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Anticoagulation Management and Heparin Resistance During Cardiopulmonary Bypass: A Survey of Society of Cardiovascular Anesthesiologists Members

Roman M. Sniecinski, MD, MSc,* Elliott Bennett-Guerrero, MD,† and Linda Shore-Lesserson, MD‡

We surveyed Society of Cardiovascular Anesthesiologists members regarding anticoagulation practices for cardiopulmonary bypass and attitudes on heparin resistance. Of 550 respondents (18.5% response rate), 74.9% (95% CI, 71.3%–78.5%) used empiric weight-based dosing of heparin, and 70.7% (95% CI, 66.9%–74.5%) targeted an activated clotting time of either 400 or 480 seconds to initiate cardiopulmonary bypass. Of note, 17.1% (95% CI, 13.9%–20.2%) of respondents reported activated clotting time targets lower than those recommended by recent 2018 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology guidelines or failed to monitor heparin effects at all. When heparin resistance was encountered, 54.2% of respondents (95% CI, 50.0%–58.4%) administered antithrombin concentrates as a first-line therapy. (*Anesth Analg* 2019;129:e41–4)

Despite its longevity of use for anticoagulation during cardiac surgery, significant variability in heparin dosing and monitoring has been reported. A 1993 survey of members of the Society of Cardiovascular Anesthesiologists and American Society of Extracorporeal Technology demonstrated that, although the activated clotting time was used by 99% of respondents, acceptable values for the conduct of cardiopulmonary bypass (CPB) ranged from 240 to 1000 seconds.¹ A survey of 54 North American institutions administered in 2008 by the Duke Clinical Research Institute and published by Lobato et al² reported a similarly wide range of target activated clotting times, with values of 400–480 seconds being used by approximately 70% of respondents. Variability in anticoagulation practices is likely the result of a gap in evidence and any formal recommendations. Only recently have the Society of Cardiovascular Anesthesiologists, American Society of Extracorporeal Technology, and the Society of Thoracic Surgeons released clinical practice guidelines for CPB anticoagulation.³

Decreased heparin responsiveness, frequently termed “heparin resistance,” is an area that lacks consensus in either

diagnosis or treatment. The reported incidence during CPB use ranges from 4% to 26%⁴ and is highly dependent on the initial bolus dose of heparin and the desired activated clotting time target for CPB initiation. Therapies for heparin resistance include antithrombin concentrates, fresh frozen plasma, and the administration of additional heparin.⁴ The 2011 blood conservation guidelines from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists recommend administration of antithrombin concentrates in preference to fresh frozen plasma in instances of antithrombin-mediated heparin resistance.⁵ However, the acceptance and impact of this recommendation remain unknown. In the report by Lobato et al,² fresh frozen plasma was the predominant treatment for heparin resistance in 85% of US and Canadian centers.²

Recently, Miles et al⁶ conducted a global survey of CPB priming practices and reported that 72.7% of respondents used an activated clotting time target between 400 and 500 seconds for initiation of CPB. That particular survey, however, asked only 1 question regarding activated clotting time values and contained no items related to heparin dosing or responsiveness. We conducted the present survey to describe both (1) current practice of anticoagulation for initiation and maintenance of CPB and (2) clinician attitudes on heparin resistance and their current use of antithrombin concentrates. In addition, since 2018 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology CPB anticoagulation guidelines have just been released,³ we wanted to use the collected survey data to determine what percentage of practitioners are already compliant with these recommendations.

METHODS

Survey Creation and Validation

The authors used SurveyMonkey online software (San Mateo, CA) to create a pilot survey, which was administered to members of the Division of Cardiothoracic Anesthesiology at Emory University. Answers pertaining to heparin dosing and antithrombin concentrate usage were compared to known institutional protocols to ensure that the survey instrument was accurately capturing actual clinical practice. The final iteration of the survey had 20 questions and is provided in Supplemental Digital Content 1, Survey,

From the *Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; †Department of Anesthesiology, Stony Brook School of Medicine, Stony Brook, New York; and ‡Department of Anesthesiology, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York.

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Address correspondence to Roman M. Sniecinski, MD, MSc, Department of Anesthesiology, Emory University Hospital, 1364 Clifton Rd, NE, Atlanta, GA 30322. Address e-mail to rsnieci@emory.edu.

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<http://links.lww.com/AA/C680>. The survey was reviewed and approved by the Society of Cardiovascular Anesthesiologists's Research Committee and the Emory School of Medicine's Institutional Review Board. The requirement for written informed consent was waived by both entities.

