ANESTHESIOLOGY

Anticoagulation Management and Antithrombin Supplementation Practice during Veno-venous Extracorporeal Membrane Oxygenation

A Worldwide Survey

Alessandro Protti, M.D., Giacomo E. Iapichino, M.D., Matteo Di Nardo, M.D., Mauro Panigada, M.D., Luciano Gattinoni, M.D., F.R.C.P.

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ABSTRACT

Background: There is a lack of consensus on how to manage anticoagulation during veno-venous extracorporeal membrane oxygenation, including antithrombin monitoring and supplementation. The authors' aim was to determine current practice in a large number of extracorporeal membrane oxygenation centers around the world.

Methods: This was an electronic survey disseminated in 2018 to directors and coordinators of extracorporeal membrane oxygenation centers as well as to extracorporeal membrane oxygenation experts. Participating centers were classified according to some covariates that may affect practice, including 2017 gross national income per capita, primary patient population, and annual extracorporeal membrane oxygenation patient volume.

Results: The authors analyzed 273 unique responses from 50 countries. Systemic anticoagulation was routinely prescribed in 264 (96.7%) centers, with unfractionated heparin being the drug of choice in 255 (96.6%) of them. The preferred method to monitor anticoagulation was activated partial thromboplastin time in 114 (41.8%) centers, activated clotting time in 82 (30.0%) centers, and anti-factor Xa activity in 62 (22.7%) centers. Circulating antithrombin activity was routinely monitored in 133 (48.7%) centers. Antithrombin supplementation was routinely prescribed in 104 (38.1%) centers. At multivariable analyzes, routine antithrombin supplementation was associated with national income, being less likely in lower- than in higher-income countries (odds ratio, 0.099 [95% CI, 0.022 to 0.45]; $P = 0.003$); with primary patient population being more frequent in mixed (odds ratio, 2.73 [1.23 to 6.0]; $P = 0.013$) and pediatric-only centers (odds ratio, 6.3 [2.98 to 13.2]; $P < 0.001$) than in adult-only centers; but not with annual volume of extracorporeal membrane oxygenation cases, being similarly common in smaller and larger centers (odds ratio, 1.00 [0.48 to 2.08]; $P = 0.997$).

Conclusions: There is large practice variation among institutions regarding anticoagulation management and antithrombin supplementation during veno-venous extracorporeal membrane oxygenation. The paucity of prospective studies and differences across institutions based on national income and primary patient population may contribute to these findings.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Managing anticoagulation during veno-venous extracorporeal membrane oxygenation varies around the world among clinical sites. Understanding clinical practice is important when developing multicenter clinical studies.

What This Article Tells Us That Is New

- Based on 273 responses from 50 countries, unfractionated heparin is used in 96.6% of centers, with partial thromboplastin time monitoring in 41.8%, activated clotting time in 30.0%, and anti-factor Xa activity in 22.7% of centers. Antithrombin is monitored in 48.7% of centers and actively repleted in 38.1% of centers, mainly in high-income regions and in pediatric patients.

Unfractionated heparin is commonly prescribed during veno-venous extracorporeal membrane oxygenation to counteract the procoagulant response to blood contact with nonbiologic surfaces. The effectiveness of heparin depends on the level of anticoagulation achieved.[1] Excessive anticoagulation can cause bleeding, whereas insufficient anticoagulation can result in thrombosis.[2] Despite its importance, there is still no consensus on how to manage anticoagulation during veno-venous extracorporeal membrane oxygenation.

The anticoagulant effect of heparin is mediated by its interaction with antithrombin, a circulating protein that inhibits thrombin, factor Xa, and other coagulation factors.

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Low antithrombin activity decreases, and antithrombin supplementation preserves or restores the anticoagulant effect of heparin during cardiopulmonary bypass.[3,4] Harmful effects of antithrombin deficiency and benefits of antithrombin supplementation during veno-venous extracorporeal membrane oxygenation are less clear. The Extracorporeal Life Support Organization acknowledges that the optimal antithrombin activity during extracorporeal life support remains unknown. Even so, the organization suggests considering correction of antithrombin deficiency in infants and children with escalating heparin requirements and/or clinically subtherapeutic anticoagulation.[5]

Two international surveys conducted in 175 centers registered with the Extracorporeal Life Support Organization have shown large variation in management of anticoagulation, antithrombin testing, and antithrombin supplementation during extracorporeal membrane oxygenation.[6,7] Most (79.4%) of respondents were from North America. The lack of separate analysis of veno-arterial and veno-venous extracorporeal membrane oxygenation possibly contributed to the observed heterogeneity across institutions.

