechanical ventilation *via* an endotracheal tube for longer than 72 hours.

Study Setting: Single large university hospital.

Participants: All adults undergoing AAR-DHCA in 2000 and 2001.

Main Results: Cohort size was 144. Antifibrinolytic exposure was 100%: aprotinin 66% and aminocaproic acid 34%. The incidence of AF was 21.5 %. PMV did not independently predict for mortality or prolonged stay in the intensive care unit. The multivariate predictors for PMV were chronic obstructive pulmonary disease, stroke, and infection. In multivariate analysis, aprotinin exposure has no significant association with PMV.

Conclusions: PMV after AAR-DHCA is common, but does not independently predict mortality or ICU stay. The risk of PMV after AAR-DHCA increases with preexisting chronic obstructive pulmonary disease, stroke and infection. Perioperative intervention should focus on protection against stroke and infection.

INTRODUCTION

Pulmonary complications after aortic arch repair with deep hypothermic circulatory arrest (AAR-DHCA) are common [1-3]. Prolonged mechanical ventilation (PMV) in this setting has a published incidence of up to 27% and significantly prolongs length of stay [1-3]. Although PMV after AAR – DHCA is common and important, its clinical predictors have not been fully described. Furthermore, the clinical studies of this perioperative complication have not accounted for aprotinin exposure, an antifibrinolytic agent in AAR-DHCA that has recently been associated with improved pulmonary outcome [4]. In the light of the above considerations, this clinical study was undertaken at the Hospital of the University of Pennsylvania with the following aims:

(1) To determine the incidence of respiratory complications (including PMV) after AAR-DHCA;

(2) To determine whether PMV after AAR – DHCA is a multivariate predictor for mortality or prolonged stay in the intensive care unit (ICU);

(3) To determine multivariate predictors for PMV after AAR – DHCA;

(4) To determine whether aprotinin exposure influences PMV after AAR – DHCA.

METHODS

Data Collection: After approval from the institutional review board, all adults undergoing AAR - DHCA from January 1st 2000 to December 31st 2001 were studied. Perioperative data sets (demographics; anesthetic and surgical descriptors; clinical outcomes) were abstracted from the medical records and subsequently electronically archived. (Microsoft Access, Microsoft, Seattle, WA, USA).

OUTCOME DEFINITIONS

(**1**) **Pulmonary:** Chronic obstructive disease (COPD) was defined by any two of the following criteria: preopera-

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1874-3218/08

tive clinical diagnosis of COPD; clinical features of chronic chest hyperinflation and expiratory obstruction; typical features of hyperinflation on serial chest radiographs, as interpreted by an attending radiologist; evidence of airway obstruction on preoperative lung function testing, as reported by an attending pulmonologist. Prolonged mechanical ventilation was defined as mechanical ventilation *via* an endotracheal tube for longer than 72 hours [5].

(**2**) **General:** Mortality was defined as in-hospital mortality. Prolonged stay in the intensive care unit was defined as longer than 5 days. Stroke was defined as a persistent central neurological deficit (focal or generalized), as assessed by the study neurologist. Prolonged vasopressor exposure was defined as any requirement for a vasopressor infusion persisting longer than 72 hours. Mediastinal exploration was defined as re-exploration for bleeding within the first 24 postoperative hours. Sepsis was defined according to international guidelines as a systemic inflammatory response with a presumed or known site of infection [6, 7]. A systemic inflammatory response was diagnosed by the presence of at least two of the following: body temperature alterations (hyperthermia or hypothermia); tachycardia; tachypnea; and, changes in the white blood cell count (leucocytosis or leucopenia) [6, 7]. Pneumonia was defined as lung infection as evidenced by at least two of the following: systemic inflammatory response; chest radiograph showing alveolar infiltrative pattern compatible with pneumonia, as interpreted by an attending radiologist; and, positive sputum cultures. Sepsis and pneumonia were also combined together as a single entity, defined as infection. Donor exposures were defined as the total number of donors for blood component transfusion within the first 24 hospital hours after induction of anesthesia. Renal dysfunction was defined as a greater than 50% increase in serum creatinine with an abnormal peak serum creatinine.

