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# Microparticles: Role in Haemostasis and Venous Thromboembolism

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## 1. Introduction

Microparticles (MP) are small membrane bound vesicles which have been described in circulation. They are derived from a variety of cells by an active process of shedding. They are bound by plasma membrane, are anucleate but may contain DNA or RNA and may be virtually derived from any cell (Ahn 2005, Mause, *et al*, Porto, *et al*). The majority of the microparticles in blood are derived from platelets. Previously considered as cell debris they are now regarded as vectors for transfer of biological information. The MP production is thought to reflect a balance between cell stimulation, proliferation and death. Based on their potential function and pathophysiologic effect, MP are thought to be physiological or pathological. MP play a role in normal haemostasis and abnormal amplification of MP production leading to a pathological state (Meziani, *et al*). For example, excessive MP from platelets may contribute to thrombosis (Siljander, *et al* 1996). Their role in vascular biology is being uncovered with increasing evidence for their role in venous thromboembolism. This chapter will explore the role of these MP in the physiology of haemostasis as well as pathology of thromboembolism. The final section will discuss the current state of art in the methods used to detect and measure MP.

### 1.1 Definition of a microparticle

Microparticles are submicron (<1.0 $\mu$ m) membrane bound circulating vesicles. Although anucleate, usually express cell surface antigen specific to the cell of origin, they may contain DNA or RNA and be virtually derived from any cell (Freyssinet 2003). The ISTH (International Society of Thrombosis and Haemostasis) vascular biology subcommittee defined these particles as being between 0.1-1.0  $\mu$ m (SSCMembers Aug 2005). However, several other nanoscale techniques have demonstrated that particles <0.1  $\mu$ m may also need to be considered as MP (Yuana, *et al*). Indeed, size range of MP is contentious with larger MP likely overlapping with small platelets and the smallest MP with exosomes (Gyorgy, *et al*, Jy, *et al*, Lawrie, *et al* 2009). Several factors may cause the production of MP from cells such as activation, complement mediated lysis, shearing stress, oxidative injury and active vesiculation (Horstman, *et al* 2004). The MP bear at least some surface characteristics of the parent cell and they differ from exosomes (0.03-0.1 $\mu$ m), which originate through the exocytosis of endocytic multivesicular bodies and play a role in antigen presentation (Freyssinet and Dignat-George 2005, Horstman, *et al* 2004, Horstman, *et al* 2007).

Cellular source of MPs	Marker	Proportion in circulation
Platelets	CD61 (GPIIIa) CD63 CD62p (P-selectin) CD41	80-90%
Leucocytes	CD45	<5%
Erythrocytes	Glycophorin A	5-10%
T helper cells	CD4	<1%
T cytotoxic cells	CD8	<1%
B cells	CD20	<1%
Monocytes/ macrophages	CD14	<5%
Endothelial cells	CD62e (E-selectin)	<5%

Table 1. Microparticle source, surface antigen expression and proportion in circulation (Enjeti, *et al* 2007, Siljander).

## 2. Microparticles: Production and role in haemostasis

### 2.1 How are microparticles produced?

Microparticles are thought to be produced by an active process of vesiculation or shedding from the cell surface and utilizing ATP in the process. Various enzymes involved in the production of MP have been studied. The balance of several enzymes regulating membrane homeostasis is believed to be key in the production of MP. An inward aminophospholipid enzyme 'translocase' or 'flippase' and an outward enzyme 'floppase' have been postulated to maintain the dynamic symmetrical state of the phospholipid bilayer membrane (Diaz and Schroit 1996, Montoro-Garcia, *et al*, Morel, *et al*). In a resting membrane the flippase enzyme is more active thereby ensuring that phosphatidyl serine (PS) is at the inner membrane. The activation of phospholipid nonspecific enzyme known as 'scramblase' is said to be responsible for disruption of membrane asymmetry and several mechanisms participating in the regulation of the transmembrane migration of phosphatidylserine (PS) in activated cells lead to microparticle shedding (Diaz and Schroit 1996, Enjeti, *et al* 2008, Morel, *et al* 2006). After stimulation, calcium is released from intracellular stores. Calcium depletion induces the activation of store-operated calcium entry (SOCE) through channels in the plasma membrane and this process is thought to be regulated by transient receptor potential channel (TRPC) proteins (Diaz and Schroit 1996, Montoro-Garcia, *et al*). The transverse redistribution of PS is under the control of SOCE. Several other process such as Raft integrity, cytoskeleton organization and MAP kinase pathway (Ras-ERK) are also involved in membrane remodelling (Diaz and Schroit 1996, Montoro-Garcia, *et al*, Morel, *et al* 2006). Microparticles typically have phosphatidyl serine on the outer surface (although PS negative MP have also been recently described) and ABCA1, a member of the ATP-binding cassette family of transporters, is a potential candidate for the transport of PS to the surface (Diaz and Schroit 1996, Morel, *et al* 2006).

