Interactive CardioVascular and Thoracic Surgery 34 (2022) 322–325
doi:10.1093/icvts/ivab251 Advance Access publication 24 November 2021

BRIEF COMMUNICATION

Cite this article as: Monteagudo-Vela M, Bowles C, Raj B, Robinson D, Simon A. Anticoagulation in syncardia total artificial heart recipients:anti-factor Xa or activated partial thromboplastin time? Interact CardioVasc Thorac Surg 2022;34:322–5.

Anticoagulation in syncardia total artificial heart recipients: anti-factor Xa or activated partial thromboplastin time?

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Received 9 March 2021; received in revised form 15 July 2021; accepted 13 August 2021

Abstract

Although the activated partial thromboplastin time (aPTT) has historically been the method of choice for anticoagulation monitoring in patients undergoing mechanical circulatory support with intravenous unfractionated heparin, it is being progressively superseded by the anti-factor Xa (anti-Xa) method. A retrospective single-arm, single-centre analysis of 20 patients who underwent total artificial heart implantation entailed simultaneous determinations of aPTT and anti-Xa. Agreement between these parameters was assessed using the Bland–Altman method. Despite a positive correlation between aPTT and anti-Xa, normal target ranges were poorly aligned: from 5th to 30th postoperative day, for anti-Xa values of 0.2 and 0.4 U/ml corresponding aPTT values were 52.1 and 65.2 s, 7.9 and 14.8 lower than predicted values, respectively. This was not associated with thromboembolic sequalae. It was not possible to demonstrate a significant relationship between the predictor variables (postoperative day; white blood cell count; C-reactive protein concentration; alanine transaminase and alkaline phosphatase level; bilirubin; haemoglobin; albumin and total protein concentration) and the agreement between aPTT and anti-Xa levels. In summary, when anti-Xa levels were used to guide anticoagulation therapy, corresponding aPTT levels were low with respect to target range. Methodology applied in this study is generalizable to other forms of mechanical circulatory support.

Keywords: Total artificial heart • Anticoagulation protocol • aPTT • Anti-FXa assay

INTRODUCTION

The activated partial thromboplastin time (aPTT) has been the historical method of choice for anticoagulation monitoring in patients undergoing mechanical circulatory support with intravenous unfractionated heparin (IVUFH). It is being progressively superseded by the anti-factor Xa (anti-Xa) method [1] yet a lack of consensus persists regarding the optimal monitoring method.

The aPTT assay reflects the function of the intrinsic and common pathways of the coagulation cascade, whereas the anti-Xa assay measures the concentration of anticoagulants that inhibit Factor Xa [2]. The reliability of the aPTT assay can be influenced by preanalytical factors that do not reflect intrinsic heparin activity resulting in erroneous adjustments to heparin dose [3]. The anti-Xa assay is less susceptible to preanalytical interference.

There are many reported comparisons of aPTT and anti-Xa values in patients treated with IVUFH. Despite the evidence suggesting that the anti-Xa assay better reflects the heparin concentration than aPTT [4], a comparison of the methods has not been reported in total artificial heart (TAH) therapy.

The aim of this study was to quantify the agreement between simultaneous aPTT and anti-Xa measurements in recipients of a Syncardia TAH receiving postoperative anticoagulation with IVUFH and to determine whether this agreement is influenced by changes in selected clinical parameters, with the ultimate aim of improving postoperative anticoagulation therapy in this group.

METHODS

Ethical statement

Following consultation with our local research ethics committee and within our institution, it was concluded that this retrospective investigation of anonymized data falls within the category of 'Clinical Audit' and that ethical approval was not required.

Study design

A retrospective, single-arm, single-centre analysis of 20 patients who underwent cardiectomy and Syncardia TAH (Tuscon, AZ, USA) implantation from July 2014 to April 2019 entailed the comparison of simultaneous aPTT and anti-Xa measurements. The study period was divided into 2 phases: postoperative days 5–30 and from day 31 until the time of systemic warfarinization. Data prior to postoperative day 5 were censored because this

period is frequently associated with haemodynamic instability and biochemical derangement.

