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Shortened Activated Partial Thromboplastin Time (APTT): A Simple but Important Marker of Hypercoagulable State During Acute Coronary Event

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1. Introduction

Haemostatic system has several important functions: to keep blood in a fluid state, to arrest bleeding at the site of vascular injury by formation of a haemostatic plug and to destroy the plug slowly when healing takes place. Normal physiology constitutes a delicate balance between procoagulant and anticoagulant properties of this system, and a deficiency or exaggeration of any one may lead to either haemorrhage or vascular thrombosis respectively. Haemostatic factors have an important role in prothrombotic state and in the pathogenesis of cardiovascular diseases. Vascular, platelet and coagulation factors contribute to the development of coronary artery disease.

The main focus here is on the general implication of acute coronary event on coagulation factors, and its effect to the haemostatic system by inducing a hypercoagulable state. This state (or also described as prothrombotic state) is defined as a tendency or propensity to develop vascular thrombosis due to an abnormality in the coagulation system. Thrombophilia is another terminology describing the same condition. Although hypercoagulable state is commonly referred to venous thrombosis when coagulation system is involved, it is not an exclusive feature to this blood vessel. Its existence will lead to a harmful effect either as recurrent thrombo-embolic (TE) event or tissue damage due to ischaemic complications.

APTT is a simple and widely available test commonly used to screen for hypocoagulable state in bleeding disorders. Whether APTT is suitable as a routine screening test for hypercoagulable state is currently unknown. It is important to understand the pathophysiology of arterial thrombosis triggered by haemostatic factors and how this affect the APTT results particularly during acute coronary event. In addition, clinical consequences of hypercoagulable state in coronary artery disease are well recognized and controlling this condition has been applied successfully to the patient management protocol. Other concern includes potential errors that can falsely lead to shortened APTT results which should be highlighted to improve the clinical and laboratory practices.

2. Haemostasis and laboratory investigations

Formation of haemostatic plug is under a regulated physiological process. Haemostatic plug or blood clot or also known as thrombus is the end product of serial activations of the haemostatic system, starting from an injury or any insult usually to the blood vessel wall or endothelium. The basic physiology of haemostatic system includes the blood vessel, platelets, von Willebrand factor (vWF) and coagulation system. The coagulation system is controlled by inhibitors especially the natural anticoagulant proteins, namely the protein C, protein S, antithrombin and others. Fibrinolytic activity is essential in maintaining the patency of blood vessel lumen by removing the haemostatic plug during its course of recovery. Each of the components in the haemostatic system plays their role at the right time and at the right place that will ensure the haemostatic plug is formed when appropriate. Knowledge on the components and serial activations of the haemostatic system is important in order to understand the pathophysiology of either thrombotic (hypercoagulable) or haemorrhagic (hypocoagulable) disorders.

There are two main types of measurements related to haemostatic disturbances in the investigations of the prothrombotic state in cardiovascular disease: measurement of levels of haemostatic factors and measurement of activation products of haemostasis. In the former type of measurements, the most promising factors identified have been fibrinogen, factor VIII (FVIII), factor VII (FVII), vWF and the fibrinolytic variables i.e tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) (Fareed et al., 1998).

Common laboratory findings indicating the presence of hypercoagulable state from the haemostatic point of view include elevated coagulation factors (FVIII and others), vWF, fibrinogen, positive activated protein C resistance (APC-R) assay, shortened APTT (mainly as a result of high factor VIII and other coagulation factors) and etc. The function of protein C system in the anticoagulation pathway can be detected by APC-R assay. In this test, the function of protein C to inactivate factor VIIIa and factor Va is assessed by special coagulation test. In brief, the presence of high FVIII (or other factors) which is usually part of acute phase protein will lead to ineffective inhibition to this factor by protein C and hence the detection of this condition as a positive APC-R assay. There are many other factors that may give rise to a positive APC-R assay but in the context of coronary artery disease, it is partly explained by high factor VIII (see below).