Survey Distribution

The target population was members of the Society of Cardiovascular Anesthesiologists at the "Active" and "Associate" levels, representing licensed physicians actively taking care of cardiac surgical patients. Members at the "Fellow/Resident" and "Career Scientist" levels were excluded. The Society of Cardiovascular Anesthesiologists membership office distributed an electronic link to the survey to all eligible members via an initial e-mail communication on August 2, 2017. Members had approximately 2 months to complete the survey, with follow-up reminder e-mails sent on August 24, 2017 and September 29, 2017. The survey closed on October 1, 2017. Members were asked to complete the survey only once.

Determination of Guideline Compliance

The recent Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology guidelines for CPB anticoagulation contain items related to "Heparin dosing for initiation and maintenance of CPB."³ The recommendations state that a clotting time should be measured and demonstrate "adequate anticoagulation" before initiation and at regular intervals during CPB.³ Guidance on minimal acceptable activated clotting time values is given as either >480 or >400 seconds when whole blood is maximally activated or microcuvette technology is used.³ Thus, respondents who either did not use activated clotting times or targeted activated clotting times <400 seconds either before initiation of CPB or during CPB (survey questions 8, 9, and 11) were considered not compliant with these recommendations.

Completion Incentive

Responses were anonymous, but participants had the option of entering an e-mail address into a random drawing for 1 of 10 Amazon gift cards valued at \$125 and 1 of 5 annual memberships to the Society of Cardiovascular Anesthesiologists (value of \$270).

Responses Analyzed

Respondents who indicated on the survey that they did not care for adult patients undergoing cardiac surgery using CPB were excluded. Responses with identical e-mail addresses entered for the incentive drawing were considered to be duplicates, and only the first completed survey was used for purposes of the incentive drawing and the analysis. Respondents who entered only demographic information for the purposes of the incentive drawing were not used in the analysis.

Statistical Analysis

Based on an estimated membership population of 3000, CIs of 95%, and a sample proportion of 0.5, we calculated that we would need 501 responses to achieve a global margin

of error of 4%. Descriptive statistics, including frequency tables with proportions and bar graphs, were used to summarize the data. Wald CIs for proportions were set at 95%. Responses to individual questions that were left blank were classified as "unknown." All calculations were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

The electronic link to the survey was distributed to 2972 Society of Cardiovascular Anesthesiologists members. We received 580 responses, of which 550 were used for analysis, giving an effective response rate of 18.5% (Supplemental Digital Content 2, Figure 2, <http://links.lww.com/AA/C681>). Respondent demographics are provided in the Table and closely mirrored the membership composition of the Society of Cardiovascular Anesthesiologists (Supplemental Digital Content 3, Figure 3A, <http://links.lww.com/AA/C682>), with 83.8% of responses coming from North America. Responses from all states within the United States were received, with the exceptions of Delaware, Idaho, North Dakota, South Dakota, and Wyoming (Supplemental Digital Content 3, Figure 3B, <http://links.lww.com/AA/C682>).

Answers to specific heparin management questions are provided in the Table. An empiric weight-based approach to determining the pre-CPB heparin bolus was used by 74.9% of respondents (95% CI, 71.3%–78.5%). Empiric weight-based doses of heparin used for initiation of CPB are provided in Figure 1A. The maximum dose of heparin that respondents would administer before initiating additional therapy to achieve a target activated clotting time is provided in Figure 1B. Heparin was also added to the CPB circuit by the majority of respondents (84%; 95% CI, 80.9%–87.0%). Adequate anticoagulation was assessed by targeting a specific activated clotting time for "initiation" of CPB and "during" CPB by 84.7% (95% CI, 81.7%–87.7%) and 88.4% (95% CI, 85.7%–91.1%) of respondents, respectively. In addition to an activated clotting time, 13.1% (95% CI, 10.3%–15.9%) also used a heparin level to determine adequate anticoagulation for initiation of CPB, and 6.7% (95% CI, 4.6%–8.8%) maintained a specific heparin level during CPB.

For those respondents who used an activated clotting time to determine adequate anticoagulation for CPB initiation, either with or without a heparin level (538 of 550), an activated clotting time value of 480 or 400 seconds was used by 70.7% (95% CI, 66.9%–74.5%). The full range of activated clotting time targets for initiation and maintenance of CPB is provided in Figure 2. Of the 550 respondents, 17.1% (95% CI, 13.9%–20.2%) provided answers inconsistent with 2018 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology guidelines regarding activated clotting time targets for initiation and/or maintenance of CPB.

