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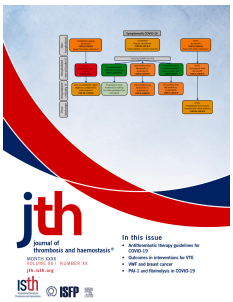

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Finding a common definition of heparin resistance in adult cardiac surgery: Communication from the ISTH SSC Subcommittee on Perioperative and Critical Care Thrombosis and Hemostasis.

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Abstract:

Ensuring adequate anticoagulation for patients requiring cardiac surgery and cardiopulmonary bypass is important due to the adverse consequences of inadequate anticoagulation with respect to bleeding and thrombosis. When target anticoagulation is not achieved with typical doses, the term heparin resistance is routinely used despite the lack of uniform diagnostic criteria. Prior reports and guidance documents that define heparin resistance in patients requiring cardiopulmonary bypass and guidance documents remain variable based on the lack of standardized criteria. As a result, we conducted a review of clinical trials and reports to evaluate the various heparin resistance definitions employed in this clinical setting and to identify potential standards for future clinical trials and clinical management. In addition, we also aimed to characterize the differences in the reported incidence of heparin resistance in the adult cardiac surgical literature based on the variability of both target activated clotting (ACT) values and unfractionated heparin doses. Our findings suggest that the most extensively reported ACT target for cardiopulmonary bypass is 480 seconds or higher. Although most publications define heparin resistance as a failure to achieve this target after a weight-based dose of either 400 U/kg or 500 U/kg of heparin, a standardized definition would be useful to guide future clinical trials and help improve clinical management. We propose the inability to obtain an ACT target for CPB of 480 or more after 500 U/kg as a standardized definition for heparin resistance in this setting.

Keywords: Anticoagulation, cardiac surgery, cardiopulmonary bypass, heparin, resistance, sensitivity

Introduction

Unfractionated heparin (UFH) is the mainstay anticoagulant for patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). In the early days of cardiac surgery using extracorporeal circulation, it was standard practice to administer a set weight-based dose (typically 300 units/kg) to a patient, much like any other drug.[1] However, it was observed that the patient response to any given dose of UFH could be quite heterogeneous with respect to the degree of anticoagulation. This suggested intraoperative monitoring was required for patient safety reasons.

Bull et al. introduced the activated clotting time (ACT) into cardiac operating rooms in the mid 1970s.[2] Since then, anticoagulation guidelines from the Society of Thoracic Surgeons, the Society of Cardiovascular Anesthesiologists, and the American Society of Extracorporeal Technology have given a Class I recommendation to employing a functional clotting test, such as the ACT, to quantify the anticoagulant effect of heparin prior to the initiation of cardiopulmonary bypass. [3] These guidelines recommend achieving an ACT target of 400 or 480 seconds, depending upon the activator used, prior to commencing cardiopulmonary bypass (Class IIa).[3]

“Heparin resistance” is the common term used to describe a lower than expected ACT in response to UFH administration in cardiac surgical patients when the typical high dose weight-based bolus administration of UFH fails to achieve the desired ACT for instituting CPB. Thus, there are 2 key components influencing the determination of heparin resistance in cardiac surgery – the dose of heparin given and the designated ACT target. Despite the existence of guidelines, multiple surveys have demonstrated tremendous variability in both of these elements in clinical practice.[4, 5] It has been difficult for clinicians to agree upon a standard definition of heparin resistance since both the typical UFH bolus dose (300-600 U/kg) and the target ACT (400 -480 seconds) vary among institutions.

We conducted the present review to characterize heparin resistance definitions in the adult cardiac surgery literature. Specifically, we aimed to identify the most common bolus dose of UFH and its corresponding ACT target that resulted in patients being classified as heparin resistant before initiating CPB. We also aimed to examine the

overall incidence of heparin resistance reported in the adult cardiac surgical literature and determine any relationship to the reported ACT target values or maximum UFH doses. A standardized definition would be useful to guide future clinical trials and help improve clinical management.

Methods

Literature Search and Included Studies

The investigation was submitted and approved by the PROSPERO register (CRD42023438555). A literature search was conducted using PubMed, Medline, Cochrane, and EMBASE databases for publications up to July 31, 2023, using the search terms: “heparin resistance” and “heparin sensitivity” in the title/abstract of the article with the terms “cardiac” and “surgery.” Preclinical studies, review articles, editorials, and case reports of 10 or fewer patients were excluded from the search. The retrieved papers were then screened by 2 reviewers (JHL, RMS) for wording defining heparin resistance. The primary outcome was a specific definition of heparin resistance based on heparin dose and target ACT.