The prothrombotic or hypercoagulable state is not easily detected by routine laboratory tests unlike the hypocoagulable state. So far, no coagulation screening test is available to detect a hypercoagulable state, whether it is due to congenital or acquired thrombotic disorders, with the exception of lupus anticoagulant (LA). In hypocoagulable state, APTT is a useful screening test in the investigation of bleeding disorders. Prolonged APTT and corrected result after mixing test is most likely to be associated with hypocoagulable disorder due to coagulation factor/s deficiency. Previous finding on the association of shortened APTT and venous thrombosis has opened some lights to the possibility of using this routine coagulation test as a screening method for the risk of TE disorder. Unfortunately there is still no consensus to use APTT as a routine screening test in clinical practice for the investigation of hypercoagulable state.

Shortened APTT could be a screening tool to be considered for hypercoagulable state during acute thrombotic episodes. However shortened APTT was also detected during venous TE

event free interval (Legnani et al., 2002; Tripodi 2004) among patients who had past history of vascular thrombosis. There was a report that showed the presence of shortened APTT at any time was related to a 10-fold increased incidence of TE events (McKenna et al., 1977). Further investigation including immunological and specialized coagulation tests may be required to find the aetiology of thrombosis in patients presenting with TE disorders.

Shortened APTT was described in acute conditions of both venous and arterial thrombosis. The role of APTT as a screening tool in asymptomatic individuals or during episodes of TE free event is probably justified, though it may not be highly sensitive. Similar application goes to the screening ability of this test in hypocoagulable conditions due to its limitation in detecting mild coagulation factor deficiency. However, using APTT as a screening test in patients with positive LA (antiphospholipid syndrome) is clearly useful and had been established for a long time. In the presence of LA, a paradoxical finding of prolonged APTT is the hallmark of this condition and its presence is strongly associated with hypercoagulable state.

In acute arterial thrombosis such as coronary artery thrombosis, similar finding of shortened APTT was also described as seen in venous thrombosis (Abdullah WZ. et al., 2010). There was a significant negative correlation between APTT and FVIII, which was described in the similar study. APTT is a robust and simple test that is available in most laboratories in all hospitals. However the natural limitation of APTT is the major reason preventing it as a powerful screening tool for both hypo and hypercoagulable states.

Abnormally shortened APTT was reported to be associated with elevated plasma level of FVIII (Ten Boekal & Bartels, 2002). Elevated FVIII levels and probably other coagulation factors play a pathogenic role in the mechanism of abnormally shortened APTT during acute coronary event or related to venous thrombosis (Abdullah WZ et al., 2010; Tripodi et al., 2004)). Hence in arterial thrombosis, presence of high coagulation factors (particularly FVIII) and positive APC-R assay were found similar to the reported findings in venous thrombosis. Majority of the patients with positive APC-R assay also could have high coagulation factors, particularly FVIII.

2.1 APTT test in clinical practice

APTT is a routine screening test for the investigation of bleeding tendency, in both acquired and congenital disorders. It is also indicated pre-operatively to detect a hypocoagulable state that can lead to excessive bleeding during or after surgery. There are many APTT reagents in the market and it is the responsibility of the laboratory personnel to ensure the results produced from this test are accurate and precise.

APTT test was originally performed to screen the function of coagulation system, mainly for the intrinsic pathway factors: factor XII, XI, IX and VIII. Various APTT reagents for different purposes are now available, including for screening of factor deficiencies and lupus anticoagulant. The normal reference ranges are expected to be different from one laboratory to another depending on the types of reagents and coagulometers. There are two major principles of clot detection for APTT test. The mechanical and optical methods, both measure the time to form a fibrin clot after adding the reagents to the test plasma. The time is commonly expressed in second (s). Plasma containing normal levels of clotting factors will clot within the time in normal ranges which should be established according to the reagent

and equipment used in the local laboratory. The reference normal range is determined by establishing the values using normal healthy volunteers of the local population. It is important for the clinical personnel to know the normal range of their local laboratory when interpreting the patients' APTT results. The same principle also applies to other coagulation tests like prothrombin time, thrombin time, fibrinogen and etc.