The primary aim of this present survey was to describe practice in a larger number of centers from all over the world, with an exclusive focus on veno-venous extracorporeal membrane oxygenation and with a special interest on antithrombin supplementation. We hypothesized that anticoagulation management and antithrombin supplementation would have clearly differed between centers similarly to other aspects related to extracorporeal membrane oxygenation (such as concurrent mechanical ventilation).[8–10] Secondary objectives were association of anticoagulation practice with some potential covariates such as national income, primary patient population treated, and annual extracorporeal membrane oxygenation patient volume.

Materials and Methods

This was an open voluntary survey using a commercial web-based instrument (SurveyMonkey.com). The survey was announced in 2018 at the 38th International Symposium of Intensive Care and Emergency Medicine held in Brussels and at the 7th European Chapter of the Extracorporeal Life Support Organization Congress held in Prague, and it was posted on the website of the Extracorporeal Life Support Organization and on ResearchGate, a free social network service for scientists (https://www.researchgate.net; accessed March 16, 2018). The survey was disseminated *via* e-mail to directors and coordinators of extracorporeal membrane oxygenation centers listed on the website of the Extracorporeal Life Support Organization or retrieved from Google (using "extracorporeal membrane oxygenation" and "director" or "coordinator" as search terms) and to the corresponding authors of publications on veno-venous extracorporeal membrane oxygenation retrieved from PubMed. New participants were searched and contacted every month, from March to December 2018, when the minimum number of unique responses (described in the section on Statistical Analysis) was reached.

The survey consisted of multiple-choice and open-ended questions organized in two pages. The first page contained questions regarding details of respondents. These data were explicitly requested to detect multiple answers from the same intensive care unit, to allow contact with participants in case of missing or unclear answers, and to acknowledge individual contributions. The second page contained questions related to four main domains: (1) center characteristics; (2) anticoagulation management; (3) antithrombin testing; and (4) antithrombin supplementation with recombinant antithrombin or antithrombin concentrate during veno-venous extracorporeal membrane oxygenation. Because the original survey did not contain enough data to estimate the percentage of patients receiving at least one dose of antithrombin while on veno-venous extracorporeal membrane oxygenation, this exact question was asked to all participants *via* e-mail after the survey had been closed. Respondents were invited to report institutional protocols rather than their personal preference. After submission, questionnaires were checked for completeness and consistency; participants were contacted, if needed. Multiple respondents from the same intensive care unit were asked to provide a single common response.

Institutional ethics oversight was considered unnecessary.[11] As stated in the invitation e-mail, we assumed that participants consented to our processing of their data, according to our local (Italian) legislation, when they submitted the questionnaire.

The full version of the questionnaire is reported in the Supplemental Digital Content (http://links.lww.com/ALN/C90). Other details on the survey design are reported in Supplemental Digital Content, table 1 (http://links.lww.com/ALN/C90).

Definitions

We decided in advance to study the impact of the following criteria on reported practice: (1) university affiliation or not; (2) registration with the Extracorporeal Life Support Organization or not; (3) 2017 gross national income per capita, categorized *a posteriori* as high (at least $12,056 USD) or non-high (less than $12,056 USD) [www.worldbank.org]; (4) primary patient population, categorized *a posteriori* as adult-only, pediatric-only (neonates and/or children), or mixed (all others); and (5) annual extracorporeal membrane oxygenation patient volume, categorized *a posteriori* in tertiles as low (less than 10 cases per year), intermediate (10 to 20 cases per year), or high (more than 20 cases per year).

Statistical Analysis

We calculated a sample size of 260 unique responses to estimate the frequency of routine antithrombin supplementation with a CI of 5% and a confidence level of 95%, presuming

that there were 750 respiratory extracorporeal membrane oxygenation centers around the world (that is, twice the number of centers reporting data to the Extracorporeal Life Support Organization in 2017 [www.elso.org]).

Data are reported as median and interquartile range or number and percentage of respondents. Differences between groups were analyzed with the Wilcoxon rank sum test or the chi-squared test. The association between covariates listed (and categorized as) above and routine antithrombin supplementation was studied with univariate and multivariable logistic regression analysis. The latter is a statistical tool for determining the independent contribution of each covariate to a (dichotomous) outcome.[12] We decided *a priori* to include university affiliation, registration with the Extracorporeal Life Support Organization, 2017 gross national income per capita, primary patient population, and annual extracorporeal membrane oxygenation patient volume in multivariable models based on their plausible importance as explanatory variables. Results are reported as odds ratio and 95% CI.

All tests were two-sided, and *P* values less than 0.05 were considered significant (SigmaPlot version 11.0, Jandel Scientific Software; USA).

Results

By December 2018, we had received 303 responses in total, including nine blank responses, 19 duplicates, and one triplicate. Participants from the same intensive care units were recontacted, and they all provided single common responses. Finally, 273 separate responses from 50 countries and five continents were available for analysis: 128 (46.9%) were from Europe, 75 (27.5%) from North America, 43 (15.8%) from Asia, 13 (4.8%) from Oceania, 10 (3.7%) from South America, and 4 (1.5%) from Africa (fig. 1). Participants are listed in the Supplemental Digital Content (http://links.lww.com/ALN/C90).