Specific answers to questions regarding heparin resistance are provided in the Table. In terms of frequency, about half of respondents felt that they encountered it in 1%–10% of the CPB cases they performed. More clinicians administered antithrombin concentrate as a first-line treatment (54.2%; 95% CI, 50.0%–58.5%) compared to those who administered fresh frozen plasma as a first-line treatment

Table. Survey Responses			
Demographics of Respondents		n (%)	
Region			
United States	430	(78.2)	
Canada	31	(5.6)	
Europe	34	(6.2)	
Australia/New Zealand	26	(4.7)	
Mexico/South America	17	(3.1)	
Asia	11	(2.0)	
Africa/Middle East	1	(0.2)	
Do you work with anesthesia residents of fellows? ("Yes" response)	332	(60.4)	
No. of CPB cases per year			
≤250	107	(19.5)	
251–500	152	(27.6)	
501–1000	172	(31.3)	
>1000	119	(21.6)	
Heparin Management		n (%)	95% CI of %
How do you determine the dose of heparin to administer before initiating CPB?			
Empiric weight based (eg, units/kg)	412	(74.9)	71.3%–78.5%
Dose–response calculation (eg, Hepcon [Medtronic, Minneapolis, MN])	135	(24.5)	20.9%–28.1%
Other/unknown	3	(0.5)	0%–1.2%
How do you determine an adequate degree of anticoagulation for initiation of CPB?			
Target an activated clotting time	466	(84.7)	81.7%–87.7%
Target both an activated clotting time and heparin level	72	(13.1)	10.3%–15.9%
Other	8	(1.5)	0.5%–2.5%
Unknown	4	(0.7)	0%–1.4%
Do you add heparin to the CPB circuit/reservoir before initiating CPB?			
Yes	462	(84)	80.9%–87.0%
No	71	(12.9)	10.1%–15.7%
Unknown	17	(3.1)	1.6%–4.5%
How do you maintain anticoagulation during CPB (ie, after CPB is already initiated)?			
Give additional heparin to target an activated clotting time	486	(88.4)	85.7%–91.1%
Give additional heparin to maintain heparin level	37	(6.7)	4.6%–8.8%
Other	20	(3.6)	2.1%–5.2%
Unknown	7	(1.3)	0.3%–2.2%
Attitudes on Heparin Resistance		n (%)	95% CI of %
Approximately what percentage of cardiac surgical cases using CPB do you encounter clinically significant heparin resistance?			
<1%	191	(34.7)	30.7%–38.7%
1%–10%	298	(54.2)	50.0%–58.4%
>10%	47	(8.5)	6.2%–10.9%
Unknown	14	(2.5)	1.2%–3.9%
Assuming the desired level of anticoagulation is not achieved with heparin alone, what is the first action you would take?			
Administer antithrombin concentrate	298	(54.2)	50.0%–58.4%
Administer fresh frozen plasma	211	(38.4)	34.3%–42.4%
Administer an alternate anticoagulant	12	(2.2)	1.0%–3.4%
Initiate CPB anyway	5	(0.9)	0.1%–1.7%
Unknown	24	(4.4)	2.7%–6.1%

(Continued)

Table. Continued			
Attitudes on Heparin Resistance		n (%)	95% CI of %
When you encounter heparin resistance, how often do you administer antithrombin concentrate?			
Always/very often	220	(40.0)	35.9%–44.1%
Often/sometimes	112	(20.4)	17.0%–23.7%
Rarely/never	192	(34.9)	30.9%–38.9%
Unknown	26	(4.7)	2.9%–6.5%
Do you agree with the 2011 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists Blood Conservation recommendation regarding use of antithrombin concentrate to treat heparin resistance?			
Yes	283	(51.5)	47.3%–55.6%
Yes, but not as a class I recommendation	89	(16.2)	13.1%–19.3%
No	7	(1.3)	0.3%–2.2%
I am not familiar with this recommendation	145	(26.4)	22.7%–30.1%
Unknown	26	(4.7)	2.9%–6.5%
When antithrombin concentrate is not used in cases of heparin resistance, the primary reason is:			
Not on my hospital's formulary	76	(32.5)	26.4%–38.5%
The cost is too high	74	(31.6)	25.6%–37.6%
I prefer to give fresh frozen plasma	44	(18.8)	13.8%–23.8%
Unfamiliar with antithrombin concentrate or recommendations	40	(17.1)	12.2%–22.0%

Results are given as n (%) of respondents selecting a particular answer. Abbreviation: CPB, cardiopulmonary bypass.

