

Monitoring Anticoagulation with Unfractionated Heparin on Renal Replacement Therapy. Which Is the Best aPTT Sampling Site?

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ABSTRACT

Background: Controlled anticoagulation is key to maintaining continuous blood filtration therapies. Objective: The study aimed to compare different blood sampling sites for activated partial thromboplastin time (aPTT) to evaluate anticoagulation with unfractionated heparin (UFH) in continuous renal replacement therapy (CRRT) and identify the most appropriate sampling site for safe patient anticoagulation and increased filter life span. **Method:** The study was a prospective observational single-centre investigation targeting intensive care unit (ICU) patients on CRRT using an anticoagulation protocol based on patient characteristics and a weight-based modified nomogram. Eighty-four patients were included in the study. Four sampling sites were assessed: heparin free central venous nondialysis catheter (CVC), an arterial line with heparinised flush (Artery), a circuit access line (Access), and a circuit return line (Postfilter). Blood was sampled from each of four different sites on every patient, four hours after the first heparin bolus. aPTT was determined using a rapid clot detector, point of care device. **Results:** A high positive correlation was obtained for aPTT values between CVC and Access sampling sites ($r(84) = 0.72$; $p < 0.05$) and a low positive correlation between CVC and Arterial sampling site ($r(84) = 0.46$, $p < 0.05$). When correlated by artery age, the young Artery (1-3 day old) correlates with CVC, Access and Postfilter ($r(45) = 0.74$, $p > 0.05$). The aPTT values were significantly higher at Postfilter and Arterial sampling site, older than three days, compared to the CVC sampling site ($p < 0.05$). **Conclusion:** Considering patient bleeding risks and filter life span, the optimal sampling sites for safe assessment of unfractionated heparin anticoagulation on CRRT during CVVHDF were the central venous catheter using heparin free lavage saline solution, a heparinised flushed arterial catheter not older than three days, and a circuit access line.

Keywords: continuous renal replacement therapy, heparin, aPTT sampling sites

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INTRODUCTION

Renal replacement technologies are life-saving therapies, as the risk of death of critically ill patients increases with the onset of acute renal injury. Approximately 4% of critically ill patients are subject to renal replacement therapy for acute renal injury, and the percentage grows when sepsis is involved [1, 2]. The various anticoagulation methods of the extracorporeal circuit vary from the safety point of view with bleeding being the most critical complication. Avoiding severe bleeding is the key to the optimisation of continuous renal replacement therapy [3].

Continuous renal replacement therapy (CRRT) requires effective anticoagulation of the circuit and different systemic anticoagulation modes are available, including systemic heparin (SAH). Over the last decade, conventional systemic heparin anticoagulation has been increasingly replaced by regional citrate anticoagulation for CRRT, in approximately 50 % of the Intensive Care Unit's (ICU) [4, 5].

Moreover, patients with severe liver failure, severe hypoxemia, or shock with lactic acidosis, are at risk for citrate accumulation and in some of these patients, a switch to an alternative anticoagulation technique is required [6]. Nevertheless, heparin continues to be

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used in a significant percentage of patients undergoing CRRT, even in those who are at high risk of bleeding [7].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest using Regional Citrate Anticoagulation (RCA) for CRRT in patients with Acute Kidney Injury (AKI) in the absence of contraindications. However, the recommendation is classified as Grade 2B, indicating that the evidence for this is weak [8].

During CRRT heparin administered in the pre-filter reaches the patient's blood reservoir by return line, producing systemic anticoagulation.

Controlling anticoagulation is essential for maintaining continuous blood filtration therapies [9], but on the other hand, many variables influence the life of the circuit such as filter size, blood-related factors, or temperature [10].

Heparin monitoring is performed by laboratory tests that measure the effect of heparin administration by prolonging the coagulation time in seconds. The most common tests are the activated partial thromboplastin time (aPTT) and the activated clotting time (ACT) [11].