To be included in the final analysis, papers had to define an ACT target for initiating CPB, a maximum dose of heparin that would be given before patients were labeled “heparin resistant”, or the administration of some type of therapeutic intervention to address heparin resistance management. In studies that included both adult and pediatric patients, only the adult data were extracted, or the paper was excluded if this could not be done. Similarly, in studies combining patients on extracorporeal membrane oxygenation (ECMO) support with CPB patients, only the CPB patient data were extracted and used. In studies including more than 1 definition of heparin resistance, only the highest bolus dose and ACT target were used.

Calculations and Statistical Analysis

The incidence of heparin resistance was calculated for each study by extracting the total number of adult patients initially enrolled in the study by the number of adult

patients labeled heparin resistant. When a study provided only the number of heparin resistant patients without disclosing how many patients were screened/enrolled, the study was not included in calculations involving the incidence of heparin resistance. Since baseline ACTs were not generally reported in studies, heparin sensitivity as described by Bull et al. could not be calculated.[6] However, a target ACT:UFH dose ratio for each study was calculated by dividing the ACT target by the maximum dose of UFH in Units/kg administered prior to initiating CPB or prior to patients receiving other interventions for heparin resistance. The goal of this ratio was to normalize the expected ACT increase per U/kg dose among studies.

Descriptive statistics were used to summarize ACT and dosage data with median values and ranges. For purposes of exploring relationships, target ACT values and maximum UFH doses were treated as categorical variables, while incidence and the target ACT:UFH dose ratio were treated as continuous. Fischer's exact test was used to compare the maximum UFH dose in studies before or after 2009 (see discussion). Notably, 2009 was used due to the report that UFH potency was reduced by 10% in 2009 as a result of new manufacturing standards).[35] Correlation between heparin resistance incidence and the target ACT to maximum UFH dose ratio was assessed using Spearman's correlation. An alpha <0.05 was considered significant. All calculations were performed using SAS 9.4 (SAS Institute, Cary, NC). Graphs were constructed using either SAS or GraphPad Prism 10.0 (GraphPad Software, Boston, MA).

Results

Literature Search, Most Frequent Targets, and Doses

A total of 116 reports were initially identified. After removal of animal data and non-cardiac surgical data, 74 reports remained and were evaluated. Following the exclusion of papers not including the required ACT and UFH dose information, 28 papers were available for data extraction. These studies and their calculated incidence of heparin resistance (when available) are presented in Table 1.[7-34]

A total of 85% of studies involved three target ACT values between 400 and 480 seconds. The most common ACT target was 480 seconds, found in 13 studies (46%), followed by 400 seconds in 6 studies (21%) and 450 seconds in 5 studies (18%). The remaining reports (15%) each had unique targets of 350, 490, 500, and 600 seconds. The most common maximum dose of UFH before being labeled heparin resistant was 300 U/kg in 8 studies (29%). Interestingly, 6 of those 8 studies were published after 2009. The second most common maximum dose was 400 U/kg in 7 studies (25%), followed by 500 u/kg in 5 studies (18%). No other maximum dose was found in more than 2 studies. There was no difference in the frequency distribution of the maximum doses reported before or after 2009 (p=0.781).

The most common combination of ACT target and maximum UFH dose was 480 seconds and 400 U/kg, although this was found in only 4 of the 28 studies (15%). Figure 1 summarizes the target ACT and maximum UFH dose for all included patients, rather than by study. The combination with the largest number of patients was 480 seconds and 500 u/kg, accounting for 5337 (47%) of subjects in the study population.

Incidence of heparin resistance and relationship to ACT target and UFH dose

The overall incidence of adult heparin resistance in the cardiac surgical literature was 17.5%, as determined from 28 studies including 11,382 total patients, of which 1,975 were classified as heparin resistant. The median target ACT to maximum UFH dose ratio was 1.15 with a range of 0.8 to 1.92. The incidence of heparin resistance by ACT target:maximum UFH dose is shown in Figure 2. The data suggested a weak relationship between incidence and the ratio (r=0.19), although this did not achieve statistical significance (p=0.369). The best fit non-linear curve is shown in Figure 2.

Discussion

Current data defining heparin resistance is primarily based on previously reported surveys in 1999, 2010, and 2019.[4, 5, 36] Unlike heparin resistance in hospitalized and critically ill patients, where anticoagulation testing typically utilizes activated partial thromboplastin times (aPTT) or anti-Xa levels to characterize UFH levels and

anticoagulant effects, cardiac surgical sites routinely use point-of-care ACT monitoring. This is because the heparin levels used in CPB exceed the monitoring ranges of aPTT and anti-Xa assays.