The DHCA Protocol: The DHCA protocol has been extensively described [8]. Three experienced aortic surgeons were collectively responsible for over 90% of these cases in the study cohort. All patients in this cohort were cared for by a dedicated group of 10 cardiothoracic anesthesiologists. Each patient underwent balanced general endotracheal anesthesia with invasive monitoring of systemic and pulmonary arterial pressures. Temperature was continuously measured in the nasopharynx and bladder. There was continuous electroencephalographic monitoring whenever possible to guide the conduct of profound hypothermia. Transesophageal echocardiography (Multiplane 5-6.2 MHz probe; Sonos 5500, Philips, Bothell, WA) confirmed surgical diagnosis, guided circulatory management and assessed the surgical intervention. All patients received an antifibrinolytic, either epsilon-aminocaproic acid or aprotinin (full Hammersmith anti-inflammatory regimen), as directed by the attending anesthesiologist. Indications for aprotinin included emergency status, previous cardiac operation, and/or coagulopathy due to preoperative anticoagulant medications such as clopidogrel and warfarin.

Anticoagulation for cardiopulmonary bypass (CPB) was with bolus heparin titrated to maintain the activated clotting time > 400 seconds, taking aprotinin exposure into account [9]. The ascending aorta was the primary site for arterial cannulation, except in acute type A dissection where the femoral artery was preferred. Venous cannulation was bicaval. During DHCA, retrograde cerebral perfusion was infused *via* the superior vena cava cannula. The left ventricle was vented through the right superior pulmonary vein. Balanced anterograde and retrograde cardioplegia were utilized for myocardial protection.

Patients were cooled on nonpulsatile CPB (Sarns Inc., Ann Arbor, MI) at flows for a cardiac index > 2.0 L/min/m^2 and a mean arterial pressure > 60mmHg. The following neuroprotective pharmacology was administered on initiation of CPB: 1g methylprednisolone, 1g magnesium sulfate, 2.5 mg/kg lidocaine, and 12.5 g mannitol. Alpha-stat arterial blood gas analysis was performed every thirty minutes to document the following metabolic goals: pH 7.35-7.45, oxygen partial pressure > 100 mmHg, carbon dioxide partial pressure (30 – 40) mmHg, and hematocrit greater than 21%. Cooling was continued till an isoelectric electroencephalogram or in the absence of this monitoring, for a total of 45 minutes [10].

After AAR-DHCA, the aortic graft was cannulated for antegrade arterial perfusion on CPB. Rewarming proceeded with less than a 5 degrees Celsius temperature gradient between nasopharyngeal and CPB perfusate temperature.

Separation from CPB was standardized. Pharmacologic circulatory support was titrated to maintain a cardiac index > 2.0 L/min/m^2 (epinephrine 2 - 6 mcg/min and/or milrinone 0.25 – 0.50 mcg/kg/min) and mean arterial pressure > 60 mmHg (phenylephrine 50 – 200 mcg/min and/or norepinephrine 2 - 8 mcg/min). Blood component transfusion triggers were a hematocrit < 25%, and/or post-protamine medical coagulopathy. All patients were managed in the intensive care unit by a dedicated intensivist.

The respiratory care after discharge from the intensive care unit was continued in the surgical ward. Patients were ambulated daily and received regular chest physiotherapy to mobilize and clear airway secretions. Patients were also taught and encouraged to utilize their incentive spirometers to assist in ongoing recovery of lung function. The respiratory therapist on the surgical ward also administered bronchodilator nebulizers as required and supervised gradual withdrawal of supplementary oxygen therapy. Perioperative pain management was aggressively maintained, including patient-controlled intravenous analgesia and patient-controlled epidural analgesia (managed in consultation with the acute pain service from the Department of Anesthesiology and Critical Care).

Data Analysis: Cohort summary data were expressed as ratios or means with standard deviations. Standard statistical software (Stata 8, StataCorp, College Station, TX, USA) was utilized for all data analysis. Statistical significance was defined as a probability value < 0.05. The chi-squared test was utilized to assess for significance between ratios. Students t-test was utilized to test for significance between means. Univariate analysis evaluated possible perioperative predictors for PMV after AAR-DHCA. Identified univariate predictors were subjected to multivariate analysis to yield the best predictive model for PMV after AAR-DHCA. The data analysis was supervised by the senior author (David R. Jobes MD) who has a masters degree in biostatistics.

RESULTS

(1) Cohort Perioperative Summary (Tables 1-4): The cohort summary is presented by antifibrinolytic exposure: 66.0% aprotinin and 34.0% aminocaproic acid. The aprotinin subgroup had significantly more emergencies (P=0.009), a significantly lower myocardial ischemic time (P=0.04), and a significantly higher protamine dose (P=0.03). Ascending aortic and arch replacement was the most common DHCA procedure.