Center Characteristics

Two hundred twenty-three (81.7%) responses were from university hospitals, and 185 (67.8%) were from centers registered with the Extracorporeal Life Support Organization. Two hundred forty-two (88.6%) responses were from high-income and 31 (11.4%) from non–high-income countries. Primary patient population was adult-only in 166 (60.8%) centers, pediatric-only in 67 (24.5%) centers, and mixed in 40 (14.7%) centers. Annual extracorporeal membrane oxygenation patient volume was low in 87 (31.9%) centers, intermediate in 99 (36.3%) centers, and high in 85 (31.1%) centers; it was unknown for 2 (0.7%) centers. The declared total annual extracorporeal membrane oxygenation patient volume, referred to all participating centers, was 5,952 cases per year.

Anticoagulation Management

Systemic anticoagulation was routinely prescribed in 264 (96.7%) centers, with unfractionated heparin being the drug of choice in 255 (96.6%). Nine (3.3%) participants reported

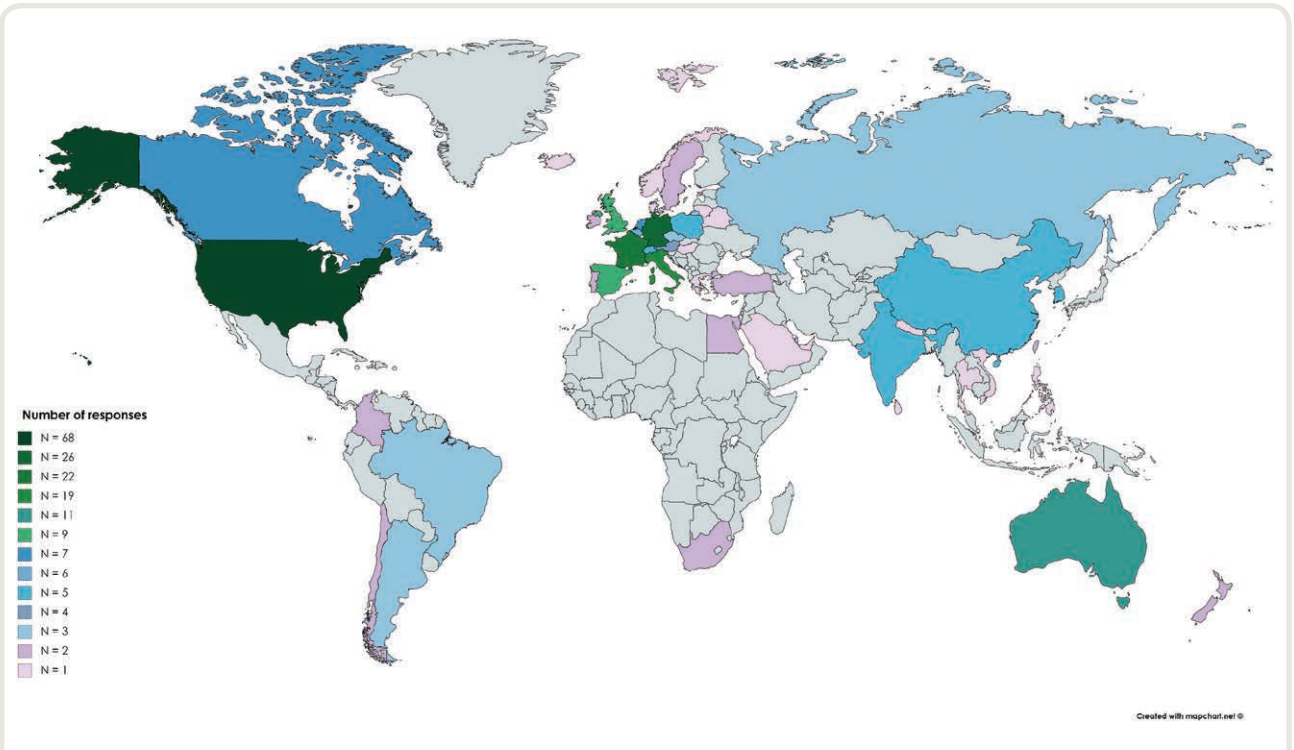

Fig. 1. Geographical distribution of the 273 centers participating in the survey.

that they did not routinely prescribe anticoagulation during veno-venous extracorporeal membrane oxygenation.

The (mutually exclusive) preferred method to monitor anticoagulation was activated partial thromboplastin time in 114 (41.8%) centers, activated clotting time in 82 (30.0%) centers, anti-factor Xa activity (anti-Xa) in 62 (22.7%) centers, and other or unclear in 6 (2.2%) centers. As a general rule, the activated clotting time was preferred to the activated partial thromboplastin time in lower-income countries, whereas the anti-Xa was most frequently used in pediatric-only centers (fig. 2).