A major limitation of the ACT is that plasma heparin concentrations do not predictably follow linear correlations with ACT values during CPB, which is due to multiple factors. These include hemodilution, factor consumption, thrombocytopenia, hypothermia, and platelet dysfunction, all of which can prolong clot based ACT measurements independent of UFH plasma level and anticoagulant effects.[37-39] Multiple factors contribute to heparin resistance that include inflammation, which increases procoagulant factor levels such as fibrinogen, thrombocytosis, and decreased antithrombin levels.[40] Similar to Bull et al.'s described use of a manual in vitro heparin dose response curve, point-of-care automated test systems have been developed to estimate in vitro heparin dose responses and provide clinicians a starting point for bolus dosing. Unfortunately, these also fail to reliably predict the needed heparin dose for a desired ACT.[41] Further, ACT measurements are affected by testing methodologies themselves, including test conditions, reagents used for contact activation (e.g., celite vs kaolin), and device platforms that create heterogeneity in testing and variability in results. [42]

Even with standardized laboratory-based testing, there is variability in clinician expectations of the magnitude of change expected from any given UFH dose, as evidenced in our recent communication about heparin resistance in critically ill patients.[43] The dosing strategy of UFH for CPB bypass typically involves a weight-based bolus of much larger doses than those administered in ICU patients, but this is also highly variable. Initial doses prior to CPB used in clinical practice can range from <300 u/kg to more than 500 u/kg.[5] This variability in the initial bolus dose of heparin, as well as the use of variable cutoff values (i.e., 300 vs 400 vs 500 U/kg of heparin) for the definition of heparin resistance between clinicians and/or centers, further complicates the ability to diagnose of heparin resistance in cardiac surgery as consensus is lacking. [5].

Based on our literature survey, the threshold of an UFH dose of 400 U/kg with failure to reach a target ACT of 480 seconds represents the most extensively reported definition of heparin resistance. However, this definition represents less than 20% of published studies and only 12% of the 28 total publications analyzed in our literature review. The largest study, a retrospective observational study including 4367 patients, in which 23.7% exhibited heparin resistance, was based on a 500 U/kg heparin dose and a target ACT of 480 seconds.[8] This same ACT target:maximum UFH dose ratio was also used by Kikura et al., in their retrospective study involving 870 patients, with a similar incidence of 21.8%.[24] Therefore, the most common definition of heparin resistance weighted by the number of patients is the failure to reach a target ACT of 480 after 500 U/kg of UFH. As a result of our investigation, we propose that the definition of heparin resistance in cardiac surgical patients requiring CPB should be the failure to reach a target ACT of 480 after 500 U/kg of UFH.

One of the interesting findings from our analysis is that the incidence of heparin resistance is not simply a function of target ACT and the dose of heparin administered. Conceptually, higher ACT targets combined with lower bolus doses would seem to lead to more cases of failing to reach the desired level of anticoagulation. However, data from the published literature suggests this relationship is weak at best. The analyzed studies may have been influenced by a number of factors unrelated to target ACT and heparin dose. The reported studies included different patient populations with substantial differences in the incidence of preoperative heparin use and duration, which has been shown to result in a decrease in antithrombin levels of 5 to 7% per day. Additionally, subjects may have had other prothrombotic tendencies which may have resulted in lower clot based ACT levels.[40, 44] Garvin et al. reported no association between antithrombin levels and heparin resistance for ACT values between 300 and 350 seconds, although at this degree of anticoagulation, variable concentrations of heparin binding proteins may be important.[41] However, some of the studies include patients receiving aprotinin, a kallikrein and serine protease inhibitor that prolongs celite but not kaolin activated ACT measurement.[45];[46] Further, the use of different ACT technologies that use different whole blood activators (e.g., celite vs kaolin), can

substantially affect ACT measurements. Similarly, different clot detection methods may result in substantially different ACT values.[47]

Another potential factor contributing to the variability reported is the potency changes of UFH during the timeframe of our literature search (1992 – 2023). In the United States, UFH potency was reduced by 10% in 2009 as a result of new manufacturing standards.[35] However, when we examined the maximum dose of heparin used in studies, we found no significant difference between those published before 2009 and those published in 2009 or later. Our data extraction did not include patient hematological profiles, particularly antithrombin levels, so it is possible that variations in the incidence of heparin resistance could be due to a substantially different percentage of patients on preoperative heparin for varying duration.