Table 1. Preoperative Cohort Variables

Preoperative Variable	Total (N=144: 100%)	Aprotinin (N=95/144: 66.0%)	Aminocaproic Acid (N=49/144: 34.0%)	Probability Value
Age (years: Mean/Standard Deviation)	64.7 ± 14.1	64.4 ± 14.2	65.2 ± 14.1	>> 0.05
Gender (Male/Female Ratio as %)	54.2%/45.8%	56.8%/43.2%	49.0%/51.0%	>> 0.05
Body Surface Area (square meters: Mean/Standard Deviation)	1.9 ± 0.2	1.9 ± 0.3	1.9 ±0.3	>>0.05
Emergency Cases (%)	40 (27.8%)	33 (34.7%)	7 (14.3%)	.009
Reoperation Cases (%)	27 (18.8%)	21 (22.1%)	6 (12.2%)	>>0.05
Previous Stroke (%)	14 (9.72%)	8 (8.42%)	6 (12.2%)	>>0.05
Previous Atrial Fibrillation (%)	15 (10.4%)	9 (9.5%)	6 (12.2%)	>>0.05
History of Hypertension (%)	103 (71.5%)	67 (70.5%)	36 (73.5%)	>>0.05
Chronic Obstructive Pulmonary Disease (%)	16 (11.1%)	8 (8.4%)	8 (16.3%)	>>0.05
Preoperative Coumadin (%)	26 (18.1%)	17 (17.9%)	9 (18.4%)	>>0.05
Preoperative Aspirin (%)	83 (57.6%)	55 (57.9%)	28 (57.1%)	>>0.05
Preoperative Statin (%)	22 (15.3%)	11 (11.6%)	11 (22.4%)	>>0.05
Serum Creatinine (milligrams/deciliter: Mean/Standard Deviation)	1.2 ± 1.0	1.2 ± 1.2	1.1 ± 0.5	>>0.05

Table 2. Cohort By Thoracic Aortic Procedure

Thoracic Aortic Procedure	Total (N=144: 100%)	Aprotinin (N=95/144: 66.0%)	Aminocaproic Acid (N=49/144: 34.0%)
Aortic Arch and Ascending Aorta	111 (77.1%)	72 (75.8%)	39 (79.6%)
Aortic Arch Only	10 (6.9%)	7 (7.3%)	3 (6.1%)
Aortic Arch and Descending Aorta	22 (15.3%)	15 (15.8%)	7 (14.3%)
Aortic Arch/Ascending and Descending Aorta	1 (0.7%)	1 (1.1%)	0 (0%)

Table 3. Intraoperative Cohort Variables

Intraoperative Variable	Total (N=144: 100%) Mean/ Standard Deviation	Aprotinin (N=95/144: 66.0%) Mean/ Standard Deviation	Aminocaproic Acid (N=49/144: 34.0%) Mean/Standard Deviation	Probability Value
Cardiopulmonary Bypass Time (minutes)	196 ± 43.5	196 ± 44.0	196 ± 42.9	>> 0.05
Myocardial Ischemia Time (minutes)	132 ± 45.8	127 ± 48.8	141 ± 38.5	.04
Deep Hypothermic Circulatory Arrest Time (minutes)	37.9 ± 15.0	38.9 ± 14.9	36.0 ± 15.3	>> 0.05
Temperature Nadir (degrees Celsius)	14.2 ± 2.4	14.1 ± 2.1	14.3 ± 2.8	>> 0.05
Fentanyl (micrograms per kilogram)	39.2 ± 17.7	38.7 ± 18.5	40.3 ± 16.2	>> 0.05
Midazolam (milligrams per kilogram)	.26 ± .17	.24 ± .08	.29 ± .26	>> 0.05
Pancuronium (milligrams per kilogram)	.15 ± .08	.14 ± .07	.17 ± .08	>> 0.05
Baseline Activated Clotting Time (seconds)	144.6 ± 51.7	144 ± 38.9	145 ± 69.5	>> 0.05
Maximum Activated Clotting Time (seconds)	887 ± 205	907 ± 203	848 ± 206	>> 0.05
Total Heparin Dose (units)	29649 ± 11983	30779 ± 11724	27459 ± 12295	> 0.05
Total Protamine Dose (milligrams)	170 ± 69.6	178 ± 72.3	155 ± 62.0	.03

Table 4A. Major Clinical Outcomes

Major Clinical Outcome	Total (N=144: 100%)	Aprotinin (N=95/144: 66.0%)	Aminocaproic Acid (N=49/144: 34.0%)	Probability Value
Mortality	16 (11.1%)	11 (11.6%)	5 (10.2%)	>> 0.05
Length of Stay in Intensive Care Unit (days)	6.7 ± 10.3	7.8 ± 11.5	4.6 ± 6.8	.02
Atrial Fibrillation	49 (34.0%)	30 (31.6%)	19 (38.8%)	>> 0.05
Stroke	12 (8.3%)	10 (10.5%)	2 (4.1%)	>> 0.05
Prolonged Vasopressor Dependence	15 (10.4%)	12 (12.6%)	3 (6.12%)	>> 0.05
Mediastinal Exploration within 24 Hours	5 (3.5%)	3 (3.2%)	2 (4.1%)	>> 0.05
Sepsis	8 (5.56%)	5 (5.3%)	3 (6.1%)	>> 0.05
Renal Dysfunction	33 (22.9%)	28 (29.5%)	5 (10.2%)	.003