The therapeutic goals adopted in each institution for the three most common monitoring tests are shown in figure 3. On average, lower and upper limits were 50 (46 to 60) and 60 (60 to 71) seconds or 1.5 (1.5 to 2.0) and 2.0 (2.0 to 2.5) times control for the activated partial thromboplastin time, 170 (160 to 180) and 200 (180 to 220) seconds for the activated clotting time, and 0.3 (0.2 to 0.3) and 0.5 (0.4 to 0.7) IU/ml for the anti-Xa.

Antithrombin Testing

Circulating antithrombin activity was routinely measured in 133 (48.7%) centers. Antithrombin testing was routine practice in 110 (49.3%) university hospitals and in 23 (46.0%) nonuniversity hospitals ($P = 0.788$); in 93 (50.3%) centers registered with the Extracorporeal Life Support Organization and in 40 (45.5%) centers not registered with Extracorporeal Life Support Organization ($P = 0.539$); in 123 (50.8%) centers from high-income and in 10 (32.3%) centers from non–high-income regions ($P = 0.079$); in 59 (35.5%) adult-only, in 20 (50.0%) mixed, and in 54 (80.6%) pediatric-only centers ($P < 0.001$); in 47 (54.0%) low-volume, in 52 (52.3%) intermediate-volume, and in 34 (40.0%) high-volume centers ($P = 0.127$).

Antithrombin Supplementation

The proportion of patients normally treated with at least one dose of recombinant antithrombin or antithrombin concentrate while on veno-venous extracorporeal membrane oxygenation was reported by 255 (93.1%) participants. It was less than 10% (none of the patients) in 135 (52.9%) centers, 10 to 50% (some of the patients) in 65 (25.5%) centers, 50 to 90% (most of the patients) in 39 (15.3%) centers, and more than 90% (all of the patients) in 16 (6.3%) centers. This proportion was larger in centers in high-income regions and in those treating only neonates and/or children (fig. 4).

Antithrombin supplementation was routinely prescribed in 104 (38.1%) centers, whenever the anticoagulation target could not be readily achieved (in 53 [51.0%] of those centers) or when the circulating antithrombin activity was lower than 70% (60 to 80%; in 51 [49.0%]; Supplemental Digital Content, fig. 1, http://links.lww.com/ALN/C90). Recombinant antithrombin and antithrombin concentrate were used in 21 (20.1%) and 83 (79.9%) centers, respectively.

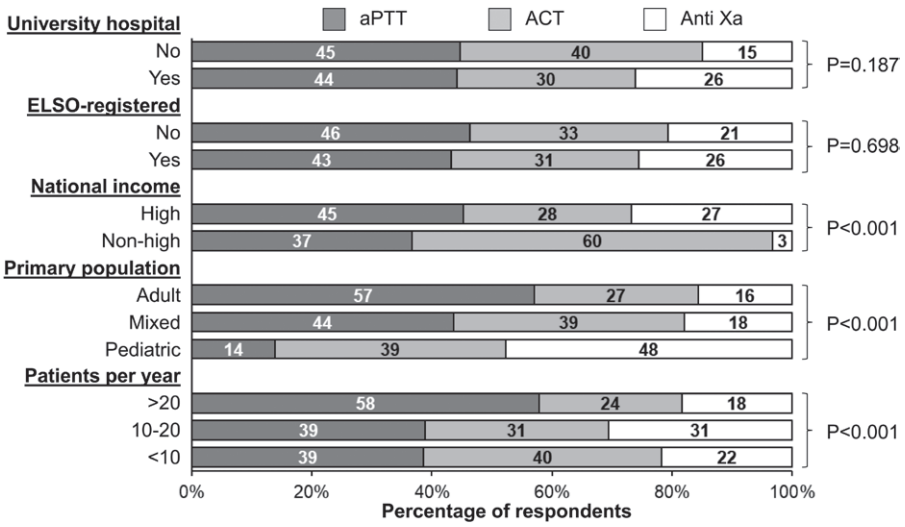

Fig. 2. The single preferred test for monitoring systemic anticoagulation during veno-venous extracorporeal membrane oxygenation. Herein we compare the frequency of monitoring anticoagulation with the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), or the anti-Xa between centers, classified according to the following criteria: (1) university hospital or not; (2) registered with the Extracorporeal Life Support Organization (ELSO) or not; (3) 2017 gross national income per capita, categorized as high (at least $12,056 USD) or non-high (less than $12,056 USD); (4) primary patient population, categorized as adult-only, pediatric-only, or mixed; (5) annual extracorporeal membrane oxygenation patient volume, categorized as high (more than 20 cases per year), intermediate (10 to 20 cases per year), or low (less than 10 cases per year). Bars and labels are percentages of respondents. *P* values refer to chi-squared test.