In addition to all of the described ACT limitations, the optimal level of anticoagulation required to initiate and maintain CPB is still unknown. Historical studies in the 1970s reported no evidence of circuit or oxygenator clotting when the ACT was over 300 seconds.[2] However, a widely quoted study evaluating cardiopulmonary bypass circuits in rhesus monkeys reported formation of fibrin with a minimum ACT of 300 seconds and suggested the ACT should be increased to a threshold value of 400 seconds. Based on a report comprising 5 pediatric patients undergoing CPB, this may not reflect differences in adult coagulation profiles.[48] Despite this early suggestion of 400 seconds, subsequent publications have suggested a higher range of 400 to 480 seconds, which has been widely adopted and reported in various guidance and guideline documents.[3,5

Summary

Ensuring adequate anticoagulation for CPB is critical to attenuate subclinical hemostatic activation and consumption of the hemostatic factors that can lead to a disseminated intravascular coagulopathy like bleeding diathesis and, less commonly, overt catastrophic thrombosis. As a result, it is important for clinicians to identify when target therapeutic anticoagulation is not achieved, which, despite the lack of formal and

uniformly accepted diagnostic could cure you, continues to be described as heparin resistance. Prior reports defining heparin resistance in patients requiring cardiac surgery and cardiopulmonary bypass, as well as guidance documents, are based on a limited number of surveys from clinicians managing patients during cardiac surgery. Our review findings suggest the most widely reported ACT target for CPB is 480 seconds. Although most publications define heparin resistance as a failure to achieve this target after a weight-based dose of either 400 U/kg or 500 U/kg of heparin, a standardized definition would be useful to guide future clinical trials and help improve clinical management. We propose the inability to obtain an ACT target for CPB of 480 or more after 500 U/kg as a standardized definition for heparin resistance in this setting. Further work and clinical studies are needed to better define heparin resistance for patients requiring CPB, to identify the implications of this occurrence, and to develop optimal therapeutic approaches for managing these patients.

AUTHOR CONTRIBUTIONS

Specific author contributions: Drs Levy and Sniecinski wrote the initial drafts and revisions and performed the literature searches, Dr Sniecinski developed tables, analyzed the data, and developed the figures, Drs Despotis and Meier reviewed and provided additional expertise on the analysis, and all of the included authors reviewed and approved the manuscript.

CONFLICTS OF INTEREST

Dr. Levy is on Advisory or Steering Committees for Merck, Octapharma, Takeda, Werfen; Dr Sniecinski reports research support from Grifols and Cerus corporations, advisory board for OctaPharma; Dr. Maier reports no COI; Dr Despotis reports PI of study funded by both Medicare and Therakos/Mallinckrodt; Dr Ghadimi reports research support from Octapharma and the Patient-Centered Outcomes Research Institute.; Dr Helms reports honoraria from Asahi Kasei, Diagnostica Stago, Pfizer PFE France, Sanofi Aventis France, Inotrem, MSD, and Shionogi; Dr Manucci reports grants and speaker's fees from CSL Behring and speaker's fees from TEM International and LFB; Dr Steiner reports no COIs; Dr Tanaka reports research funding from Instrumentation Laboratory, CSL Behring, Octapharma data safety committee; Dr. Connors reports Scientific Ad Boards and Consulting: Abbott, Anthos, BMS, Pfizer, Roche, Sanofi, Werfen,

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Figure legends

Figure 1: Bubble plot showing the ACT targets of the included studies (x-axis) with their corresponding threshold for maximum dose of unfractionated heparin (UFH) administered before being designated heparin resistant (y-axis). The size of the bubble corresponds to the number of patients. The color of the bubble represents the reported incidence of heparin resistance for that combination of ACT target and maximum dose of heparin. When multiple studies contributed to the same point, the incidence of that combination was averaged together. Bubbles in black did not have a reported incidence of heparin resistance.

Figure 2: Scatterplot of the target ACT to maximum unfractionated heparin (UFH) dose ratio against the incidence of heparin resistance for the 24 studies which reported an incidence. Each green dot represents an individual study. The combined incidence of all studies was 17%, as indicated by the black dashed line. The blue curve is the best-fit curve obtained using the penalized B-spline method, with its 95% confidence intervals indicated by the shaded area. As indicated in the text, there was only a weak correlation between target ACT and maximum UFH dose.