There are limitations with APTT test, for example possible pre-analytical errors that could occur during venepuncture procedure or during sample collection. Inappropriate blood taking procedure may lead to coagulation factors activation and falsely giving a shortened APTT results. Other problem with APTT is the consistency in reporting the results. The coagulation laboratory should practice an appropriate quality procedure, including accuracy and precision testing, participation in internal and external quality assurance programme, establishment of a normal reference ranges and other related requirements.

Validation process should be done regularly whenever changes occur in the reagents (including lot number), equipments and etc. Laboratories running APTT and other haemostatic tests should follow the standard guideline for coagulation study to avoid errors (pre-analytical, analytical and post analytical) by practicing a regular auditing, considering the use of uncertainty of measurement in the results reporting (or when consulted) and verifying the correct normal reference ranges for local use. By doing this, the finding of shortened APTT can be recognized consistently in cases with high coagulation factors or due to other reasons that can contribute to this effect. Ability to detect the evidence of hypercoagulable state through this test is strictly dependent on the laboratory performance in their practice.

2.2 Haemostatic investigations related to hypercoagulable state

TE event involving venous thrombosis is the outcome of a hypercoagulable state and usually related to increased haemostatic factors or decreased natural anticoagulant proteins. Direct and indirect involvements of haemostatic system in arterial thrombosis have been also well recognized and hence hypercoagulable state is a pathological condition present in both arterial and venous thromboses (Virchow's triad). Anti-phospholipid syndrome, APC-R assay, deficiencies of protein C, protein S and antithrombin are the most common causes being investigated when patients present with venous TE disorders.

The group of tests performed in the investigation of hypercoagulable state is also known as thrombophilia study. Congenital protein C, protein S, antithrombin deficiencies, factor V Leiden and prothrombin gene mutations are among the genetic factors associated with venous thrombosis included in the thrombophilia study. Among specialised haemostatic tests in the investigation of TE disorders are protein C, protein S, antithrombin activity/antigen assays, APC-R assay and LA tests to detect underlying thrombophilic disorders. Thrombosis is the outcome of multiple contributing factors and hence the above mentioned factors might be compounded with other conditions such as medical diseases, hyperhomocysteinaemia, high levels of coagulation factors (for example secondary to oral contraceptive pills) and etc.

Arterial thrombosis is associated with medical conditions such as smoking, diabetes mellitus, obesity, hypertension and etc. The laboratory investigation for arterial thrombosis is mainly related to the traditional risk factors mentioned above, for example lipid profile,

glucose levels, biochemical tests and etc. Some local guidelines include thrombophilia investigation similar to venous thrombosis for young patients presenting with 'premature' arterial thrombosis (for example less than 40 years old) or recurrent arterial events. Currently only homocysteine measurement and antiphospholipid antibodies detection are clearly indicated in the investigation of arterial thrombosis (hypercoagulable risk factors) especially in young patients without other known risk factors. In arterial thrombosis, the association with other conditions (including heritable thrombophilia) is unproven and not sufficient to change therapy for primary or secondary prevention of the disease.

APC-R state can be due to acquired or inherited disorders. APC-R assay is a form of specialised coagulation test which is done mainly for the screening of APC-R state due to factor V Leiden (FVL) mutation. This condition is associated with hypercoagulable state and has been reported to be high among Caucasians. FVL mutation is associated with venous thrombosis and the risk is higher in homozygous state than the heterozygous state. The mutated factor V molecule in FVL results in failure or ineffective inactivation by the protein C (protein S functions as cofactor).

The coagulation assay to detect this FVL mutation is sensitive and was also reported to be specific. However similar to other coagulation studies, there are certain limitations with APC-R assay in which the positive results could be due to other variables (high FVIII & other coagulation factors or protein S deficiency). Confirmation with molecular test is therefore the standard method to diagnose FVL mutation. However in coronary artery thrombosis, its association with FVL mutation was debatable (Cushman et al., 1998). There is probably a weak association of this mutation with coronary artery disease particularly in young smoking females. The presence of high coagulation factors may lead to a positive APC-R assay but not due to the FVL mutation. Hence positive APC-R assay is an evidence of hypercoagulable state, whether it is due to FVL or related to haemostatic factors.