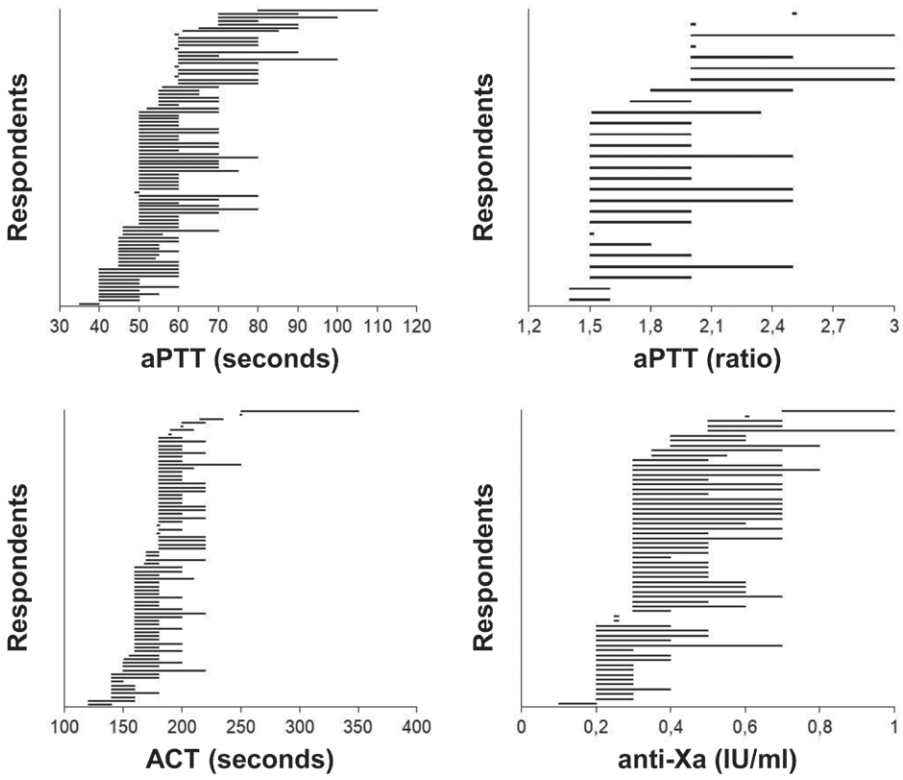

Fig. 3. Targets for systemic anticoagulation during veno-venous extracorporeal membrane oxygenation. Herein we report the usual therapeutic target for the most common tests for monitoring heparin-induced anticoagulation during veno-venous extracorporeal membrane oxygenation. As for the activated partial thromboplastin time (aPTT), the therapeutic range was reported in seconds by 85 (75.9%) participants and relative to control (as ratio) by 27 (24.1%) participants. Each line connects the lower and the upper limits of the therapeutic target declared by each respondent. For example, in the panel labelled "ACT (seconds)," the top line corresponds to a target of 250 to 350 s; the second line corresponds to a target of 250 s. ACT, activated clotting time.

Antithrombin supplementation (with recombinant antithrombin or antithrombin concentrate) was not routinely prescribed in 169 (61.9%) centers, including 79 (28.9%) where fresh frozen plasma was the drug of choice to increase antithrombin activity (Supplemental Digital Content, table 2, http://links.lww.com/ALN/C90).

As shown in table 1, regular antithrombin supplementation was associated with national income (being less likely in lower-income countries), primary patient population (used in as many as 44 [65.7%] pediatric-only centers), but not with other covariates, both at univariate and multivariable analysis. Practice differed between Europe and North America, the two most represented (high-income) regions, with antithrombin supplementation being more common in the former (Supplemental Digital Content, table 3, http://links.lww.com/ALN/C90). This result was valid even when the analysis was restricted to pediatric-only centers: antithrombin was routinely prescribed in 17 (89.5%) centers in Europe and in 25 (64.1%) in North America ($P = 0.042$). Of note, cost of antithrombin reported by participants to the survey was on average six times lower in Europe than in North America (Supplemental Digital Content, table 4, http://links.lww.com/ALN/C90). As for Italy, our own country, antithrombin was routinely prescribed in 18 of 19 (94.7%) centers. Fifteen of these centers were part of the national network for respiratory support ("Rete specializzata nell'insufficienza respiratoria acuta" - ReSpIRA) and had some protocols in common.

Reasons for routinely prescribing or not prescribing antithrombin supplementation are summarized in table 2.

Other results are reported in the Supplemental Digital Content (http://links.lww.com/ALN/C90).

