INTRODUCTION

Microparticles are intact vesicles originating from cell membrane activation processes, and from apoptosis. Their size varies from 0.2–2.0 μm. They released by various types of cells (leukocytes, endothelial cells and platelets). Similar microparticles can arise from red cells. Platelet microparticles (PMP) have procoagulant activity and involved pathophysiology of vascular disorders. ***(Piccin et al; 2007)***

Types of microparticles:

1-Platelet microparticles (PMP) were first recognized when platelet-free plasma contains a precipitable factor that could accelerate thrombin generation**.** Platelet MPs may also be generated by megakaryocytes, and are typically identified by the expression of constitutive platelet markers such as CD41, CD42b or CD61. PMPs express various antigens from the platelet surface such as glycoprotein (GP) Ia, GPIb, GPIIa, GPIIb, GPIIIa, VWF, P-selectin, thrombospondin and chemokine receptors ***(Shantsila et al; 2010).*** PMP were increased in polycythaemic patients with high platelet counts, and decreased in thrombocytopenic patients ***(Ramacciotti et al; 2009).***

2- Endothelial microparticles (EM) were derived from human umbilical vein endothelial cells (HUVECs) after stimulation by tumour necrosis factor alpha (TNFa). They were detected in healthy individuals and in patients with a prothrombotic coagulation abnormality. These endothelial microparticles expressed the same antigens as the corresponding cell surface, both in resting and activated conditions ***(Combes et al; 1999).***

3- Monocyte microparticles could be generated after stimulation of monocytes by lipopolysaccharide (LPS) ***(Satta et al; 1994).***

4- Red cell microparticles are generally smaller in size than those described for other cell types above. They are approximately 0.15 μm in diameter, and are accompanied by a smaller type of vesicle of approximately 0.06 μm, termed nanovesicles. Microparticle formation in red blood cells occurs physiologically in normal erythrocyte maturation and aging and is also marked during storage of red cells for transfusion ***(Greenwalt; 2006)***.

5- Exosomes are cup-shaped membrane vesicles originating from exocytosis of multivesicular bodies. Multivesicular bodies are endosomes formed by inward budding

of the cell membrane. Exosomes have proven to be involved in the transfer of material such as mRNA from one cell to another ***(Bucciarelli et al; 2011).***

6- Exosome-like vesicles are small irregular vesicles released from multivesicular bodies, though the pathway of exosome-like vesicle release is still not known. These small vesicles has diameters ranging from 20 nm to 50 nm, and they are often recognized by their expression of tumour necrosis factor receptor type 1 (TNFR1) ***(Chirinos et al; 2005).***

7- Apoptotic bodies are small membrane particle released from cells undergoing apoptosis. The size of apoptotic bodies can vary from 500 nm to as high as 3 μm in diameter. The function of apoptotic bodies is still not known ***(Dragovic et al; 2011).***

AIM OF THE WORK

The aim of the resent study is to focus on the role of circulating micropaticles in ICU patients, and through more light on their value in pathosphysiology of dseases and in clinical practice.

ROLE OF CIRCULATING MICROPARTICLES

1. Sepsis
2. Cerebrovascular diseases
3. Coronary artery syndrome
4. Aortic aneurysm
5. Deep vein thrombosis and pulmonary embolism
6. Coagulopathy

1-Role of microparticles in sepsis

Sepsis is a clinical syndrome characterized by a systemic inflammatory response to infection ***(Annane, et al; 2005).*** It is characterized by the activation of the coagulation system, inhibition of anticoagulant mechanisms, and fibrinolysis leading to disseminated intravascular coagulation (DIC) with microvascular thrombosis. The up-regulation of inflammatory responses and neuroendocrine systems leads to vascular hyporeactivity, and enhanced apoptosis which may contribute to multiple organ dysfunction and septic shock ***(Schouten et al; 2008).***

- **Microparticles are messengers during sepsis**

In sepsis inflammation plays a key role in the acute activation of the vascular wall and is associated with local thrombosis and changes in vasomotricity. The endothelium-derived TF initiates the coagulation process and a proteolytic cascade. The endothelial damage furthermore leads to the expression of adhesion molecules and other vasoactive factors involved in inflammation and coagulation ***(Reid and Webster, 2012).***