Table 4B. Pulmonary Outcomes

Pulmonary Outcome	Total (N=144: 100%)	Aprotinin (N=95/144: 66.0%)	Aminocaproic Acid (N=49/144: 34.0%)	Probability Value
Prolonged Mechanical Ventilation	31 (21.5%)	24 (25.3%)	7 (14.3%)	.09
Pneumonia	11 (7.64%)	7 (7.37%)	4 (8.16%)	.56
Tracheal Re-intubation	25 (17.4%)	19 (20.0%)	6 (12.2%)	.18
Tracheostomy Required	18 (12.5%)	16 (16.8%)	2 (4.08%)	.02

Further perioperative outcomes between antifibrinolytic subgroups were similar except for length of ICU stay and renal dysfunction. These outcome differences have been addressed in prior publications [11,12].

The incidence of PMV was 21.5%, with no significant relationship to aprotinin exposure. Further pulmonary outcomes are detailed in Table **4B**: the tracheostomy rate was significantly higher in the aprotinin subgroup.

(2) Multivariate Predictors of Mortality and Prolonged ICU Stay (Tables 5,6): Multivariate predictors for mortality were sepsis, stroke, and mediastinal exploration within 24 hours [13]. Multivariate predictors for prolonged ICU stay were stroke, prolonged vasopressor dependence, and renal dysfunction [11]. Prolonged mechanical ventilation was not an independent multivariate predictor of mortality or prolonged ICU stay after AAR-DHCA.

Table 5. Multivariate Predictors for Mortality

Multivariate Predictor	Odds Ratio/ Confidence Interval/ P-Value
Sepsis	21.3: 1/3.8-121/0.001
Stroke	7.4: 1/1.9-28.7/0.004
Mediastinal Exploration within 24 Hours	7.7: 1/1.3-45.1/0.02

(3) Multivariate Predictors of Prolonged Mechanical Ventilation (Table 7,8): Candidate PMV predictors were statistically evaluated in univariate analysis. The identified univariate predictors were then subjected to multivariate analysis to yield the following clinical predictors for PMV after AAR - DHCA: chronic obstructive pulmonary disease; stroke; and, infection.

Table 6. Multivariate Predictors for Prolonged Stay in the Intensive Care Unit

Multivariate Predictor	Odds Ratio/ Confidence Interval/ P-Value
Stroke	15.1:1/3.6-64.0/0.001
Prolonged Vasopressor Dependence	7.3:1/1.3-41.3/0.024
Renal Dysfunction	4.8:1/1.7-13.6/0.003

Table 7. Univariate Predictors for Prolonged Mechanical Ventilation

Univariate Predictor	Odds Ratio/ Confidence Interval/ P-Value
DHCA Duration	1.04:1/1.01 – 1.07/0.003
Packed Red Blood Cell Transfusion	1.26:1/1.1 – 1.5/0.002
Stroke	6.25:1/2.2 – 17.7/0.001
Renal Dysfunction	11.0:1/4.3 – 28.4/< 0.0001
Chronic Obstructive Pulmonary Disease	13.3:1/2.54 – 69.9/0.002
Infection	45.7:1/9.50 – 219/0.0001

DISCUSSION

This study confirms that PMV after AAR-DHCA remains common with an incidence of 21.5%. This incidence,

however, was in the reported range [1-3]. However, series from high-volume thoracic aortic centers focused predominantly on descending thoracic aortic procedures with or without DHCA [1-3, 5, 14]. These procedures typically involve major thoracotomy (as compared to sternotomy) and extensive diaphragmatic dissection, In contrast, this clinical study focuses on all aortic arch repairs in which 84% were *via* sternotomy. Adult AAR-DHCA has a significant incidence of PMV, regardless of surgical incision. The explanation for this observation lies in the multivariate predictors for PMV which will be discussed later in this section.