Discussion

According to this survey, there is large variation among institutions from all over the world regarding anticoagulation management and antithrombin supplementation during veno-venous extracorporeal membrane oxygenation. This finding probably reflects the paucity of prospective studies on best practice in this very specific setting. Other variables, such as national income and primary patient population, are likely to play an important role too.

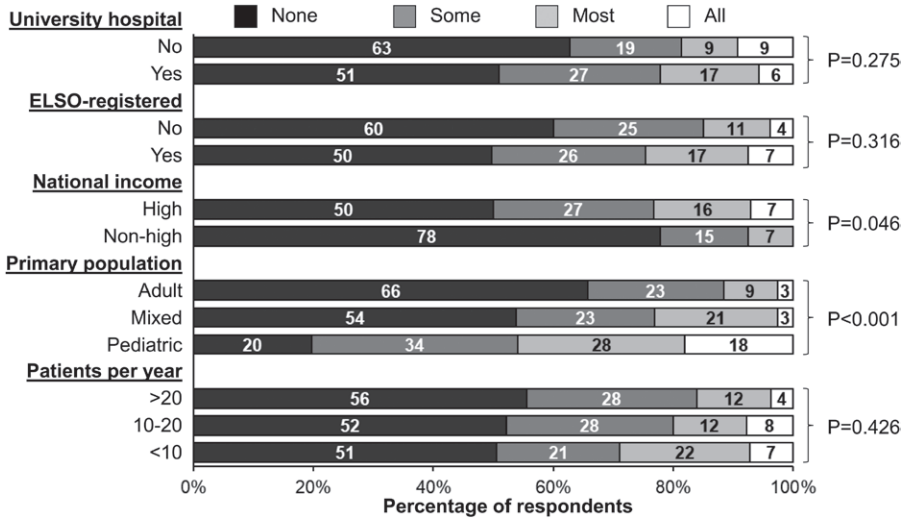

Fig. 4. Proportion of patients receiving recombinant antithrombin or antithrombin concentrate during veno-venous extracorporeal membrane oxygenation. Herein we compare the percentage of patients normally treated with antithrombin while on veno-venous extracorporeal membrane oxygenation (none [less than 10%], some [10 to 50%], most [50 to 90%], or all [more than 90%]) between centers, classified according to the following criteria: (1) university hospital or not; (2) registered with the Extracorporeal Life Support Organization (ELSO) or not; (3) 2017 gross national income per capita, categorized as high (at least $12,056 USD) or non-high (less than $12,056 USD); (4) primary patient population, categorized as adult-only, pediatric-only, or mixed; (5) annual extracorporeal membrane oxygenation patient volume, categorized as high (more than 20 cases per year), intermediate (10 to 20 cases per year), or low (less than 10 cases per year). Bars and labels are percentages of respondents. *P* values refer to chi-squared test.

Table 1. Factors Associated with Routine Antithrombin Supplementation during Veno-venous Extracorporeal Membrane Oxygenation

	Routine AT Supplementation						
Independent Variable	**Yes (n [%])**	**No (n [%])**	***P* Value**	**Unadjusted OR (95% CI)**	***P* Value**	**Adjusted OR (95% CI)**	***P* Value**
University hospital							
• No	18 (36.0)	32 (64.0)		1.00 (ref.)		1.00 (ref.)	
• Yes	86 (38.6)	137 (61.4)	0.860	1.12 (0.59 to 2.11)	0.860	0.94 (0.45 to 1.98)	0.878
ELSO-registered							
• No	75 (40.5)	110 (59.5)		1.00 (ref.)		1.00 (ref.)	
• Yes	29 (33.0)	59 (67.0)	0.283	1.39 (0.81 to 2.36)	0.283	0.62 (0.319 to 1.19)	0.148
National income							
• High	102 (49.6)	140 (51.4)	< 0.001	1.00 (ref.)		1.00 (ref.)	
• Non-high	2 (6.5)	29 (93.5)		0.095 (0.022 to 0.41)	< 0.001	0.099 (0.022 to 0.45)	0.003
Primary patient population							
• Adult	43 (35.0)	123 (65.0)	< 0.001	1.00 (ref.)		1.00 (ref.)	
• Mixed	17 (42.5)	23 (57.5)		2.11 (1.03 to 4.3)	0.060	2.73 (1.23 to 6.0)	0.013
• Pediatric	44 (65.7)	23 (34.3)		5.5 (2.97 to 10.1)	< 0.001	6.3 (2.98 to 13.2)	< 0.001
Annual ECMO patient volume							
• >20	28 (32.9)	57 (67.1)	0.872	1.00 (ref.)		1.00 (ref.)	
• 10–20	40 (40.4)	59 (59.6)		1.38 (0.75 to 2.53)	0.372	1.08 (0.55 to 2.13)	0.814
• <10	36 (41.4)	51 (58.6)		1.44 (0.77 to 2.68)	0.324	1.00 (0.48 to 2.08)	0.997