(38.4%; 95% CI, 34.3%–42.4%). The majority of respondents were in agreement with the 2011 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists recommendation to use antithrombin concentrate, although about one-third rarely or never utilized it in cases of heparin resistance. The primary reason antithrombin concentrates were not used in this situation was cost being too high and antithrombin concentrates not being on the hospital formulary.

DISCUSSION

Our survey of Society of Cardiovascular Anesthesiologists members regarding anticoagulation practices for CPB consisted mostly of clinicians in North America but included a balanced distribution of small-, medium-, and large-volume centers, as well as a close split between programs with and without trainees. Like the survey conducted in 2008 by Lobato et al,² we found that empiric dosing of heparin with activated clotting time targets of 400 or 480 seconds is used by the majority of practitioners. Of note, however, is that >15% of respondents reported using anticoagulation therapy falling outside of recent 2018 Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology guidelines³; it may be useful to use this number as a starting point to gauge adoption of these recommendations. It is also interesting to note that more clinicians now use antithrombin

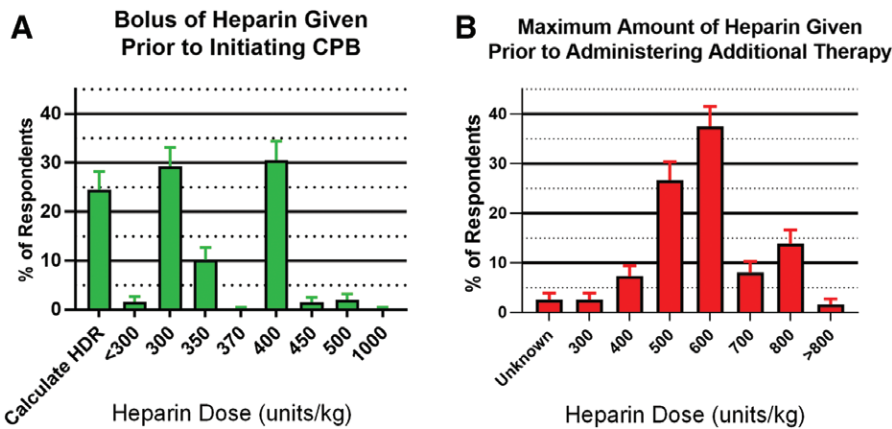


Figure 1. Bar graphs of (A) percentage of respondents indicating either empiric weight-based dose or a calculated dose based on heparin dose–response (HDR) curve, which is typically administered before the initiation of cardiopulmonary bypass (CPB), and (B) percentage of respondents indicating what the maximum dose of heparin they would give before administering additional therapy to achieve the desired level of anticoagulation for CPB. Doses are given in U/kg. Error bars indicate Wald 95% CIs of the proportion.

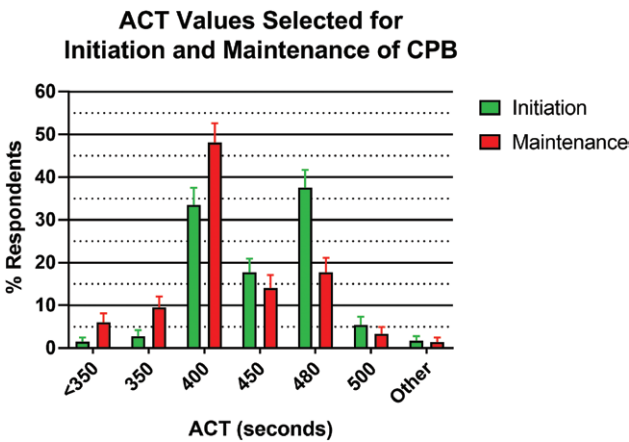


Figure 2. Bar graph of percentage of those respondents who utilized activated clotting times (ACTs) targeting a specific ACT value for initiation (green bars) and maintenance (red bars) of cardiopulmonary bypass (CPB). Error bars indicate Wald 95% CIs of the proportion.

concentrate in cases of heparin resistance compared to 10 years ago. In conclusion, while anticoagulation targets for CPB, as determined by the activated clotting time, have remained steady over the past decade, antithrombin concentrate utilization has increased when those targets are felt to be inadequately met. ■■

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DISCLOSURES

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Name: Elliott Bennett-Guerrero, MD.
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Name: Linda Shore-Lesserson, MD.
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