Thromboelastography (TEG) is a haemostatic analyser which has been introduced in clinical practice many years ago, serving as a form of point of care testing. However it is not widely available routinely. TEG parameters reflect the function of the haemostatic components and able to detect both hypo and hypercoagulable states. Previous studies have shown that certain parameters of TEG are useful indicators for the presence of prothrombotic state such as, maximum amplitude (MA). One study showed that this parameter of TEG predicted post operative thrombotic complications including myocardial infarction (McCraith et al., 2005).

So far, basic coagulation tests to detect the presence of hypercoagulable state are still under-utilised but shortened APTT and positive APC-R assay could be applied for this purpose although with some limitations, as described above. Unlike APTT, APC-R assay is usually done in a specialised coagulation laboratory and not easily available in most hospitals. Ideally this investigation should be interpreted by an experienced scientist or haematologist rendering its usefulness as a screening test for hypercoagulable state is limited.

3. Haemostasis and coronary artery disease

Acute coronary syndrome (ACS) is a condition described for coronary artery atherothrombosis which compromised the blood supply to the myocardium and followed by clinical and/or laboratory evidences of ischaemia. ACS comprises of unstable angina,

non-ST segment elevation myocardial infarction and ST segment elevation infarction. Association of haemostatic factors with ACS has been widely investigated and thoroughly discussed in the literatures (Cooper *et al.*, 2000; Fuster *et al.*, 2005). The insult on the coronary vessel is mainly from atherosclerotic process and its complication (example plaque rupture) leading to an acute thrombotic event from the haemostatic activation. The formation of blood clot (fibrin) from this activity gives a sudden blockage of the vessel lumen and produced the signs and symptoms of ACS mainly chest pain, electrocardiographic and biochemical changes. The schematic drawing of coagulation cascade activation and fibrinolytic activity is shown in figure 1.