Herein we compare centers where antithrombin is routinely supplemented or not, according to the following criteria: (1) university hospital or not; (2) ELSO-registered or not; (3) 2017 gross national income per capita, categorized as high (at least $12,056 USD) or non-high (less than $12,056 USD); (4) primary patient population, categorized as adult-only, pediatric-only, or mixed; (5) annual ECMO patient volume, categorized as low (less than 10 cases per year), intermediate (10 to 20 cases per year), or high (more than 20 cases per year). From left to right, *P* values refer to the overall chi-squared test, univariate (unadjusted) regression analysis, and multivariable (adjusted for the independent variables listed above) regression analysis. As for multivariable logistic regression analysis, responses with missing values were deleted; significant correlation between covariates was excluded (all variance inflation factors were less than 2.0). AT, antithrombin; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization, OR, odds ratio; Ref., reference.

Table 2. Reasons for Routinely Prescribing or Not Routinely Prescribing Recombinant Antithrombin or Antithrombin Concentrate during Veno-venous Extracorporeal Membrane Oxygenation

Reasons for routinely prescribing antithrombin (n [%])	
• It helps achieve and maintain the anticoagulation target	81 (77.9)
• It corrects heparin resistance	62 (59.6)
• It prevents heparin resistance	22 (21.2)
• Other	4 (3.8)
• Missing	0 (0.0)
Reasons for not routinely prescribing antithrombin (n [%])	
• Anticoagulation is usually not an issue during veno-venous ECMO	68 (40.2)
• There is no robust scientific evidence to justify it	65 (38.5)
• It is too expensive or it is not available in my center	63 (37.3)
• I'm worried of possible side effects (bleeding for instance)	29 (17.2)
• Other	6 (3.6)
• Missing	9 (5.3)

Percentages were computed against 104 (centers where antithrombin supplementation is habitual) or 169 (centers where it is not habitual, including those where it is never prescribed). Respondents were allowed to select more than one answer. A definition of "heparin resistance" was not provided. Other reasons for routinely supplementing antithrombin were that it will correct disseminated intravascular coagulation if this occurs (1 [1.0%]), antithrombin is the most important endogenous anticoagulant (1 [1.0%]), antithrombin possesses anti-inflammatory properties (1 [1.0%]), antithrombin helps achieve effective prophylaxis (1 [1.0%], and this is a center where unfractionated heparin was used only for deep vein prophylaxis). Other reasons for not routinely prescribing antithrombin were that it is not required when anticoagulation is provided with argatroban (2 [1.2%]) or bivalirudin (1 [0.6%]), when anticoagulation is not prescribed at all (2 [1.2%]), or when subjects on veno-venous ECMO are rapidly transferred to a referral center (1 [0.6%]). ECMO, extracorporeal membrane oxygenation.

Anticoagulation Management

Providing systemic anticoagulation with unfractionated heparin remains by far the most common practice during veno-venous extracorporeal membrane oxygenation. Even so, there is no consensus on how to measure the degree of anticoagulation or on the goal that should be targeted.[5] When asked to report the single preferred method to monitor anticoagulation at their institution, quite similar proportions of participants indicated activated partial thromboplastin time (most commonly expressed in seconds), activated clotting time, or anti-Xa. Independently from the test, the therapeutic ranges sometimes largely differed across centers, with identical values regarded as too low by some participants whereas appropriate if not too high by others (fig. 3).

All tests designed for measuring heparin-induced anticoagulation have some limitations, and none of them has been properly validated during veno-venous extracorporeal membrane oxygenation. The activated partial thromboplastin time is a plasma-based coagulation assay primarily used to treat deep vein thrombosis or prevent recurrent thromboembolism. The therapeutic ranges reported in our survey were derived from those settings, and even there the supporting evidence remains scarce.[13,14] The activated partial thromboplastin time strongly depends on reagents and instruments being used. Therefore, therapeutic ranges adopted in one center can hardly be compared with those of others, especially if they are expressed in seconds.[15] Moreover, the activated partial thromboplastin time is a global clotting assay that primarily reflects the function of the intrinsic and common pathways of the coagulation cascade. It can underestimate heparin activity when factor VIII and/or fibrinogen levels are high as during inflammation or pregnancy.[16] The activated clotting time is a whole-blood point-of-care assay well validated for monitoring anticoagulation during cardiopulmonary by-pass. It can be run 24/7 with no need for laboratory machines and personnel. Thus, it is readily available even in low-income regions. The activated clotting time may be quite inaccurate during veno-venous extracorporeal membrane oxygenation, when the activated clotting time target is lower and heparin dosage smaller than during cardiac surgery.[17,18] Finally, anti-Xa is a plasma-based assay that reflects heparin dose better than activated partial thromboplastin time and activated clotting time.[19] This assay is run in a central laboratory and is expensive. Similarly to activated partial thromboplastin time, its therapeutic target (commonly defined as 0.3–0.7 IU/ml) was derived from small studies in adults with deep vein thrombosis.[20] In addition, anti-Xa levels are less influenced by other factors that may contribute to the overall hemostatic balance, including abnormal platelet count, fibrinogen level, or factor VIII level. Anti-Xa activity is more specific for heparin activity but less sensitive to other risk factors for bleeding or thrombosis than the activated partial thromboplastin time and the activated clotting time. In our survey, anti-Xa levels were the single preferred monitoring method in pediatric-only centers, probably because the immature coagulation system of neonates and young children causes large variation in individual response to heparin.[21]