Microparticles act as mediators of cellular communication. They are actors and possible mediators in the interplay between thrombosis and inflammation, a process previously described for vascular injury in inflammatory diseases. They can transfer receptors, organelles, mRNA and other proteins to target cells and also comprise a secretion pathway for several cytokines, such as mature IL-1 β. The multiple properties of MPs and the variety of their possible cellular targets support them having a key role in cell reprogramming and tissue remodeling with physiological or pathological consequences. Thus, MPs could play a major role in propagating proinflamatory and procoagulant states in sepsis ***(Meziani et al; 2010).***

- **Role of microparticles in haemostasis during sepsis**

Haemostasis is activated during sepsis and septic shock, leading to thrombin and fibrin generation with dual effects: limitation of pathogen diffusion and invasion and fibrin deposition in vessels, resulting in thrombotic microangiopathy or disseminated intravascular coagulopathy. MPs are efficient

effectors in the haemostatic response and pathogenic markers of thrombotic disorders.

- **Role of microparticles in thrombin generation**

Thrombin generation requires activation of coagulation factors, which is made possible after their assembly on a catalytic surface constituted of anionic phospholipids. Cell activation is the first step by furnishing exposed phosphatidylserine with a negative charge. The required remodeling of plasma membrane, resulting in phosphatidylserine translocation to the outer leaflet of the plasma membrane, occurs in platelets, endothelial cells and monocytes at sites of vascular damage or injury. Calcium ion-mediated interactions between gamma carboxyl groups of vitamin-K-dependent factors and phosphatidylserine comprise the key step in this assembly, explaining the efficacy of anti-vitamin K treatments in hypercoagulable states ***(Lane et al; 2005).***

At the monocyte surface a possible encrypted preformed tissue factor (TF) would be de-encrypted by plasma membrane remodeling, thereby allowing the auto-activation of factor VII. Indeed, TF expression at the surface of monocyte-derived MPs

has been demonstrated during in vitro endotoxin stimulation. Although TF is the primary initiator of blood coagulation, whether there is a blood-borne TF (activity) is still debated, but there is growing evidence that this activity is directly tied to MPs ***(Key, 2010).***

Circulating MPs bearing active TF have been associated with a thrombotic status in human meningococcal sepsis ***(Nieuwland et al; 2000),*** and a primate Ebola fever model ***(Geisbert et al; 2003),*** pointing to their possible role in the dissemination of a procoagulant potential.

- **Microparticles amplify thrombin generation**

Activated platelets, and released GPIb α -FXIa bearing MPs, may be responsible for increased thrombin generation. Polymorphonuclear (PMN)-derived MPs are likely contribute to an additional amplification loop in the generation of thrombin mediated by MPs. Also MPs could contribute to such amplification loops in sepsis. ***(Pluskota et al; 2008).***

- **Role of microparticles in fibrinolysis during sepsis**

Several cellular models showed that αMβ2 exposed at the MP surface can interact with other ligands, such as urokinase plasminogen activator, plasminogen and metalloproteases MMP-2 and -5, suggesting a role in fibrinolysis and in local tissue remodelling. MPs may also display antithrombotic activities, which would be overwhelmed by procoagulant activities when MPs are released under highly thrombotic conditions, as observed during sepsis or myocardial infarction. Indeed, in purified monocyte suspensions, thrombomodulin anticoagulant activity and TF coexist at the MP surface, but when released by lipopolysaccharide treatment, the TF activity is predominant on MPs ***(Lacroix et al; 2007 and Pluskota et al; 2008).***

The presence of the anticoagulant endothelial protein C receptor (EPCR) at the surface of endothelial-derived MPs (mpEPCR) is another example of a cytoprotective element attached to MPs; EPCR is involved in the activation of anticoagulant protein C by the thrombin-thrombomodulin complex. MpEPCR, released in response to activated protein C (APC), may switch the procoagulant properties of endothelial MPs to anticoagulant and anti-apoptotic properties. On the

surface of MPs bearing mpEPCR, APC inactivates procoagulant cofactors factor Va and factor VIIIa, thereby down-regulating thrombin generation. Because a circulating soluble form of EPCR (sEPCR) has been described in sepsis, and its concentration possibly correlates with the severity of the illness, the respective contributions of mpEPCR and sEPCR is a matter of clinical importane. sEPCR binds protein C and APC, thereby blunting their actions. The efficacy of therapeutic activated protein C (rhAPC; drotrecogin alfa (activated)) may depend on the balance between circulating sEPCR and mpEPCR ***(Meziani et al; 2010).***