Anticoagulation monitoring

A normal target range of aPTT of 60–80 s for the aPTT is considered equivalent to a range of 0.2–0.4 units/ml for the anti-FXa assay. Based on these test results, the heparin dose is adjusted as per hospital protocol.

Statistical analysis

Agreement between the aPTT and anti-Xa values was assessed as follows. First, for the periods from postoperative days 5–30 and postoperative day 31 until cessation of IVUFH therapy, aggregate aPTT measurements are presented against corresponding anti-Xa values in the form of scatter plots with demarcation of target ranges for the 2 parameters. The distribution of samples according to target range is presented as percentages. Second, a method was developed to facilitate the assessment of the agreement between the aPTT and anti-FXa values by rescaling both parameters to a common arbitrary target range of -10 to +10.

If the data had been normally distributed, this would have been achieved as follows:

$$\text{aPTT} = \text{aPTT}-70, \quad (1)$$

$$\text{anti}-\text{Xa} = 100 * (\text{anti}-\text{Xa}-0.3). \quad (2)$$

However, because the aPTT data were right-skewed, a natural logarithm transformation was applied to normalize distribution. Therefore, equation (1) becomes

$$\ln(\text{aPTT}) = 69.5212 * \left(\ln(\text{aPTT})-4.2382\right). \quad (3)$$

Thus, agreement between the 2 parameters can be quantified as the difference between ln(aPTT) and anti-FXa as follows:

$$\Delta = \ln(\text{aPTT})-\text{anti}-\text{Xa}. \quad (4)$$

Complete agreement between aPTT and anti-Xa values would result in a Δ value of zero. If the aPTT value was lower than the anti-Xa value, then Δ would be negative and if aPTT was higher than the anti-Xa, Δ would be positive. With these transformations, a lenient definition of 'reasonable agreement' would be a Δ value in the range -10 to +10.

Third, a Bland–Altman [6] method was applied with inclusion of plot pertaining to the early study period, i.e. 5th–30th postoperative day (Fig. 1A) using the transformed anti-Xa and transformed aPTT values.

Investigation of the dependence of Δ on selected clinical predictor variables

The following predictors were investigated: postoperative day, white blood cell count, C-reactive protein concentration, alanine transaminase and alkaline phosphatase level, bilirubin, haemoglobin, albumin and total protein concentration.

To determine whether the discrepancy between aPTT and anti-Xa measurements was associated with the predictor variables, the agreement term Δ was regressed on each variable, in turn, using the General Estimating Equations method. This method was applied separately for the early and late study periods with an AR1 autoregressive correlation within-patient. A Bonferroni correction was applied to take account of multiple testing (18 tests in total). Thus, a *P*-value of 0.05/18 = 0.0028 was considered significant.

