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CORRESPONDENCE

Thoracic epidural analgesia in a lung transplant patient with an activated partial thromboplastin time falsely elevated by C-reactive protein

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To the Editor,

Measuring the activated partial thromboplastin time (aPTT) is a standard coagulation test that is often performed before invasive procedures such as neuraxial analgesia. Evidence has shown that the aPTT can be prolonged in the presence of elevated C-reactive protein (CRP).[1] Nevertheless, assays used to measure aPTT differ in their sensitivity to interference by CRP. Therefore, a CRP-insensitive aPTT may be a more accurate indicator of coagulation status.[1,2]

A middle-aged female (who consented to this report) with hypersensitivity pneumonitis underwent successful bilateral lung transplantation that utilized cardiopulmonary bypass. She was not on any anticoagulation medication and her preoperative coagulation profile was normal (including aPTT = 33.2 sec). Intraoperative anticoagulation was achieved with heparin and reversed with protamine.

Postoperatively, thoracic epidural analgesia (TEA) was considered but initially deferred because of an isolated prolonged aPTT (measured by the STA-PTT Automate; Diagnostica Stago, Asnieres, France) despite no heparin being given for > 12 hr (Table). An anti-Xa assay, mixing study, antiphospholipid panel, and thromboelastogram were also measured from the same blood sample and indicted normal coagulation (Table). Given these results and her clinical picture, a falsely elevated aPTT was suspected. This was confirmed using the original blood sample using a CRP-insensitive aPTT (Table; HemosIL SynthASil, Instrumentation Laboratory, Bedford, MA, USA). We proceeded with TEA and there was an improvement in analgesia; no complications occurred.

Prolongation of the aPTT by CRP has been shown both *in vitro*[1] and *in vivo*[2] and is thought to be due to CRP binding to phospholipids, which normally act as catalytic surfaces of coagulation factors, thus increasing the coagulation time. This effect is even more pronounced when the aPTT reagent contains low levels of phospholipids[2] and is reversible as the addition of phospholipids to plasma with an elevated CRP decreases aPTT significantly utilizing the STA Cephascreen aPTT assay (Diagnostica Stago, Asnieres, France).[2]

The level of interference by an elevated CRP on aPTT varies among aPTT assays. For example, two studies utilizing the STA Cephascreen reported a maximum prolongation of 10.7[2] and 38 sec[3] with CRP concentrations of 11.0 and 20.0 $mg{\cdot}dL^{-1}$, respectively. Conversely, a small study showed that the Dade Actin FS (Siemens Healthcare Diagnostics, Marburg, Germany) was only slightly affected by CRP.[2] Our laboratory's CRP-insensitive aPTT utilizes a HemosIL SynthASil assay with a synthetic phospholipid reagent. Unfortunately, there are many other reagents available on the market where the degree of interference by CRP is unknown.

CRP increases in response to a variety of insults; one study showed a median peak of 12.3 $mg{\cdot}dL^{-1}$ [4] following lung transplantation. Therefore, a significant number of patients may develop a falsely prolonged aPTT when using a conventional aPTT assay. The level at which CRP started to interfere with the aPTT has been shown to have significant inter-individual variability, ranging from 1.2 to 9.3 $mg{\cdot}dL^{-1}$.[2] This may be due to a variety of factors

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Table Laboratory data

Lab	Value	Reference range and units
aPTT	80.3	25.4–36.9 sec
INR	1.1	0.9-1.1
Anti-Xa	<0.10	<0.10 $U \cdot mL^{-1}$
aPTT (1:1 mix with normal plasma)	51.6	25.4–36.9 sec
aPTT (lupus sensitive reagent)	72.5	25.4–36.9 sec
Anti-cardiolipin IgM	7.1	0–12.5 MPL
Anti-cardiolipin IgG	5	0–15 GPL
Beta-2-glycoprotein IgM	1	0–20 SMU
Beta-2-glycoprotein IgG	2	0–20 SGU
Phosphatidylserine/prothrombin IgM	5.6	<30 M units
Phosphatidylserine/prothrombin IgG	6.1	<30 G units
TEG-CK		
R	3.6	5–10 min
K	1.1	1–3 min
Angle	74.6	53–72°
MA	74.4	50–70 mm
EPL	1.3	0–15%
TEG-CKH		
R	3.6	5–10 min
K	0.9	1–3 min
Angle	76.1	53–72°
MA	73.3	50–70 mm
EPL	1.1	0–15%
CRP	9.4	<0.5 $mg \cdot dL^{-1}$
CRP-insensitive aPTT	29.4	25.1–36.6 sec

aPTT = activated partial thromboplastin time; CRP = C-reactive protein; INR = international normalized ratio; EPL = estimated percent lysis; GPL = microgram of IgG antibody; K = clot kinetics; MA = maximum amplitude; MPL = microgram of IgM antibody; R = reaction time; SGU = standard IgG anti-beta-2 glycoprotein 1 units; SMU = standard IgM anti-beta-2 glycoprotein 1 units; TEG-CKH = thromboelastography-citrated kaolin with heparinase

influencing the binding kinetics of CRP on phospholipids, including age, sex, race, environmental factors such as smoking or stress, and genetics.[2]

This is the first published case report of TEA utilized successfully and safely in a patient with an isolated prolonged aPTT but a normal CRP-insensitive aPTT. It is possible that a CRP-insensitive aPTT may provide a more accurate assessment of coagulation status than conventional aPTT in the setting of an elevated CRP; however, further research is needed. Clinicians should investigate the specific aPTT assay used at their institution and consider comparing it with a CRP-insensitive aPTT to investigate for any interference. Understanding the role of CRP in aPTT assays is critical and may help improve patient outcomes by permitting the use of regional anesthesia in patients who would otherwise be considered contraindicated.

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