### 2.2 Role of MP in coagulation and haemostasis

Normal coagulation is a complex process triggered by endothelial damage and exposure of tissue factor and collagen which initiates a platelet plug formation at the site of injury. This

leads to activation of a cascade of enzymes, which forms a fibrin clot. Microparticles of different cell origin could play a role in fibrin clot formation, enhance platelet leukocyte interactions and influence other plasma proteins such as von Willebrand’s factor. Given that platelet MP constitute the majority of the circulating MP, they are considered an important effector of the haemostatic process (Morel, *et al* 2006). Some MP have also been described to carry molecules with anticoagulant function on their surface (Freyssinet 2003). The balance of pro and anticoagulant bearing MP in the endovascular milieu is likely to influence the propensity to bleed or clot in a particular patient.

Type of MP	Example of surface marker on MP
Procoagulant	von Willebrand's Factor Tissue Factor Platelet Factor 3 activity
Anti-coagulant	Tissue Factor Pathway inhibitor Protein C/S Thrombomodulin

Table 2. The possible pro and anticoagulant markers on the surface of microparticles (Enjeti, *et al* 2007, Morel, *et al* 2006).

## 2.3 Platelet MP

### 2.3.1 Platelet MP and coagulation

Traditionally, platelets major function was thought to be due to their aggregability and ability to plug damaged endothelium and capillary vessels. More recently, they are thought to form an important substrate for the coagulation pathway with their membrane providing the surface for the formation of the prothrombinase complex (comprising the Xa and Va complex). This enzyme complex leads to conversion of fibrinogen to fibrin which in combination with a variety of other factors leads to a stable clot at the site of injury. The presence of platelet microparticles at the site of blood vessel injury may contribute to this process by providing a large source of surface membrane for assembly of the enzymatic process. Indeed the exposure of phosphatidylserine at the site of thrombin generation increases the enzymatic catalytic effect by several hundred fold (Aleman). Platelets thus appear to have two major physiological roles for achieving haemostasis - form a platelet plug at the site of endothelial injury and generate microparticles which provide a surface for activation of the coagulation cascade leading to formation of the fibrin clot. The third possible role for the platelet MP could possibly be in maintaining the integrity of normal resting endothelium (Cambien, 2004). This area is still being actively explored. The role of MP in haemostasis is illustrated in figure 1.

Apart from procoagulant function MP could also be involved in anticoagulant activity. Microparticles with TFPI (tissue factor pathway inhibitor) and antithrombin activity have been described (Morel, *et al* 2006, Siljander). However, the anticoagulant MP have not been as extensively studied and it would be interesting to evaluate these MP - its association with pathologic conditions.

