How to interpret a prolonged prothrombin time or activated partial thromboplastin time

Clotting tests are among the most common tests performed in clinical medicine. These include the prothrombin time and activated partial thromboplastin time. Prothrombin time and activated partial thromboplastin time are frequently used to assess whether patients have coagulation disorders that put them at risk of bleeding.

For normal haemostasis to occur, the following parts of the haemostatic system must function correctly: platelets, clotting factors (procoagulant and anticoagulant), fibrinolytic pathway, and vascular endothelium. Coagulation is also influenced by calcium, acid–base balance and temperature. Clotting tests assess whether pro-coagulant clotting factors are present and working normally, but do not assess the other features necessary for normal haemostasis.

Prothrombin time assesses whether there are clotting factor deficiencies in the extrinsic (tissue factor) pathway or final common pathway. A prolonged activated partial thromboplastin time suggests a factor deficiency in the intrinsic (contact activated) pathway, or final common pathway (*Figure 1*). Differential diagnoses for abnormalities in clotting tests are listed in *Table 1*.

These tests were initially designed for the identification of inherited bleeding disorders. However, their use has expanded into many other settings. Prothrombin time and activated partial thromboplastin time are often checked before performing invasive procedures in an attempt to predict whether a patient is prone to bleeding. However, they are a poor predictor of this and taking a good bleeding history to guide the use of clotting tests is essential. Abnormalities in these tests should be interpreted in light of the personal and family history of bleeding.

Empirically checking prothrombin time and activated partial thromboplastin time preoperatively in patients without a personal or family history of bleeding is not recommended and may result in unneces-

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Figure 1. Clotting pathways. *Factor deficiencies in the extrinsic pathway result in a prolonged prothrombin time. †Factor deficiencies in the intrinsic pathway result in a prolonged activated partial thromboplastin time. ‡ Factor deficiencies in the final common pathway result in prolongation of both the prothrombin time and activated partial thromboplastin time. These pathways reflect the way clotting is tested in the laboratory, not the way it occurs in vivo.

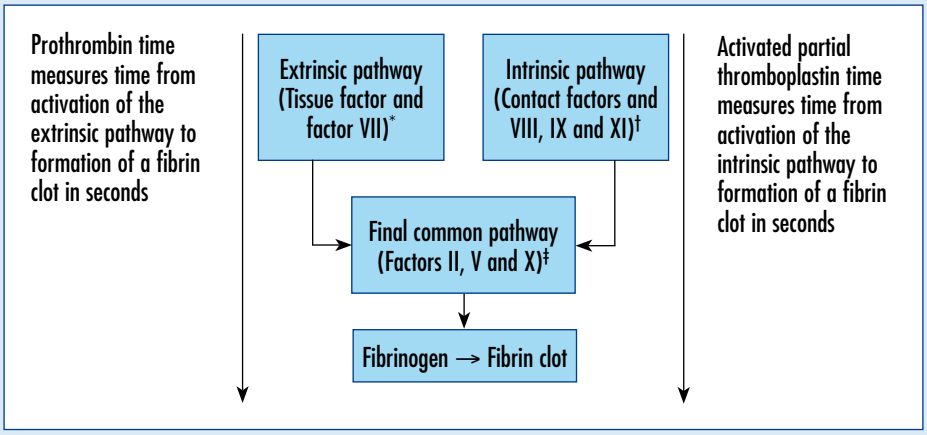


Table 1. Clotting pathways and differential diagnoses for prolonged prothrombin time and activated partial thromboplastin time

Abnormal result	Clinically significant causes
Prolonged prothrombin time only	Early vitamin K deficiency or early use of vitamin K antagonist
	Factor VII deficiency
	Occasionally seen with a lupus anticoagulant or deficiencies of factor II, V or X (if activated partial thromboplastin time less sensitive)
Prolonged activated partial thromboplastin time only	Deficiencies of contact factors, or factors VIII, IX, XI
	Heparin and direct thrombin inhibitors (prothrombin time may also be prolonged)
	Lupus anticoagulant
	Occasionally seen with deficiencies of factor II, V or X (if prothrombin time less sensitive)
Prolonged prothrombin time and activated partial thromboplastin time	Deficiencies of factor II, V or X, fibrinogen
	Vitamin K deficiency or antagonism
	Disseminated intravascular coagulation
	Liver failure
	Heparin and direct thrombin inhibitors (prothrombin time may not be significantly prolonged) and factor Xa inhibitors
	Massive blood transfusions
	Occasionally seen with a lupus anticoagulant

sary delays to procedures and unnecessary administration of blood products and procoagulant agents for patients who are not at increased bleeding risk.

Why are these tests poor predictors of bleeding risk?