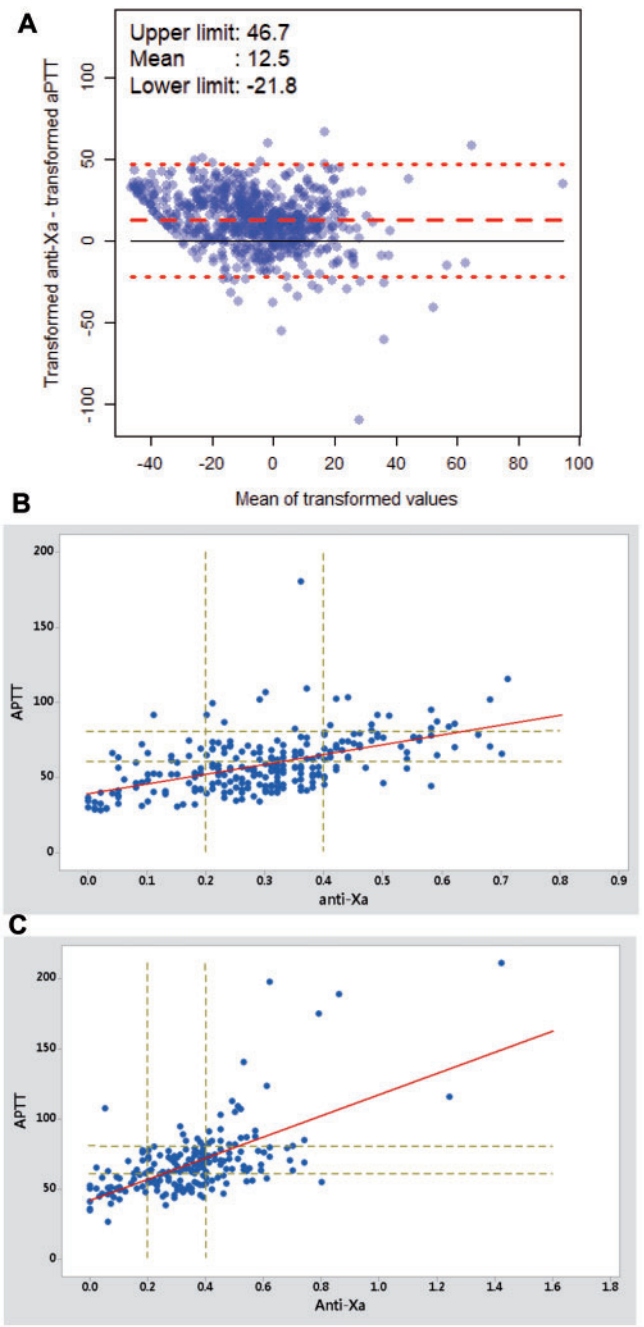

Figure 1: (**A**) Scatter plot of aPTT against anti-FXa (aggregate data from postoperative days 5–30, inclusive) with target ranges illustrated with dashed lines and linear regression in red. (**B**) Scatter plot of aPTT against anti-FXa (aggregate data from postoperative day 31 until termination of heparin therapy) with target ranges illustrated with dashed lines and linear regression in red. (**C**) Bland–Altman plot of the agreement term Δ (transformed aPTT - transformed anti-Xa) versus mean of transformed values for the early study period (postoperative days 5–30). Red dashed lines indicate 95% confidence limits. Anti-Xa: anti-factor Xa; aPTT, activated partial thromboplastin time.

RESULTS

A total of 460 venous blood samples from 20 patients were analysed during the study period of 493 days (251 between postoperative days 5–30 and 209 from postoperative day 31 until the termination of heparin therapy).

The basic relationship between all aPTT and anti-Xa study measurements made between postoperative days 5 and 30 is illustrated as a scatter plot in Fig. 1B. Despite a positive correlation between the 2 parameters, the target ranges are poorly aligned. At anti-Xa values of 0.2 and 0.4 U/ml (the lower and upper limit of the normal target range), predicted aPTT values were 52.1 and 65.2 s, respectively. Both aPTT values were less than predicted (60 and 80 s, respectively). Table 1 shows that only 16.3% of results fall within the target according to both criteria.

A disparity between anti-FXa and aPTT values was also observed from postoperative day 31 until discontinuation of IVUFH therapy (Fig. 1C). At anti-Xa values of 0.2 and 0.4 U/ml predicted aPTT values were 57.1 and 72.1 s, respectively. Table 1 shows that 27.3% of results fell within the target according to both criteria.

A Bland–Altman plot pertaining to the early study period, i.e. postoperative days 5–30, is presented in Fig. 1A and shows that the 95% limits of agreement extend beyond the delta value range of -10 to +10.

The results of the regression analyses are presented in Table 2 in supplemtary material, A (early study period) and B (late study period). No significant relationships were identified between any of the predictor variables and the agreement term, delta.