Insufficient heparin anticoagulation can lead to clots in the filter and tubing, but on the other hand, heparin overdosing may favor spontaneous bleeding, therefore monitoring heparin therapy is not only essential but vital to protect the patient from these complications. An aPTT level ranging from 1.5-2.5 times the baseline value is considered to be the optimal therapeutic range and has gained wide clinical acceptance [12].

In an ICU, the aPTT blood sample for monitoring systemic anticoagulation with unfractionated heparin can be obtained from the patient's indwelling peripheral arterial (Artery) or central venous line (CVC) [13].

During CRRT procedures using heparin anticoagulation, aPTT blood samples, in most procedural protocols, were usually collected from venous line [14] or postfilter according to producer's manuals.

None of the published studies regarding monitoring anticoagulation with unfractionated heparin on CRRT studied different sites for blood aPTT sampling.

The study aimed to:

- Assess if there is a correlation between the extracorporeal circuit and indwelling line blood-sampling sites.
- Determine which blood sampling site better reflects a patient's safe anticoagulation during Continuous renal replacement therapy so it can be

used for monitoring anticoagulation with unfractionated heparin.

The null hypothesis is:

- There is no correlation between the extracorporeal circuit and the indwelling line blood-sampling sites.

■ METHODS

The study was conducted from March 1st to July 31st, 2017 in the ICU department of the Emergency County Hospital in Cluj Napoca.

The study was approved by the Ethical Committee of the University of Medicine and Pharmacy Iuliu Hațieganu and Cluj-Napoca County Hospital, approval no 102/ March 2017.

Written, informed consent was obtained for all patients or from the next of kin before starting data collection.

In the timeline, 498 medical and surgical patients were admitted to the ICU.

In this cohort, there were 177 patients treated with extracorporeal blood filtration therapies.

Inclusion criteria:

- patients receiving continuous venovenous haemodiafiltration (CVVHDF) therapy using unfractionated heparin (UFH) anticoagulation (n = 84)

Exclusion Criteria:

- Plasmapheresis therapies (n=16)
- Regional citrate therapies (n=31)
- Patients undergoing procedures with a major risk for bleeding(n=16)
- Patients presenting severe thrombocytopenia (n=22)
- Patients with catheter-related problems after therapy debut (n=3)
- Patients who did not consent (n=5)

Blood APTT measurement was used to monitor heparin anticoagulation using a rapid clot detector, (POC) point-of-care device.

For each patient included in the study, aPTT values were measured four hours after the administration of an initial heparin bolus.

Four different sampling sites were used:

- Two from indwelling lines.

- heparin free central venous catheter (CVC)
- arterial line –(Artery)
- Two from the extracorporeal circuit.
- access line (Access)
- extracorporeal return line (Postfilter).

The aPTT values from the CVC (heparin free port) sampling site were considered as a reference value for the patient anticoagulation status.

Samples were obtained following the principle of avoiding false contamination when using central venous and arterial catheters. Therefore, the total amount of blood aspirated from the system (CVC) before obtaining the sample for clotting studies was 6 mL, which is four times the volume of the CVC catheter system dead space (1.5ml).

For arterial sampling, an inline close sampling device was used so that no blood volume is discarded from a closed system (Edwards, TruWave/VAMP Adult combo set).

For the extracorporeal circuit, sampling was done by a needle from the dedicated sampling ports.

Continuous venovenous hemodiafiltration (CV-VHDF) was applied using Prismaflex™ machines with the Prismaflex ST150™ set and an AN69ST membrane (Gambro Lundia, Lund, Sweden), and a Multifiltrate Machine (Fresenius Medical Care, Bad Homburg, Germany) with a KIT 6 set, and an Ultraflux® AV600S membrane (Fresenius Medical Care, Bad Homburg, Germany).

Medium blood flow of 180-230 ml/min was maintained, and a third of the total substitution volume in pre-filter was used, at a replacement rate of 25-35 ml/kg/h.