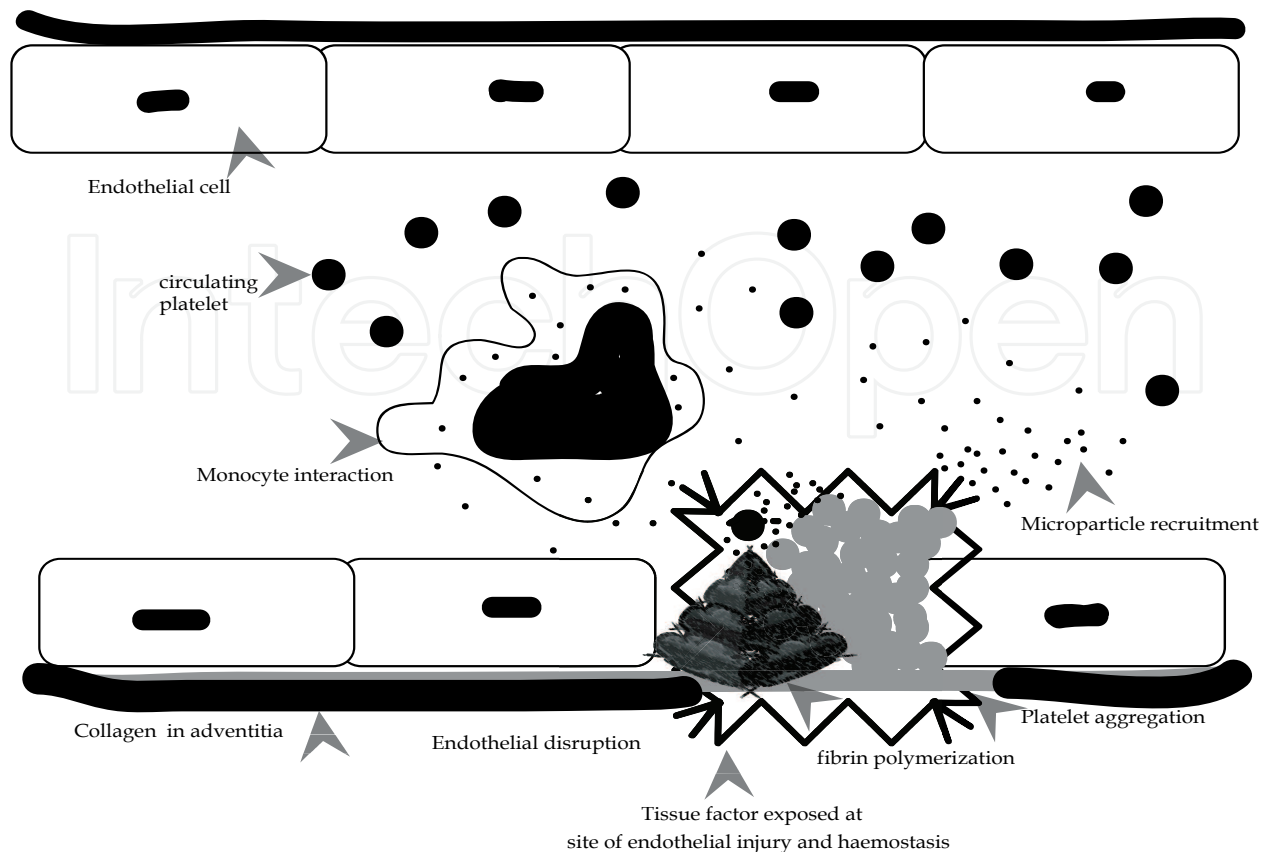


Fig. 1. The interaction of MP of platelet and monocyte origin being recruited in thrombus formation at site of endothelial injury.

### 2.3.2 Molecular interactions of Platelet MP

Platelet MP also bear a number of antigens such GPIIb/IIIa, GPIa, von Willebrand's factor and arachidonic acid which may all be important effectors in the clotting mechanism. The understanding of the molecular mechanisms of haemostasis has now led to the thinking that coagulation can be described as an interaction between p-selection, tissue factor thrombin and microparticles (Furie and Furie 2004). P-selectin is an adhesion molecule expressed at the platelet endothelial interface which is thought to be critical for tissue factor activity and leukocyte adhesion in the thrombus (Myers, 2003). Some authors have even described P-selectin on microparticles, tissue factor and clotting proteins as being the molecular triad for coagulation (Polgar, 2005).

Another potential role of MP may be in the interaction of endothelium, von Willebrand's factor and platelets. The platelet derived microparticles could interact with the protease ADAMTS-13 (A Disintegrin And Metalloproteinase with Thrombospondin-1-like motifs, member 13 of this family of metalloprotease), which regulates the activity of high molecular weight von Willebrand's factor. Increased microparticles in circulation could potentially compete in binding ADAMTS-13, reducing its interaction with the endothelium and influencing multimer cleavage (Jy, *et al* 2005). This may then contribute to the increased rates of thrombosis observed in these patients with thrombotic thrombocytopenic purpura though the evidence for this process is very preliminary.