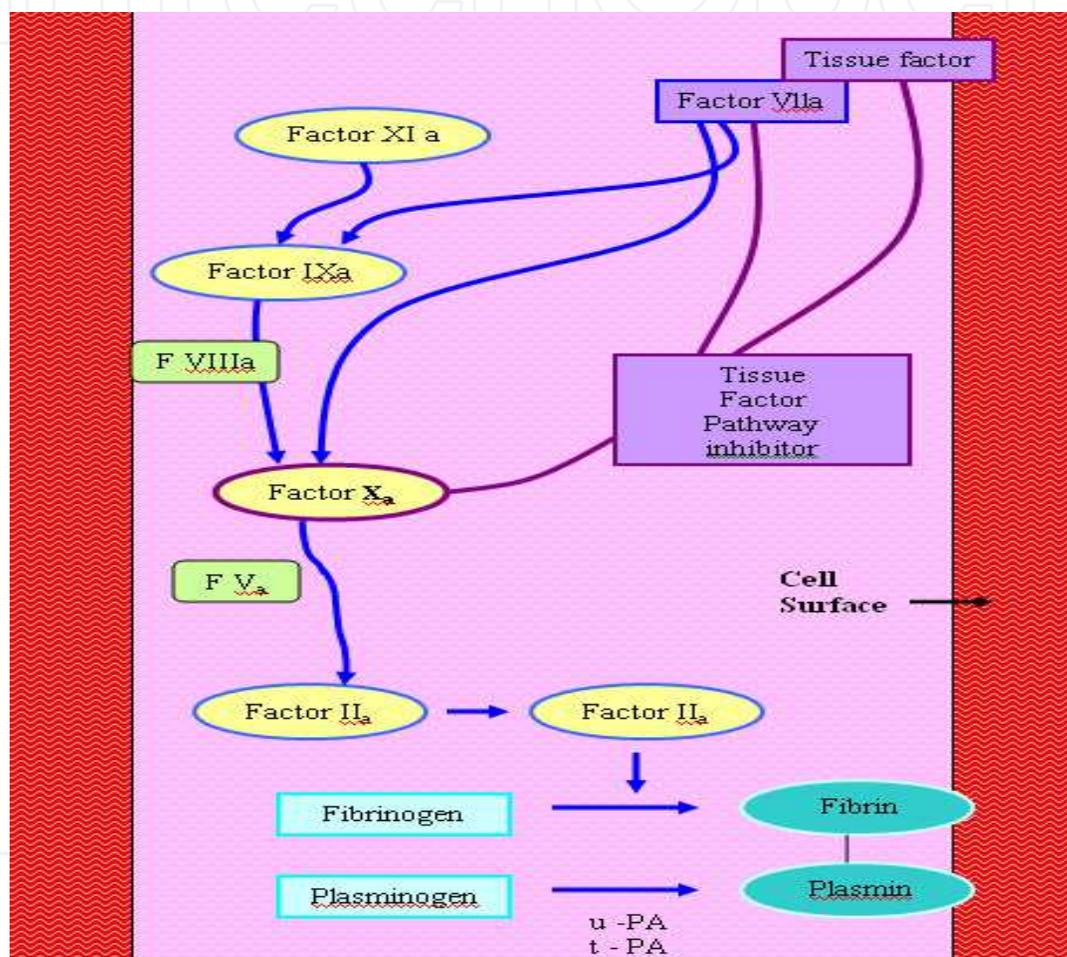


Fig. 1. Coagulation activation, fibrinolysis and tissue factor pathway inhibitor. (u-PA, urokinase plasminogen activator; t-PA, tissue plasminogen activator)

The mechanism of thrombosis according to Virchow's triad explained the hypercoagulable process. Most of the risk factors for venous thrombosis are caused by stasis or changes in overall total blood coagulability, while vessel wall damage is the main cause of thrombogenicity in arterial thrombosis. Vascular endothelium is involved in a wide range of homeostatic functions including maintaining the balance of anticoagulant and procoagulant forces. On the anticoagulant side, the endothelium releases heparin sulfate and prostacyclin, expresses thrombomodulin, t-PA, tissue factor pathway inhibitor and endothelial nitric oxide synthase which provide a non-thrombogenic cell-surface membrane. On the prothrombotic side, endothelial cells release von Willebrand factor and plasminogen

activator inhibitor type-1, expose critical binding sites for coagulation factor complexes and some other functions. The endothelium is capable of integrating multiple feedbacks and capable of shifting the haemostatic balance from time to time that allows the haemostatic system with tremendous flexibility (Rosenberg and Aird, 1999). However the endothelium is also vulnerable to focal dysfunction resulting in many ways including narrowing of the lumen and increased risk of sudden obstruction as seen in the various phases of atherothrombosis.

Although Protein C, protein S and antithrombin do not confer an increased risk of arterial thrombosis, other anticoagulant mechanisms must be responsible for maintaining the patent of vascular lumen, particularly in coronary vessels. Fibrinolytic enzymes play a critical role to keep the lumen patent by preventing fibrin deposition within the vascular bed of the heart. These enzymes are t-PA and urokinase-type plasminogen activator. Binding of t-PA to fibrin enhances the conversion of thrombus-bound plasminogen into plasmin. Plasmin is capable to digest the fibrinogen, fibrin and factor VIII. The anticoagulant property of tissue factor pathway inhibitor helps to control the procoagulant activity of the extrinsic coagulation factors (FVIIa and tissue factor). Similarly APC stimulates fibrinolysis by destroying plasma inhibitors of t-PA. Haemostatic balance within the coronary vessels is controlled by a vascular bed-specific circuit or feedback system. Hence there is a strong possibility that thrombosis in coronary artery arises through the interplay of plaque rupture and an alteration of local haemostatic circuit (Rosenberg and Aird, 1999).

In addition to the consequences of atherosclerotic plaque rupture where the thrombus formed in the coronary artery, the systemic effect of this acute event is seen almost immediately. In one study, shortened APTT was significantly different in ACS patients compared to stable coronary artery disease patients (SCAD) when they presented early to the hospital (Abdullah WZ., et al 2010). High FVIII levels were also found to be significant in ACS patients compared to the SCAD group. None of the SCAD patients had shortened APTT result in their study although some of them were having elevated FVIII levels (which did not affect the APTT results). Significantly high vWF and fibrinogen were seen among ACS patients compared to the SCAD patients and most patients with APCR state also had high FVIII levels. (Abdullah WZ., et al 2011). Interestingly, inversed relationship between FVIII and APTT was shown among coronary heart disease patients indicating that shortened APTT is partly explained by increased FVIII levels (Figure 2 and table 1).