Experiments on human endothelial cell reported that free rhAPC and rhAPC bound to mpEPCR have similar effects. rhAPC cleaves protease activated receptor-1 and induces significant changes in the activation/inhibition of genes with direct anti-apoptotic effects or indirect cell barrier protective effects, the latter requiring transactivation of KDR (vascular endothelial growth factor receptor 2/kinase insert domain receptor) via the phosphoinositide 3-kinase-Akt pathway and S1P1 (sphingosine 1-phosphate receptor). In sepsis, procoagulant

MPs of endothelial, platelet, erythroid, and leukocyte origins have been reported ***(Perez-Casal et al; 2009).***

- **Microparticles have a proinflammatory effect in sepsis**

Microparticles have procoagulant activity with thrombin generation in vivo via a tissue factor/ factor VIIa-dependent mechanism, and enhanced coagulation by microparticles was seen in patients with fulminant DIC. Endotoxin stimulation in healthy subjects was also associated with an increase in tissue factor procoagulant activity in circulating monocytes. Taken together, tissue factor and phosphatidylserine exposure to microparticles may play an important role in the pathogenesis of DIC in sepsis ***(Meziani et al; 2010).***

Changes in the cellular populations of microparticles seem to reflect the degree of cellular activation and apoptosis in sepsis. The production of leucocyte-derived microparticles is significantly increased and associated with increased oxidative

activity. Paradoxically, circulating levels of monocyte-derived microparticles are reduced in sepsis compared with controls and may reflect monocyte deactivation and dysfunction in severe sepsis. In patients with sepsis, activated leucocytes enhance the production of leucocyte-derived microparticles with increased expression of adhesion molecules. Further, interaction between activated leucocytes and endothelium derived microparticles through adhesion molecules is enhanced in patients with systemic inflammatory response syndrome and these microaggregates increase oxidative activity. Microparticles may therefore serve as important bioeffectors of inflammation and thrombosis in sepsis and contribute to tissue injury and organ *dysfunction* ***(Reid and Webster, 2012)****.*

Circulating MPs provoke vascular inflammation during sepsis via lysophosphatidic acid and facilitate chemotactic migration of platelets and/or leukocytes to the endothelium, thus playing the role of trigger in the production of monocyte cytokines (IL-1β, IL-8 and tumour necrosis factor-α) ***(Reid and Webster, 2012).***

- **Microparticles modulate endothelial function**

During sepsis, the endothelial function is altered and the endothelial surface becomes proadhesive, procoagulant and antifibrinolytic. Arachidonic acid exposed by platelet MPs promotes the up-regulation of cyclooxygenase-2 (COX-2) and intercellular adhesion molecules in endothelial cells. Platelet-derived MPs have been shown to modulate interactions between monocytes and endothelial cells. Released proinflammatory endothelial cytokines may themselves also contribute to the production of MPs, thereby amplifying the inflammatory response and the consecutive alteration of the vascular function. Platelet activating factor present in endothelial cells and leukocytes is also involved in the proinflammatory effect of MPs ***(Meziani et al; 2010).***

- **Endothelial microparticles and inflammatory status**

Circulating MPs of endothelial origin may thus vary with respect to quantity and phenotype according to the endothelial response and have been reported in inflammatory diseases and disorders; the endothelial response to inflammation stimuli may be immediate, delayed or reflect a chronic endothelial activation.

They were reported to participate in the regulation of arterial tone in several diseases in which oxidative stress is involved, such as human acute coronary syndromes or preeclampsia associated with altered NO bioavailability ***(Meziani et al; 2010).***

Sepsis induces a phenotypic change of the endothelium and the endothelial surface becomes proinflammatory, expresses cell adhesion molecules (intercellular cell adhesion molecule 1, vascular cell adhesion molecule 1) and becomes prothrombotic through the increased expression of membrane TF and the inhibition of thrombomodulin and EPCR synthesis. In parallel, endothelial cells become capable of recruiting and activating platelets ***(Reid and Webster, 2012).***

- **Role of microparticles in spreading of inflammatory and prothrombotic vascular status**

MPs may be considered as both the cause and the consequence of inflammatory diseases through multiple amplification and regulatory loops affecting vascular cell functions. *In vitro* incubation of leukocyte-derived MPs with endothelial cells secrete inflammatory IL-6 and produce TF. Furthermore, platelet MPs are able to deliver regulated upon