## 2.4 Tissue factor bearing MP

In an intact blood vessel tissue factor is usually restricted to adventitia and protected by the endothelial layer. However, small amounts of monocyte related tissue factor have been isolated in circulation (Key). The presence of tissue factor (TF) bearing microparticles, mainly derived from monocytes, in circulation has been shown to participate in initiation of fibrin polymerization (Eilertsen and Osterud 2004, Key). Although usually found to be in very small numbers in normal circulation, these increase dramatically at the site of injury. The interaction between tissue factor bearing MP and platelet MP is also of interest as there appears to be some evidence that they may be complementary in terms of thrombin generation potential (Key and Kwaan).

## 2.5 Modelling MP in thrombosis

The evidence for the involvement of these MP in its various physiological roles in haemostasis comes from the following models.

### 2.5.1 Cell based haemostasis model

The initial evidence for the role of MP in haemostasis comes from the cell based model. In this model plasma coagulation proteins are activated on the membrane surface after exposure to tissue factor. This leads to enzymatic cleavage of thrombin from prothrombin which ultimately converts fibrinogen to fibrin. This forms the fibrin clot and leads to haemostasis along with other components of the clot such as platelets and monocytes (Biro, *et al* 2003, Chirinos, *et al* 2005).

### 2.5.2 Live imaging model

Studies using intravital microscopy have shown that TF bearing MP derived from haemopoietic cells are incorporated into a thrombus. A laser injury model using the cremaster muscle arterioles of the mouse showed that MP participate in thrombosis (Falati, *et al* 2003). Although these studies visualize incorporation of TF bearing MP into the thrombus, it is not yet known if these MP are actually functional.

### 2.5.3 Animal models

These studies have involved introducing exogenous MP from patients or other source into animal models. In one such study MP from patients with acute coronary syndrome were introduced in to a rat model triggered venous thrombosis (Mallat, *et al* 2000). This study supports the role of TF bearing MP in promotion of VTE, However, the cellular sources of this TF has not been entirely clarified in other studies (Shantsila, *et al*).

### 2.5.4 Scott Syndrome

Scott Syndrome is an extremely rare hemorrhagic disorder characterized by bleeding diathesis ( only three well documented cases of Scott syndrome have been reported to date) (Zwaal, *et al* 2004). The bleeding tendency is thought to be due to impaired procoagulant activity of stimulated platelets - the platelets being unable to expose anionic phospholipids and to shed procoagulant microparticles. The exposure of the aminophospholipids, mainly

phosphatidylserine, on surface of stimulated platelets or derived microparticles, is critical for the formation of enzyme complexes in the clotting process (Zwaal, *et al* 2004, Zwaal, *et al* 2005). Mutations involving the ABCA1 ATP transporter have been reported in this syndrome (Zwaal, *et al* 2004).

There are several other mechanisms by which MP influence the endovascular system. They may modulate endothelial function and carry proangiogenic molecules (Lozito and Tuan). Recently MP bearing Sonic hedgehog have been shown modulate angiogenesis (Soleti, *et al* 2009, Soleti and Martinez 2009). They may also serve as novel carriers for transport of genetic material – such as mRNA or microRNA and these are currently areas of intense research (Rak).

### 3. Role in thrombosis

From their role in physiology of haemostasis it can be extrapolated that excess production of MP will lead to a pathological state. Indeed, increase in circulating MP have been described in a wide variety of states. The role of MP in various thrombotic states is discussed below.

#### 3.1 Venous Thromboembolism (VTE)

##### 3.1.1 Idiopathic VTE

Venous thromboembolism is the result of a complex interaction between the circulating proteins, cells/platelets and the endothelium (Collen and Hoylaerts 2005). There is no known provoking or identifiable precipitating factor in idiopathic VTE. A recent study looked at the interactions between the MP of various origin - platelet, endothelial and monocyte and endothelial derived MPs were found to be elevated in association with VTE. One report suggests that the combination of total circulating MP, P-selectin levels and D-dimer levels may help predict VTE (Rectenwald, *et al* 2005). This approach had a sensitivity of 73% indicating the need for further refinement for application in clinical practise.