Table 1: Included studies on adult patients undergoing cardiac surgery with cardiopulmonary bypass (CPB)

1st Author, Year, Reference	Study Type	Total Patients	HR Patients	Incidence Of HR	CPB Target (s)	Max UFH Dose (u/kg)	Primary Outcome / Comments
Horkay 1992 [7]	PRO Obs	20	4	20.0%	450	300*	Examined heparin levels on CPB. *Adult data extracted, data from 22 children excluded.*
Staples 1994 [8]	RETRO Obs	4367	1036	23.7%	480	500	Investigated factors related to heparin resistance, particularly intra-aortic balloon pumps and pre-op heparin.
Jobes 1995 [9]	PRO Interv	46	2	4.3%	400	300	Effect of pre-op heparin on ACT and protamine dosing.
Rannucci 1999 [10]	RETRO Obs	200	53	26.5%	450	380	Factors influencing heparin resistance. *Alternate definition of <400s on ACT after 300 u/kg of UFH.*
Shore-Lesserson 2000 [11]	PRO Obs	64	15	23.4%	480	300	Effect of pre-op heparin on ACT and high dose thrombin time.
Williams 2000 [12]	RCT	2270	85	3.7%	480	450	Antithrombin concentrate vs. additional UEH for cases of heparin resistance.
Nicholson 2001 [13]	PRO Obs	42	18	42.9%	400	300	Effect of pre-op UFH on ACT and effect of additional 5000 units of UFH once deemed “heparin resistant.”
Rannucci 2002 [14]	PRO Obs	500	104	20.8%	480	300	Factors related to heparin resistance. *Alternate definition of heparin sensitivity index < 1.0.*
Lemmer 2002 [15]	PRO Interv	NR	53	NA	600	600	Effect of antithrombin supplementation on ACT.
Koster 2003 [16]	PRO Interv	NR	100	NA	480	500	Investigation of management of patients deemed heparin resistant.
Neema 2004 [17]	PRO Interv	100	6	6.0%	350	300	Examination of standard heparinization protocol based upon heparin sensitivity.
Avidan 2005 [18]	RCT	296	54	18.2%	480	400	Recombinant antithrombin vs placebo in restoring heparin responsiveness.
Chan 2006 [19]	PRO Obs	400	32	8.0%	400	500*	Factors influencing heparin resistance.
DeBois 2006 [20]	RETRO Obs	300	79	26.3%	480	400	Development of a heparin sensitivity test.
Rodriguez-Lopez 2008 [21]	PRO Obs	44	16	36.4%	480	400	Restoring heparin responsiveness with recombinant antithrombin concentrate.
Na 2009 [22]	PRO Obs	64	20	31.3%	480	460	Outcomes of patients having surgery for infective endocarditis.
Casthely 2010 [23]	PRO Obs	80	NR	NA	450	400	Examination of heparin antibodies effect on hemodynamic parameters; high titers also required more heparin.

Kikura 2012 [24]	RETRO Obs	870	190	21.8%	480	500	Effect of nafamostat mesilate on the treatment of heparin resistance.
Knapik 2012 [25]	RETRO Obs	756	31	4.1%	480	400	Outcomes in patients with heparin resistance. *Alternate definitions of ACT <400 with 300 u/kg*
Ranucci 2013 [26]	RCT	199	55	27.6%	450	400	Effect of pre-op antithrombin supplementation on post-op antithrombin levels.
Bagheri 2014 [27]	RETRO Obs	100	3	3.0%	400	400	Frequency of heparin resistance.
Fang 2018 [28]	RETRO Obs	66	11	16.7%	480	300	TEG profiles of patients with heparin resistance and CHD. *Study included 5% adults, whose data was extracted.*
Ciolek 2018 [29]	RETRO Obs	NR	19	NA	490	500	Cost analysis of inappropriate antithrombin supplementation.
Saydam 2019 [30]	RETRO Obs	139	29	20.9%	400	450	Effect of pre-op UFH on OR ACT. *Alternate definition of heparin sensitivity index <1.3.*
Kimura 2021 [31]	RETRO Obs	287	88	30.7%	400	350	Effect of endocarditis on ACT. *Maximum bolus ranged from 250 u/kg to 350 u/kg.*
Stammers 2021 [32]	RETRO Obs	140	10	7.1%	500	600	Testing effectiveness of antithrombin replacement algorithm.
Ma 2022 [33]	PRO Obs	42	10	23.8%	480	250*	Influence of selected genetic markers on heparin sensitivity.
Breel 2023 [34}	PRO Obs	70	24	34.3%	450	300	Comparison of ROTEM parameters between infective endocarditis patients and controls undergoing cardiac surgery.

*=dose in paper provided as mg/kg and was converted to 1 mg = 100 u of UFH per convention. RETRO=retrospective, PRO=prospective, Obs=observational, Interv=interventional, HR=heparin resistance, UFH=unfractionated heparin, NR=not reported, NA=not available.