Table 1: Agreement between anti-Xa and aPTT values for the period postoperative days 5–30, and from postoperative day 31 until termination of heparin therapy relative to target ranges, expressed as percentage values

		Anti-Xa			
Postoperative days 5–30					
aPTT		Below	Within	Above	Total
	Below	20.3	34.7	2.4	57.4
	Within	3.6	16.3	13.5	33.5
	Above	0.4	3.2	5.6	9.2
	Total	24.3	54.2	21.5	100
Postoperative day 31 until termination of heparin therapy					
aPTT		Below	Within	Above	Total
	Below	14.4	17.7	4.8	36.8
	Within	4.3	27.3	13.9	45.5
	Above	0.5	3.8	13.4	17.7
	Total	19.1	48.8	32.1	100

Anti-Xa: anti-factor Xa; aPTT: activated partial thromboplastin time.

DISCUSSION

In this study, the agreement between aPTT and anti-Xa assay results was assessed in 20 patients during the early and late postoperative periods following TAH implantation and the dependence of this relationship on selected clinical parameters was investigated. Despite a positive correlation between the results of the anticoagulation assays, when the anti-Xa values were within range, corresponding aPTT values were generally lower than predicted values. The poor agreement between aPTT and anti-Xa values is also illustrated by the Bland–Altman plot, which shows that the 95% limits of agreement extend beyond the delta value range of -10 to +10, which was predefined as a 'reasonable agreement'.

We observed that for anti-Xa values within the normal target range of 0.2 and 0.4 U/ml corresponding aPTT values were 52.1 and 65.2 s, i.e. lower than the normal target range of 60–80 s. However, this was not associated with adverse thrombotic events implying that pro-haemorrhagic effects predominate over thrombotic effects in this clinical setting. In contrast, Adatya *et al.* [5] observed that levels of aPTT were elevated relative to corresponding anti-Xa levels in patients with long-term continuous-flow left ventricular assist devices (cf-LVADs). This resulted in the overestimation of heparin concentration and sub-therapeutic anticoagulation and was associated with pump thrombosis episodes.

The absence of thromboembolic complications in this study in spite of periods of sub-therapeutic anticoagulation may have been attributable to the relatively high TAH flow rates, with high and uniform wall shear stresses, which potentiate self-cleaning and reduce blood-residence time within the TAH. An alternative explanation is the propensity of TAH patients to bleeding complications, which could predispose to dilutional coagulopathy and provide protection against thromboembolic complications under conditions of sub-therapeutic anticoagulation.

The scarce literature about this topic and MCS is focused on cf-LVADs, which are associated with attenuated systemic arterial pulsatility, however, the implications in pulsatile Mechanical Circulatory Support [6, 7]. It is reported that bleeding is higher in cf-d due to the high shear stress forces [8] that generate inducing an acquired von Willebrand factor deficiency. This leads to bleeding complications by making the multimers that bridge with platelets less haemostatic, thus impeding proper clot formation [9]. Wever-Pinzon *et al.* [10] proved that the higher the pulsatility, the less bleeding complications.

Limitations

First, we present a small cohort of patients with a course that was generally characterized by profound preoperative biochemical derangement and end-organ dysfunction. Thus, it was challenging to demonstrate a statistically significant association between Δ and the predictor parameters. Second, it is unclear to what extent these findings are generalizable to other forms of MCS.

CONCLUSION

In this study, the agreement between simultaneous aPTT and anti-Xa measurements in patients undergoing TAH therapy with IVUFH was investigated. We conclude that inadvertent selection of comparatively low levels of anticoagulation was not associated with adverse sequalae because pro-haemorrhagic effects prevail over prothrombotic effects in this group in the early postoperative period. The effect of the transition to greater reliance on the anti-Xa assay on the incidence of haemorrhagic and thromboembolic complications warrants further investigation in different forms of MCS.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

Conflict of interest: none declared.

Author contributions

María Monteagudo-Vela: Conceptualization; Data curation; Writing—original draft. **Christopher Bowles:** Writing—review & editing. **Binu Raj:** Data curation. **Derek Robinson:** Formal analysis; Methodology. **Andre Simon:** Supervision; Validation.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Francesco Formica, Carlos A. Mestres and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

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