Haemostatic system involves in the initiation of ACS through haemostatic activation (platelet and coagulation system activation) and hypercoagulable state is a finding following this event, as evidenced by high vWF, fibrinogen and FVIII levels. The net outcome of the effect of these hypercoagulable factors is detected as shortened APTT as shown by the above study.

Patients with arterial thrombosis also have a form of hypercoagulable state, manifested by higher baseline concentrations of fibrinogen and elevated factor VII activity. Increased fibrinogen concentration is a strong and independent predictor of cardiovascular risk in apparently healthy person as well as in person manifested as coronary heart disease (Thomas and Roberts, 1997). Clinical studies have shown that subjects with higher plasma levels of procoagulant proteins (including vWF and coagulation factors) had an increased risk of myocardial infarction (Rosenberg and Aird, 1999).

The role of platelet and vWF in arterial thrombosis is not elaborated in details here. Obviously there is an integrated process from various haemostatic components that eventually promote a hypercoagulable state throughout the entire process. Furthermore shortened APTT does not account for the platelet reactivity in atherothrombosis. The contribution of haemostatic system in the development of atherothrombosis has been greatly discussed in literatures. It is also interesting that this system may also determine the outcomes of the disease. The beneficial effects from anti-platelet, anticoagulation and anti-thrombotic therapies in prevention and treatment of ACS proved that hypercoagulable state should be controlled to avoid its harmful effects in coronary artery disease.

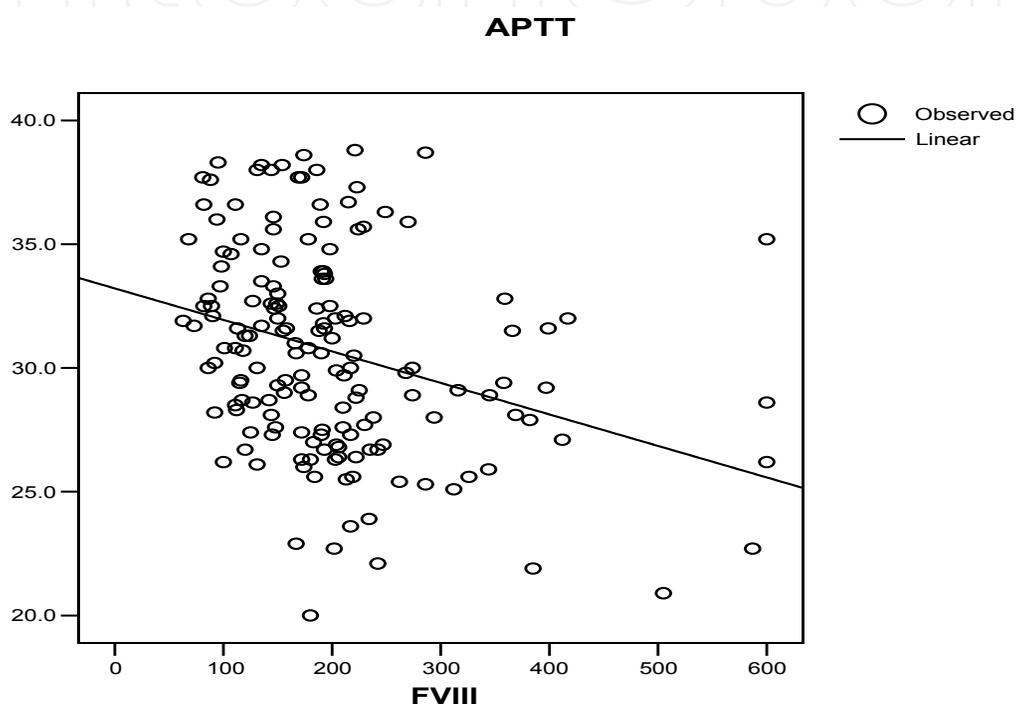


Fig. 2. The correlation between FVIII and APTT among coronary heart disease patients.