For vascular access, 20 cm lengths of 13.5 French double-lumen Joline®) hemodialysis catheters (Joline

GmbH, Hechingen, Germany) were inserted into either the femoral or internal jugular vein. Catheter characteristics include catheter tip without side holes that ensures less clotting and low recirculation.

When anticoagulation was used, the most common strategies rely on heparin or citrate. In the present study, critical care nurses started the procedures by following ICU protocols for setting up the lines and using saline with 5000 UI/ml unfractionated Heparin sodium, (Laboratoires Panpharma, Z.I du Clairay, France) as a priming solution.

A modified unfractionated weight-based heparin nomogram [14], was used (Table 1).

The initial dose of UFH was 50 UI/kg with a maintenance rate of 10-15 UI/Kg/h.

The physician in charge followed the hospital protocol and gave special consideration to patients' baseline anticoagulation status, previous therapies, and possible risks that could generate clotting or bleeding [15]. This protocol was applied to all ICU patients on CRRT, except for consecutive therapies when no initial bolus was administered.

Laboratory Samples

The aPTT was measured using a Hemochron Signature Elite © system (Accriva Diagnostics, San Diego, USA) that uses clot-activator cuvettes and mechanical clotting detection. The aPTT is determined from whole blood, and testing is performed immediately on site. Results were displayed as whole blood aPTT and plasma aPTT and expressed in seconds. Sampling was performed beginning from the CVC line then the Artery site, followed by the extracorporeal sites.

Only 0.15 ml of blood is required to evaluate one anticoagulation parameter. The normal plasma equivalent aPTT values programmed into the Hemochron

Table 1. Protocol for bolus and dose adjustment when using UFH on CRRT

Modified unfractionated weight-based heparin nomogram

Target: aPTT x2 Initial Dose (Bolus) 50 UI/Kg * Maintenance 10- 15 UI/Kg/H

Plasma aPTT found	Continuous rate action	Bolus	Check time
Plasma aPTT <35 sec	+ 4 UI/Kg/h	Rebolus 50 UI/Kg	aPTT after (3h)
Plasma aPTT 35- 45 sec	+ 2 UI/Kg/h	Rebolus 20 UI/Kg	aPTT after (3h)
Plasma aPTT 46- 60 sec	+ 2 UI/Kg/h	-	aPTT after (3h)
Plasma aPTT 60- 70 sec	-	-	aPTT after (4h)
Plasma aPTT 71- 90 sec	- 2 UI/Kg/h	-	aPTT after (3h)
Plasma aPTT > 90 sec	- 3 UI/Kg/h	Stop Cont. inf 60 min	aPTT after (2h)

First aPTT (4 h) after the initial bolus

* If BW > IBW x 1.3, then use ABW to estimate initial heparin bolus

BW (Body Weight), IBW (Ideal Body Weight), ABW (Adjusted Body Weight)

system are approximate plasma equivalents for use in the clinical setting. No patient was subjected to any invasive procedures used for collecting data which were not routinely approved and used in the ICU.

Statistical analysis

The data was collected in Excel and expressed in seconds. The consistency between sampling sites was tested using the correlation coefficient to analyse the degree of association between two variables. aPTT values were analysed using the Pearson correlation coefficient tests in iMedCalc® (Vers. 19.1.3)

The correlation coefficient “r” and the determination coefficient, “r²” and p-value of <0.05 were considered enough to determine the sampling sites correlation, using a 95% confidence interval.

The correlation coefficient was considered as being either moderately positive (0.5 - 0.7), high positive (0.7 - 0.9), and very high positive (0.9 - 1.00).

The paired samples t-test was performed to determine the normal distribution of differences using the D’Agostino-Pearson test, selecting a 90% confidence interval for equivalence testing.

The significance level was set at $\alpha = 0.05$

After initial statistical analysis of the eighty-four patients included in the study, this group was subdivided according to artery age:

A young Artery group (n=45), defined as a site, had been used for 1-3 days.