Table 8. Multivariate Predictors for Prolonged Mechanical Ventilation

Multivariate Predictor	Odds Ratio/ Confidence Interval/ P-Value
Stroke	4.56:1/1.3 – 16.7/0.022
Chronic Obstructive Pulmonary Disease	12.1:1/1.8 – 80.1/0.009
Infection	33.7:1/6.6 – 172/< 0.0001

The identified multivariate predictors for mortality and prolonged ICU stay in this study do not include PMV, as reported previously [2]. Closer inspection explains this paradox. The mechanisms of all three outcomes (mortality; prolonged ICU stay; PMV) overlap significantly with respect to stroke and sepsis. Thus, PMV results from stroke and sepsis which are also independent predictors for mortality and prolonged ICU stay in the adult AAR-DHCA population.

It must be remembered, however, that mechanical ventilation itself does predispose to lung injury due to ventilator-associated pneumonia and pulmonary inflammation [15-17]. With respect to lung stretch and inflammation, conventional mechanical ventilation strategies were employed in this study: tidal volumes were 8-10 ml/kg, and positive end-expiratory pressure was frequently utilized (5 -7.5 cm water) [14]. In this study, clinical pneumonia only became a multivariate predictor when combined with sepsis as infection. Furthermore, in regard to ventilator-associated pulmonary inflammation, modulators of the inflammatory response such as aprotinin, statins and systemic steroids will have to be considered in future trial design. On the basis of this clinical trial, the precise contribution of these pathophysiologic mechanisms cannot be fully quantified. Further study of PMV after AAR-DHCA is required to fully delineate whether these interactions achieve clinical significance.

The identified multivariate predictors for PMV make sense. Chronic pulmonary obstructive disease is a commonly present in the AAR-DHCA population and represents a significant etiology of decreased pulmonary reserve. Therefore, perioperative injury is more likely to result in clinical dysfunction, namely PMV. This finding of the predictive power of decreased pulmonary reserve is consistent with PMV in major noncardiac surgery, as well as cardiac and thoracic aortic surgery [2, 3, 18, 19].

The remaining multivariate predictors, stroke and infection, represent perioperative opportunities for intervention. They have discussed in prior publications about their role in mortality and prolonged ICU stay after AAR-DHCA.[11-12] Stroke prolongs mechanical ventilation due to the consequent interference with adequate protection and maintenance of the airway (e.g. impaired cough; swallowing dysfunction with aspiration risk). Infection, especially pneumonia, prolongs mechanical ventilation due to decreased functional pulmonary parenchyma. A full discussion of prevention and risk reduction for these 2 perioperative complications after AAR-DHCA is beyond the scope of this article. Their correlation with PMV adds further priority to focus perioperative intervention on the protection against brain injury and infection after AAR-DHCA.

What about the relationship of aprotinin to PMV after AAR – DHCA? Due to its anti-inflammatory properties, aprotinin could protect against lung injury by modulating the inflammatory response to cardiopulmonary bypass. Although randomized trials in pediatric and adult cardiac surgery have shown a pulmonary protective effect of aprotinin, it has not been a consistent observation in meta-analysis [20-23]. A recent retrospective clinical trial in adult thoracic aortic surgery detected a significant association between aprotinin exposure and reduced pulmonary complications [24]. The cohort in this study was only 66.1% AAR-DHCA [24, 25].

In the present study, the cohort is 100% AAR-DHCA, but aprotinin, just as in the aforementioned trial, was not randomized. In multivariate analysis, aprotinin exposure was not associated with PMV. However, aprotinin exposure was significantly more common in the emergency cases which were significantly more likely to have prolonged stay in the intensive care unit, and require tracheostomy. Clearly, on the basis of these results confounded by association, further study is required to conclusively answer this question. Ideally, it would be a randomized trial of aprotinin in AAR-DHCA, adequately powered to detect a clinically meaningful reduction in PMV. Given the withdrawal of aprotinin from the world market recently due to safety concerns, this further evaluation of aprotinin in adult AAR-DHCA is on hold till the safety issues are resolved [26, 27].

LIMITATIONS OF THIS STUDY

Firstly, this study is retrospective and so can only detect association but not causality. Secondly, aprotinin exposure was not randomized. Thirdly, this AAR-DHCA cohort consists of surgically distinct subgroups that may have different levels of risk for PMV after AAR-DHCA. These limitations must be taken into account when considering the main findings of the study.

CONCLUSION

Prolonged mechanical ventilation after AAR-DHCA is common, but does not independently predict mortality or ICU stay. Chronic obstructive pulmonary disease, stroke and infection are independent predictors of PMV after AAR-DHCA. Perioperative intervention should focus on protection against stroke and infection.

ACKNOWLEDGEMENTS

Study Support: Department of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania.

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Received: November 20, 2007 Revised: January 20, 2008 Accepted: February 24, 2008