Variable	β (S.E)	(95% CI)	<i>p</i> value*
FVIII	-0.013(0.003)	(-0.019,-0.007)	< 0.0001

(R square = 0.097 (10%), predictor = FVIII, dependent variable = APTT. **p* value is significant when ≤ 0.05)

Table 1. The correlation between FVIII level and APTT among coronary heart disease patients.

4. Consequences of hypercoagulable state following ACS

The after effect of acute coronary thrombosis may further complicate both the local coronary artery and systemic circulation by the burden of this hypercoagulable state. This condition can be harmful and leads to an imbalance state between the natural anticoagulant and procoagulant activities. Hypercoagulable state potentially caused repeated episodes of vascular thrombosis and may lead to increased in morbidity and mortality. This is especially true if this state is not controlled adequately with the given treatment, especially the

anticoagulant and antiplatelet therapy. Resistance to certain anti-platelet drugs have been reported and extensively discussed in the literatures, which partly explained why some patients developed repeated thrombotic event despite on adequate therapy (Flaherty MP., et al 2011).

5. Conclusion

ACS by definition is a hypercoagulable state and shortened APTT is a useful haemostatic marker. Shortened APTT is associated with increased coagulation factors for example fibrinogen and FVIII. Previous studies have shown a consistent association of increased haemostatic factors in acute coronary artery thrombosis. It is now understood that hypercoagulable state is likely to be present before or after this event. Limited investigation is recommended pertaining to haemostatic tests in coronary artery thrombosis.

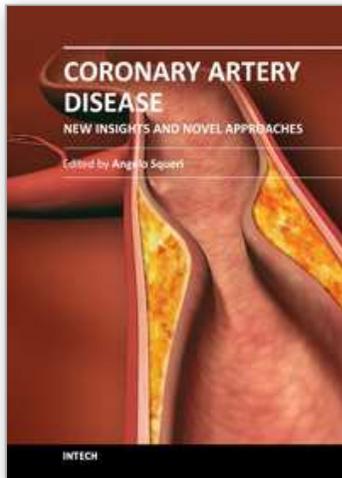
Haemostatic activities for example thrombin generation, platelet activation and abnormal fibrinolysis may significantly influence the outcomes of patients with this disease. In patients with risk factors of coronary artery disease, the presence of shortened APTT at the onset of acute clinical presentation is associated with higher chance of ACS. There is a relationship of shortened APTT and hypercoagulable state during acute thrombotic episodes, although the possibility remains that an acute phase responses (increase fibrinogen and FVIII) present at a wide range of time since the initial onset of vascular injury during the atherosclerotic process.

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Coronary Artery Disease - New Insights and Novel Approaches

Edited by Dr. Angelo Squeri

ISBN 978-953-51-0344-8

Hard cover, 260 pages

Publisher InTech

Published online 16, March, 2012

Published in print edition March, 2012

Coronary Artery disease is one of the leading causes of death in industrialized countries and is responsible for one out of every six deaths in the United States. Remarkably, coronary artery disease is also largely preventable. The biggest challenge in the next years is to reduce the incidence of coronary artery disease worldwide. A complete knowledge of the mechanisms responsible for the development of ischaemic heart disease is an essential prerequisite to a better management of this pathology improving prevention and therapy. This book has been written with the intention of providing new concepts about coronary artery disease pathogenesis that may link various aspects of the disease, going beyond the traditional risk factors.

How to reference

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Wan Zaidah Abdullah (2012). Shortened Activated Partial Thromboplastin Time (APTT): A Simple but Important Marker of Hypercoagulable State During Acute Coronary Event, *Coronary Artery Disease - New Insights and Novel Approaches*, Dr. Angelo Squeri (Ed.), ISBN: 978-953-51-0344-8, InTech, Available from: <http://www.intechopen.com/books/coronary-artery-disease-new-insights-and-novel-approaches/shortened-activated-partial-thromboplastin-time-aptt-a-simple-but-important-marker-of-hypercoagulabl>

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