An old Artery group (n=39), defined as a site, had been used for 4-6 days.

The aim of this was to assess whether samples from anticoagulated indwelling lines of different timespans may influence clinical decisions.

RESULTS

A total of 336 blood samples from 84 patients, four samples for each patient, were collected.

Correlations for aPTT values were computed among four sample sites on data from 84 patients.

The results suggested that all correlation coefficients were low and moderate positive, statistically significant and were greater or equal to $r \geq 0.43$, (D’Agostino-Pearson test, $p < 0.05$), with the exception, high positive correlation for CVC versus Access aPTT values, $r=0.72$ (D’Agostino-Pearson test, $p < 0.05$) (Table 2, Figure 1). There is no correlation between the extracorporeal circuit and the indwelling line blood-sampling sites.

Since Artery sites arterial catheter samples were taken from the closed system, washed continuously with a heparinised solution, we tested correlations differently according to the artery age. We found for aPTT values a high positive correlation only when sampling patients with young Artery (1-3 days) when compared with CVC, paired samples. ($r=0.74$, D’Agostino-Pearson test, $p < 0.01$).

A low positive correlation was obtained when assessing sampling sites from patients with Artery sites

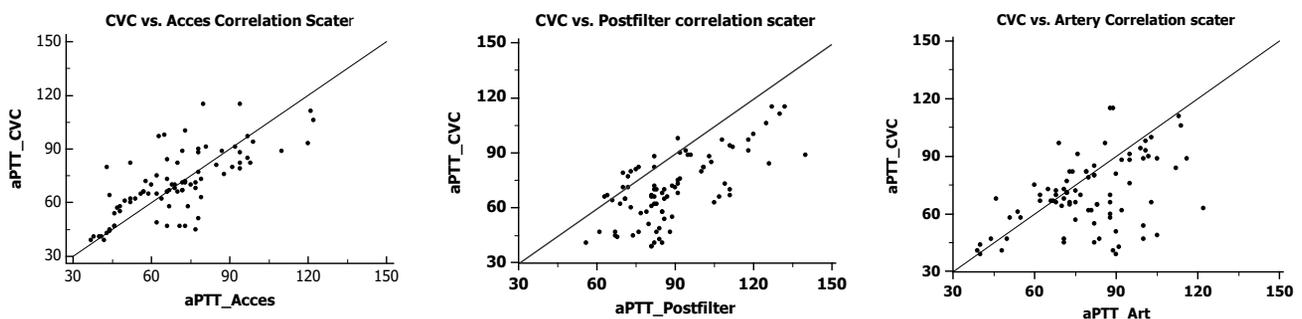


Fig. 1. Correlation aPTT plots reported to CVC sampling site

Table 2. Correlations and Descriptive Statistics (N = 84) - aPTT values for CVC, Access, Postfilter and Artery

Variables	1	2	3	4
1 CVC (sec.)	-	0.72 (r)	0.69 (r)	0.46 (r)
2 Access (sec.)	0.72 (r)	-	0.62 (r)	0.43 (r)
3 Postfilter (sec.)	0.69 (r)	0.62 (r)	-	0.47 (r)
4 Artery (sec.)	0.46 (r)	0.43 (r)	0.47 (r)	-

aPTT values: 1 (CVC)= heparin free central venous nondialysis catheter; 2 (Access) = circuit access line; 3 (Postfilter) = circuit return line; 4 (Artery) = arterial line with heparinized solution.
r - correlation coefficient (r). Coefficients printed in bold are significant ($p < 0.05$).

in place for 4-6 days, vs CVC sites ($r = 0.23$, D'Agostino-Pearson test, $p = 0.1$) (Table 3).

In all patients group (n84), a statistical difference was obtained for CVC aPTT values vs Postfilter and Arterial aPTT values. No differences were found when comparing CVC and Access values. (Student's t-distribution test, $p = 0.74$) (Table 4 Section A).