In some cases, the prothrombin time or activated partial thromboplastin time will be prolonged despite there being no bleeding risk. The activated partial thromboplastin time is dependent on phospholipids. The presence of antiphospholipid antibodies in the form of lupus anticoagulant can result in a prolonged activated partial thromboplastin time (and less commonly a prolonged prothrombin time). These patients have a tendency towards thrombosis, not bleeding (Keeling et al, 2012). Factor XII deficiency, which conveys no bleeding risk, may prolong the activated partial thromboplastin time. Under-filled tubes (and a consequent decrease in the ratio of plasma to citrate) also lead to a falsely prolonged prothrombin time and activated partial thromboplastin time.

Some patients may have a severe risk of bleeding which will not be detected by these tests. Disorders that can cause a significant bleeding tendency such as factor XIII deficiency or platelet disorders will not be detected. Prothrombin time and activated partial thromboplastin time may also not detect mild haemophilia A and von Willebrand disease, emphasizing the importance of the bleeding history (Chee et al, 2008).

How should bleeding risk be assessed?

Bleeding history should be used to guide the potential need for further tests of coagulation. In two prospective studies, patients with a positive bleeding history had between a 2% and 23% risk of bleeding, although it should be noted that the difference between patients with a bleeding history and those without did not reach statistical significance when predicting the risk of future bleeding (Houry et al, 1995; Gabriel et al, 2000). The bleeding history should guide the use of clotting tests rather than replace them. For instance, patients undergoing neurosurgery with a prolonged activated partial thromboplastin time or bleeding history alone did not have an increased risk of bleeding compared to normal controls. However, in the presence of a positive bleeding history and a prolonged activated partial thromboplastin time, patients were at significantly higher risk of bleeding than matched controls (Schramm et al, 2001).

A bleeding history should include the following points (Sramek et al, 1995):

- Personal history of any bleeding problems and when they started. This can be useful to determine whether the problem is congenital or acquired
- The site of bleeding if any has occurred: mucocutaneous bleeding is more commonly associated with platelet disorders or von Willebrand disease, whereas deep tissue bleeds are more strongly associated with clotting factor deficiencies
- It is important to ask about previous challenges to the patient's haemostatic system to see if there is evidence of excessive bleeding, e.g. tooth extraction, previous surgery or menstrual periods for woman
- Past medical history of bleeding disorders, liver disease, alcohol abuse or renal disease
- Drug history should include checking for previous or current use of anticoagulants such as heparin, warfarin or direct thrombin inhibitors. Antiplatelet agents such as aspirin and clopidogrel can result in easy bruising or bleeding but do not cause changes in the prothrombin time or activated partial thromboplastin time
- Check family history for any evidence of a congenital bleeding disorder. For instance the inheritance of von Willebrand disease is often autosomal dominant (although it can be recessive), haemophilia A and B are X-linked recessive, and platelet function disorders and other rare disorders of coagulation are often autosomal recessive.

Approach to the acutely bleeding patient with prolonged bleeding times

In the case of a patient with major haemorrhage there may not be time to wait for the results of specialist coagulation tests (although these should still be performed before blood component transfusions) and in any event such patients will receive fresh frozen plasma as part of a massive transfusion protocol. As empirical transfusion with fresh frozen plasma is a poor method for treating many clotting disorders this approach should be avoided if time allows (Chowdary et al, 2004). Other factors contributing towards bleeding such as hypothermia, hypocalcaemia, acidaemia and renal failure should be treated and a source of bleeding should be sought and treated surgically if necessary (Ho and Leonard, 2011). If the cause of a prolonged prothrombin time or activated partial thromboplastin time is not clear in a bleeding patient, the case should be discussed with a haematologist to reach a diagnosis rapidly.

How to investigate a prolonged prothrombin time

The cause of a prolonged prothrombin time or combination of prolonged prothrombin time and activated partial thromboplastin time can often be deduced from the clinical history alone (*Table 1*). In each case, treating the underlying cause is the most important step in management.

If the cause is not obvious from the history then the first tests should be a thrombin time and/or a fibrinogen level. It may also be useful to know the platelet count and the D-dimer level. Early discussion with a haematologist is recommended if the diagnosis is unclear. A 50:50 mix, in which the patient's plasma is mixed with an equal volume of plasma that is known to contain all the clotting factors, may be useful but is more often so in the investigation of an isolated prolonged activated partial thromboplastin time (see below).

How to investigate a prolonged activated partial thromboplastin time

Investigations and management should again be guided by the history (those with a bleeding history should be discussed with a haematologist). A 50:50 mix should be performed and it should be tested immediately for correction of the activated partial thromboplastin time and then again after a period of incubation.