In another larger investigation no association was found between levels of total circulating MP and risk of recurrent VTE (Ay, *et al* 2009). Interestingly, a study comparing patients with cancer who had VTE and those with idiopathic VTE found raised tissue factor bearing MP only in cancer patients (Thaler, *et al*). In another report, plasma levels of tissue factor MP were not raised in those with pulmonary embolism suggesting that that perhaps other subtypes of MP may have to be studied in more detail to explain the relationship found in experimental models (Garcia Rodriguez, *et al* 2010). Owen and co authors looked at the recurrence of VTE and found that the procoagulant activity but not number of MP was increased in cases of recurrence (Owen, *et al*).

The role of MP in predicting thrombosis in those with heritable thrombophilia has also been explored. It has been found that total circulating MP levels were increased in subjects with heterozygote factor V Leiden status but there was no difference between those who had had VTE and those without (Enjeti, *et al* 2010). This finding and other studies seems to suggest that although total microparticles have been shown to be increased in those with VTE or those prone for VTE, there appears to be no convincing data that MP help to predict or monitor VTE. However, in a recent study that investigated this issue further, looked at MP levels by a different approach by comparing percentiles of MP measured in a retrospective

case-control fashion. In those with circulating MP above the 90th percentile of the control population's distribution, a five fold increased risk was observed (Bucciarelli, 2011). They found that elevated MP were indeed an independent risk factor for VTE and this warrants a confirmation in a prospective cohort study.

The draw back of the studies in this area of VTE include the variability of type of MP studied, the techniques employed for measurement of MP and retrospective nature of investigations undertaken.

### 3.1.2 Immune related VTE

In contrast to idiopathic VTE, there is strong evidence for involvement of MP in thrombogenicity in patients with underlying immune disorders. Important examples include antiphospholipid antibody syndrome and heparin induced thrombocytopenia with thrombosis syndromes (Combes, *et al* 1999, Dignat-George, *et al* 2004, Walenga, *et al* 2000). Markedly elevated platelet derived MP have been described in both clinical syndromes (Hughes, 2000). There is experimental evidence to suggest that circulating autoantibodies trigger the formation of excess MP contributing to the prothrombotic process in these patients. Circulating MP in these syndromes have been shown to expose GPIIb/IIIa, P-selectin and thrombospondin all of which help promote thrombosis (Jy, *et al* 2007).

### 3.1.3 Microparticles, VTE and cancer

In contrast to the above discussion for idiopathic VTE - thrombosis, cancer and microparticles seem to have a more definitive relationship. The MP are thought to reflect a balance between cell stimulation, proliferation and death which may be important in cancer related thrombosis. Cancer increases the risk of VTE by four fold and addition of chemotherapy further increases the risk by six to eight fold (Furie and Furie 2006). It is possible that circulating MP shed from cancer cells represent an indication for tumours to metastasize in the absence of any other clinical evidence for metastasis. A recent report states that platelet MP markedly stimulated the metastatic potential of 5 different cancer cell lines (Rak). It has also been shown that human tumor derived MP when injected into mice activated coagulation by virtue of their TF procoagulant activity (Thaler).

Procoagulant properties of tumor cell MP have been an area of intense study. A range of endothelial, monocyte and leukocyte MP along with tissue factor bearing MP appear to have a coagulant potential and have shown to be elevated in various such as cancers such as pancreatic, breast and prostate (Pilzer, *et al* 2005, Simak and Gelderman 2006).

A recent in vivo live microscopy mouse model with pancreatic cancer demonstrated that TF bearing MP released from the cancer cells entered circulation and participated in the thrombus formation at a distant site (Thomas, 2009).

The most important evidence for role of MP in VTE and cancer comes from clinical studies showing increased numbers and procoagulant activity of MP in cancer (Langer). Elevated levels of tissue factor bearing MP were associated with VTE events in those with advanced malignancy particularly pancreatic cancer. The microparticle levels in cancer patients also predicted the development of thrombosis, with the one year estimate of those with TF



bearing MP being about 34% (Thaler, 2011). In contrast those who did not develop thrombosis did not have a detectable level of tissue factor bearing microparticles.