The young Artery group showed a statistical difference when comparing CVC and Postfilter aPTT values (Student's t-distribution test, $p < 0.01$).

No statistical difference was seen when comparing CVC with Access and young Artery sites. (Student's t-distribution test, $p = 0.74$ and $p = 0.63$) (Table 4 Section B).

In the old Artery group (39), a statistical difference was obtained when comparing CVC values with both the Postfilter and old Artery sites (Student's t-distribution test, $p < 0.01$).

No statistical difference was found when comparing CVC with Access values. (Student's t-distribution test, $p < 0.46$) (Table 4 Section C).

The null hypothesis that there is no correlation between the extracorporeal circuit and the indwelling line blood-sampling sites is partially rejected.

DISCUSSION

Heparin is the anticoagulant of choice when a rapid anticoagulant effect is required because of its immediate onset of action when administered by IV injection.

The heparin therapeutic is effect dosage-dependent. At therapeutic doses, heparin is cleared predominantly through a rapid saturable, dose-dependent mechanism and its anticoagulant effects are nonlinear, with both

the intensity and duration of effect rising disproportionately with increasing dose. Clearance involves a combination of a rapid saturable and a much slower renal mechanism [16, 17].

In CRRT anticoagulation, UFH is used to increase filter life span together with other methods such as regional citrate or non-pharmacological techniques, to maintain extracorporeal circuits from developing clots.

When given in therapeutic doses, the anticoagulant effect of heparin is usually monitored using the aPTT. The aPTT value is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa and it is standard practice to monitor the heparin dose against the measured aPTT and adjust the heparin dose accordingly.

The inconsistency between the aPTT results in patients undergoing the same anticoagulant protocol has been noted in previous studies, indicating the need for the assessment of unfractionated heparin monitoring protocols and an awareness of their shortcomings [18].

Variations in measurements occur at low and high aPTT level, both within an analyser and between different analysers [19].

Despite serious limitations, the reliance on the aPTT is likely to continue because of its ready availability and familiarity of clinicians with the test. The focus of clinicians who manage unfractionated heparin therapy should be to ensure that an adequate starting dose of unfractionated heparin is used and that the aPTT method is standardised [20].

Having in view those variations, our study was undertaken to see if there were differences between aPTT

Table 3. Correlations and Descriptive Statistics depending on artery age

aPTT values for patients with Artery younger than 3 days ---- (n=45)				
Variables (sec.)	1	2	3	4
1 CVC	-	0.80 (r)	0.71 (r)	0.75 (r)
2 Access	0.80 (r)	-	0.62 (r)	0.67 (r)
3 Postfilter	0.71 (r)	0.62 (r)	-	0.57 (r)
4 Artery	0.75 (r)	0.67 (r)	0.57 (r)	-
aPTT values for patients with Artery age between 4 to 6 days---- (n=39)				
Variables (sec.)	5	6	7	8
5 CVC	-	0.60 (r)	0.64 (r)	0.23 (r)
6 Access	0.60 (r)	-	0.61 (r)	0.35 (r)
7 Postfilter	0.64 (r)	0.61 (r)	-	0.45 (r)
8 Artery	0.23 (r)	0.39 (r)	0.45 (r)	-

aPTT values: Samples from patients with young artery 1-(CVC) = heparin free central venous nondialysis catheter; 2- (Access) = circuit access line; 3-(Postfilter) = circuit return line; 4-(Artery) = arterial line with heparinized solution. Sites aPTT values from patients with old Artery 5-(CVC), 6- (Access), 7-(Postfilter), 8-(Artery). r - correlation coefficient (r). Coefficients printed in bold are significant ($p < 0.05$).