If the problem is a factor deficiency, the activated partial thromboplastin time will normalize immediately after mixing and remain normal when the mix is incubated. If this is the case, ask the advice of a haematologist who is likely to check factors VIII, IX and XI. Factor XII is often not

checked, as factor XII deficiency is not clinically significant.

If the activated partial thromboplastin time does not correct, or only corrects a little on the immediate mix, this suggests that lupus anticoagulant is present (antiphospholipid antibody). If this is the case, it is confirmed using further tests such as dilute Russell's viper venom time, IgG anti-cardiolipin antibodies and IgG anti-β2-GP1 antibodies. These patients do not have an increased bleeding risk and in fact have an increased clotting risk (Keeling et al, 2012). Consequently, tests for a lupus anticoagulant are most appropriate for the investigation of non-bleeding patients.

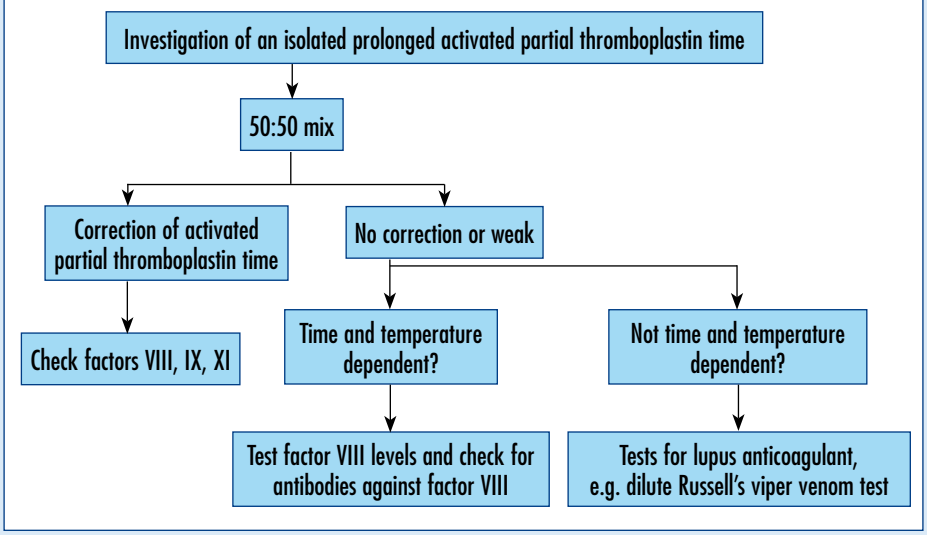
Very rarely, a prolonged activated partial thromboplastin time that corrects immediately with a 50:50 mix may be the result of acquired (autoimmune) haemophilia which is a severe bleeding disorder. In this case, the activated partial thromboplastin time of the 50:50 mix subsequently prolongs after a period of incubation (i.e. it is time and temperature dependent) (Collins and Percy, 2010) (*Figure 2*).

Severe congenital disorders of haemostasis such as haemophilia A are usually picked up in childhood and consequently are an unusual cause of a prolonged activated partial thromboplastin time in an adult. However, milder congenital diseases and even mild haemophilia A may not be detected until adulthood (Tagliaferri et al, 2012). In patients with a suggestive history and normal clotting results, further tests can be performed but the advice of a haematologist should be sought first.

Conclusions

Clotting tests are often overused in clinical practice and false positives and negatives from this may result in inappropriate treatment. It is important to take a bleeding history from patients before considering performing clotting tests, as this will guide the tests that are performed and will help in the interpretation of the results. BJHM

Figure 2. Approach to investigation of a prolonged activated partial thromboplastin time. Adapted from Collins and Percy (2010).



KEY POINTS

- A bleeding history should be taken if a patient is suspected of having a bleeding disorder.
- Investigations should be guided by the clinical history.
- There are a broad range of differential diagnoses for a prolonged activated partial thromboplastin time and/or prothrombin time, not all of which are clinically significant.
- The first test to investigate a prolonged activated partial thromboplastin time should be a 50:50 mix.
- In the event of a major haemorrhage fresh frozen plasma will usually be given but abnormal coagulation test results should be investigated if they persist after recovery.

Conflict of interest: none.

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TOP TIPS

- Always take a bleeding history before performing coagulation tests when assessing a patient's risk of bleeding.
- It is particularly useful to ask about times when the patient's haemostatic system has been challenged before, such as menses, dental extractions or previous surgery, when assessing bleeding risk.
- If a patient is not bleeding and has no history suggestive of a risk of bleeding, a clotting disorder is very unlikely and testing the prothrombin time or activated partial thromboplastin time is unnecessary and may yield confusing results.
- A 50:50 mix is a helpful test to determine whether a prolonged activated partial thromboplastin time is caused by a factor deficiency or an inhibitor.