### 3.1.4 Disease groups associated with venous or arterial thrombosis

There are a number of conditions associated with elevated MP. Most of these disease states are associated with an increased risk of thrombosis. They essentially seem to reflect the health and pathophysiology of the endovascular system. Table 3 below gives a list of conditions where they have been found to be elevated.

Condition	Specific example where MP were elevated (reference)
<b>Cardiovascular disease</b>	Hypertension (Boulanger) Myocardial infarct/angina (Nagy) (Exner, 2005 ) Stroke (Merten, 2004) Diabetes (Alkhatatbeh) Thromboembolism (Cimmino)
<b>Myeloproliferative Disorder</b>	Polycythemia vera (Duchemin) Essential Thrombocytosis (Villmow, 2002) Myelofibrosis (Villmow, 2002)
<b>Thrombotic Microangiopathies</b>	Thrombotic thrombocytopenic purpura (Ahn, 2002) Pre-eclampsia of pregnancy (Aharon)
<b>Autoimmune diseases</b>	Antiphospholipid antibody syndrome (Combes, 1999; Dignat-George, 2004) Systemic lupus erythematosus (Nielsen; Pereira, 2006)
<b>Cancer related</b>	Metastatic solid tumours (Dass, 2007) Chemotherapy induced (Kim, 2002; Kim) Neoangiogenesis (Goon, 2006 )

Table 3. List of conditions associated with thrombosis and elevated MPs in circulation.

### 3.2 Microparticles and atherothrombosis

The role of MP in promoting atherothrombosis has also been another area of study (Cimmino). In one report, shed membrane microparticles were seen to be produced in human atherosclerotic plaques and were a critical determinant of thrombogenicity after plaque rupture (Mallat, 1999). The apoptosis occurring after plaque disruption or rupture was closely associated with TF expression on cell membranes leading to thrombogenicity. These MP were observed to express phosphatidylserine and some expressed CD11a which is an adhesion molecule (Martinez, 2005) (Morel, 2006). Given the links between inflammation and thrombosis, the emerging role of MP in atherothrombosis is not surprising (McGregor, 2006; Meerarani, 2007).

## 4. Measuring microparticles

There are several approaches to detection and measurement of MP. The methods are usually based on the ability of the assay to either enumerate or assess functional activity of the MP.

### 4.1 Functional assays

Most of the assays under this section relate to either the prothrombotic function of MP or measuring the phospholipid content of MP. This can be done in the liquid phase e.g. a clot based assay such as the XACT test or by estimation of prothrombinase activity using an ELISA (Exner, 2003). The advantages of these approaches are that they provide an indication of the procoagulant activity of MP. The drawback is that the cell of origin for the MP cannot be determined.

### 4.2 Quantitative assays

Flow cytometry is the most widely employed quantitative technique. The gating of small particles continues to be a challenge but flow cytometry continues to be the only robust technique which can demonstrate the cell of origin for the MP. This is an important asset of flow cytometry. However, there is significant variability amongst flow cytometers and the ISTH subcommittee on vascular biology recently conducted a workshop on standardization of MP by flow cytometry (Lacroix). It remains a popular approach for detection of MP for the following reasons: 1) Rapid turn around time 2) Both fresh and frozen specimens may be used 3) The expression of two or more antigens on the MP may be simultaneously demonstrated 4) Easy method for quantification using commercial beads.

However it has the following drawbacks: 1) The detection of particles less than  $0.3\mu\text{m}$  is difficult by flow cytometry as the detection is limited by particle size in the same order of magnitude wavelength of the laser ( about 488 nm 2) Different machines have different sensitivities 3) It is difficult to automate 4) Centrifugation speeds for sample processing are variable and not standardized (Freyssinet, 2005). Several new approaches to flow cytometry include using impedance flow cytometry and using Raman microspectrophotometry effect to cover the size and particle discrimination issues (Ayers, 2011).

The capture of MP into immobilized annexin V or cell specific antibodies using an ELISA based assay have been the other major approaches (Enjeti, 2007). Solid phase assays have the advantage of picking up microparticles irrespective of size. However interference of soluble antigens, variable quality of antibodies used for antigen capture and non-exclusion of microsomes are some of the disadvantages.