Based on all these considerations, the Extracorporeal Life Support Organization currently recommends developing institutional anticoagulation monitoring protocols, based on local expertise and available resources, and using more than one method to monitor anticoagulation during veno-venous extracorporeal membrane oxygenation.[5] This aspect was not investigated in our survey.

Antithrombin Testing and Supplementation

Antithrombin management during heparin infusion and veno-venous extracorporeal membrane oxygenation is another matter of debate. The optimal circulating antithrombin activity remains unknown. Even so, use of recombinant antithrombin or antithrombin concentrate during veno-venous extracorporeal membrane oxygenation is becoming more and more common.[22,23] In our survey, antithrombin was routinely monitored by 48.7% of the participants and/or routinely supplemented in 38.1% of centers. These percentages rose to 80.6% and/or 65.7% in pediatric-only centers, probably because circulating antithrombin activity is lower in neonates and young children than in adults.[21] During veno-venous extracorporeal membrane oxygenation, circulating antithrombin activity frequently declines below

normal values.[22] Once again, the rationale for supplementation is mainly derived from cardiac surgery, where it prevents or corrects heparin resistance.[3,4] However, veno-venous extracorporeal membrane oxygenation differs from cardiac surgery. It requires lower anticoagulation target and smaller heparin dosage, is more frequently complicated by hemorrhage than thrombosis, and can be associated with other possible explanations for abnormal heparin sensitivity, such as overt inflammation.[22] Some conflicting responses highlight persisting uncertainty. For instance, the reasons most commonly reported to justify routine antithrombin supplementation were "it helps achieve and maintain the anticoagulation target" and/or "it prevents or corrects heparin resistance." But at the same time, the most commonly reported reason for not supplementing antithrombin was indeed "anticoagulation is usually not an issue during veno-venous extracorporeal membrane oxygenation" (table 2). We are currently running a small randomized controlled trial on the relationship between antithrombin supplementation, heparin dosage, and adequacy of anticoagulation in patients treated with veno-venous extracorporeal membrane oxygenation (ClinicalTrials.gov Identifier: NCT03208270). Results will hopefully improve our understanding of this particular issue.

Strengths and Limitations of This Work

To the best of our knowledge, this is the largest available survey on anticoagulation management during veno-venous extracorporeal membrane oxygenation, with 273 respondents in total, including 198 from outside North America and 88 not registered with the Extracorporeal Life Support Organization. In particular, we investigated the association between institutional practice and national income (significant), primary patient population (significant), and annual extracorporeal membrane oxygenation patient volume (not significant). As for major limitations, surveys can be subject to different types of bias.[24,25] If respondents differ from nonrespondents, results cannot be generalized to the entire study population. Most respondents to our survey were from university hospitals and high-income regions. On one side, this probably reflects the real distribution of extracorporeal membrane oxygenation centers. On the other hand, it may have been influenced by the way we approached and selected potential respondents (corresponding authors of scientific publications on veno-venous extracorporeal membrane oxygenation) with some risk of sampling bias. We did not record the number of total contacts. Therefore, we cannot determine the response rate and the associated risk of nonresponse bias (that is, people who did not respond to the survey may have significantly and systematically differed from those who did). Similarly, the number of centers performing veno-venous extracorporeal membrane oxygenation worldwide was (and remains) unknown, and so we cannot calculate what percentage of the entire sampling frame took part to the survey. Finally, we cannot exclude some response bias: some people may have tried to guess a purpose behind the survey and behaved in accordance with their preset expectations. If so, some responses differed from actual practice. Another limitation of our survey is that it does not clarify how best to manage anticoagulation during veno-venous extracorporeal membrane oxygenation.

Conclusions

There is large practice variation in the way anticoagulation is currently managed during veno-venous extracorporeal membrane oxygenation. The paucity of prospective studies and differences across institutions based on national income and primary patient populations may contribute to these findings.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Protti: Department of Anesthesia and Intensive Care Units, Humanitas Clinical and Research Center, Milan, Italy. alessandro.protti@hunimed.eu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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