Table 4. Comparison of CVC, Access, Postfilter and Artery aPTT values

Section A	All patients group (84)	Mean (SD)	p value	
	Access (sec.)	73 (±20)	p = 0.74	
	Postfilter (sec.)	92 (±19)	p < 0.01	75 (±18)
	Artery (sec.)	82 (±18)	p < 0.01	
Section B	Young Artery group (45)	Mean (SD)	p value	CVC (sec.)
	Access (sec.)	75 (±17)	p = 0.74	
	Postfilter (sec.)	91 (±19)	p < 0.01	74 (±18)
	Artery (sec.)	76 (±20)	p = 0.63	
Section C	Old Artery group (39)	Mean (SD)	p value	CVC (sec.)
	Access (sec.)	63 (±16)	p = 0.46	
	Postfilter (sec.)	86 (±16)	p < 0.01	66 (±18)
	Artery (sec.)	85 (±14)	p < 0.01	

aPTT mean (SD) values expressed in seconds compared to CVC sampling site. Section A - All 84 patients; Section B - Young artery group (patients that at assessment time had indwelling arterial line not older than three days); Section C - Patients group with older artery line. Data printed in bold had statistical significance (p < 0.05)

results from different sample sites used when assessing the anticoagulation status on CRRT. A fast “point of care” system was used. In the ICU, point-of-care (POC) devices are beneficial due to fast and on-site results. In previous studies, POC aPTTs showed concordance with the laboratory aPTT [21-23].

The CVC was used as a reference sampling site for aPTT assessment because administered heparin on CRRT generates a systemic effect; eventually, two small studies showed no benefit in filter life from different sites of heparin delivery [24, 25].

Postfilter aPTT values compared with CVC values have a moderate correlation but significantly higher values than CVC samples (Table 3).

Those results lead us to believe that those means may be modified by heparin contaminating the sample. In Postfilter, it is assumed that the sample is receiving some heparin infused at the site immediately before the filter.

Infusing heparin continuously before filter and monitor heparin effect by aPTT in Postfilter might not a better practice, even if some of the unfractionated heparin is involved in filter clearance.

For middle molecules, clearance is dependent on membrane permeability characteristics and the amount of ultrafiltration volume [26]. This is because unfractionated heparin can be considered as middle molecules, and for these, clearance is dependent on membrane permeability characteristics and the amount of ultrafiltration volume [26].

Based on a higher postfilter aPTT, the nurse response using a heparin nomogram is to reduce con-

tinuous heparin infusion, probably shortening the filter life span.

Indwelling lines, CVC and Artery are the main easy, rapid access points to assess anticoagulant status. We agree with previous studies which that showed shortcomings exist for coagulation assessment from Artery [27]. Conversely, to minimize the line replacement, patient discomfort and to obtain accurate measures, maintaining the patency is essential. There is level one evidence to support heparin as a flush solution once the timeframe exceeds 48 hours [28].

The study data indicated that CVC aPTT values showed high correlations when compared to Young Artery and low correlation with Old Artery.

Artery walls probably develop heparin-binding properties in more than three days, and this may explain the low correlation with CVC.

Samples from Access correlate well with those from CVC, in our opinion, this is applicable only in good flow on dialysis Catheter. Recirculation at the tip of the catheter cannot be measured nor underestimated [29].

The dose-effect mechanism of heparin is responsible for the duration of effective filter service, and this can be highly variable since there are circuit-related factors associated with filter function [26].

The limitations of the study include the small number of samples with only one sample evaluated after starting UFH heparin for CRRT procedure. The limitations of a single-centre study contribute to the generalizability of the reported results.

Never the less, this is the first study in which different sampling sites for heparin monitoring anticoagula-

tion in CRRT are compared.

Additionally, no previous study has reported on whether the age of indwelling Artery arterial line can influence the accuracy of aPTT values when the line is continuously washed with heparinised saline.

■ CONCLUSION

Considering patient bleeding risks and filter functional life-span, the optimal sampling sites for safe assessment of unfractionated heparin anticoagulation on CRRT during CVVHDF were CVC heparinised flushed Young Artery site not older than three days, and the Access site.

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■ CONFLICT OF INTEREST

None to declare.

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