### 4.3 Nanoscale and newer technologies

In the recent years there has been an adaptation of nanoscale technologies such as atomic force microscopy and nanoparticle measurement techniques. These methods claim to accurately measure particles in the nanoscale size range (Yuana). For example , one such nanoscale technique uses the brownian motion of these small particles to detect and measure them (Harrison, 2009). These methods are expensive, intensive to perform and not yet widely available (Lawrie, 2009). Moreover, the clinical utility of such techniques is not yet established. Recently a proteomic approach to analysis of MP has been described,

however, the clinical utility of this approach is also as yet unknown (Howes ; Ramacciotti). Automated devices to analyse MP are also being developed (Wagner, 2010).

#### **4.4 Measuring microparticles: Future directions**

There are several outstanding issues such as standardization of preanalytical and analytical variables as well as integration of the various approaches in measuring MP. Several novel approaches are now being considered. 'Megamix beads' is novel approach to standardizing of gating of microparticles using flow cytometry. It uses a mix of a 0.9 $\mu$ m and 0.3 $\mu$ m sized beads to try and capture all events within the gate set by the beads (Robert, 2009 ;Robert, 2011). One of the problems of using this approach is the lack of linearity in the relationship between the size of beads and forward scatter at that particle size. A recent commercially available nanoscale technology known as 'Nanosight' has incorporated antibody tagging of small particles for accurate identification and counting in this size range (Harrison, 2009).

### **5. Conclusions**

Utility of Measuring MP in venous thromboembolism is yet to be fully established . The case for measuring MP in cancer related VTE is perhaps stronger. There are three areas within which the potential for detecting and measuring MP with respect to venous thromboembolism may be relevant.

#### **5.1 Diagnostic**

The evidence for using measurement of MP in a diagnostic setting is limited. The studies so far have shown variable results depending on whether TF bearing MP, functional activity or total MP were measured. With respect to VTE MP have been assessed in the paradigm of VTE, diagnosis in a small pilot study where it was shown that D-dimer, P-selectin and total MP levels predicted thrombosis as demonstrated on Doppler ultrasound (Ramacciotti; Rectenwald, 2005). The role of MP in diagnosis of VTE warrants confirmation in prospective cohort studies. The standardization of measurement of MP will go a long way in ensuring comparability of such studies.

#### **5.2 Prognostic**

The potential for MP as a prognostic tool is dependent on reliable, reproducible and easily available tools to measure microparticles. There is emerging data that MP may predict VTE in cancer patients and may be able to provide prognostic information in several other conditions.

#### **5.3 Therapeutic**

An interesting dimension to this area is the approach to use or modify MP for therapeutic benefit. The possibility of bioengineered and/or harvested membrane microparticles in tissue repair or angiogenesis is being investigated (Soleti, 2009). The MP are also being studied as a drug delivery tool (Benameur, 2009). Microparticles could potentially be specifically targeted to reduce or prevent thrombotic complications or end organ damage (Myers, 2005). This is an promising and exciting new area for researchers and clinicians working in this area.

Microparticles have therefore emerged as key role players in vascular biology and pathophysiology of thrombosis. They remain an important research tool and their clinical applications are being actively investigated with potential to be applied in diagnostic, prognostic and therapeutic arenas. They are small yet powerful effectors for the pathophysiology of the endovascular system.

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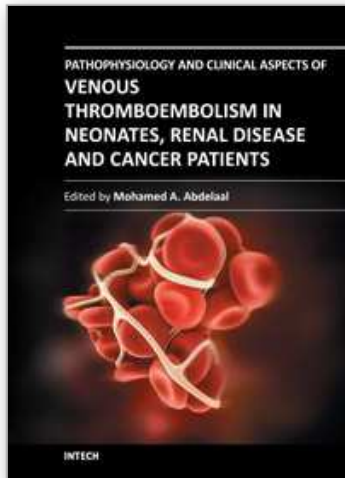
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Venous Thromboembolism remains a major health challenge in many countries because of the morbidity and mortality it inflicts, mainly in hospitalized patients. This book, with contributions from distinguished experts in the field, depicts some hot aspects on aetiologies of VTE, the disease burden in neonates, renal disease and cancer patients as well as issues relevant to prophylaxis and the concept of VTE as patient injury content.

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