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CONTRIBUTIONS TO THE ANTHROPOLOGY OF FLUIDO-COAGULANT BALANCE

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Abstract
Blood fluidity is controlled by complex physiological systems. Normally, the fine balance between coagulation and fibrinolysis prevents both bleeding and thrombosis. The accelerated urbanization we are living last decades modifies the basic environment, confining the human being to biochemical and metabolic remodeling. The alteration of this balance in favour of coagulation leads to thrombosis, the major challenge of the 21st century medicine. There are interesting changes not only in human's anthropological evolution, but also from birth to death. The HORUS study performed by american and egyptian researchers investigated the prevalence of atherosclerosis in antique and modern Egyptians. Despite the belief that atherosclerosis is a modern disease, it seems to be evidences of atherosclerosis in Egyptian mummies. Despite multiple differences, between 30 and 60 years, the prevalence of atherosclerosis was quite similar in antique and modern Egyptians, respectively.

Keywords: anthropology, fluido-coagulant balance, Egyptians.

1. INTRODUCTION

The physiological systems controlling blood fluidity are complex and elegant. Blood must remain fluid inside the vascular tree, but coagulates quickly when exposed to subendothelial surfaces with vascular lesions. Once intravascular thrombi formed, the fluidity is quickly restored by immediate activation of fibrinolytic system. In normal conditions, the fine balance between coagulation and fibrinolysis prevents both bleeding and thrombosis.

The human body fluido-coagulant system is very well adapted for bleeding resolution, so frequent in older times at hunting or war settings.

In contrast, the modern humans are at risk for thromboembolic diseases (e. g. acute myocardial infarction occurring in coronary arteries, or other infarctions occurring in various other vascular territories, like cerebral, mesenteric, renal, pulmonary, peripheral limbs, etc.), rather than hemorrhagic diseases (especially with the hope that traffic accidents will be abolished by smart cars). The human fluido-coagulant system is also adapted for these settings, by thrombomodulin and endogenous t-PA. This paper consists in phrases and paraphrases on HORUS Study.

2. MATERIALS AND METHODS

The HORUS study performed by american and egyptian researchers investigated the prevalence of atherosclerosis in antique and modern Egyptians. Despite the belief that atherosclerosis is a modern disease, it seems to be evidences of atherosclerosis in Egyptian mummies.

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Methodologically, the authors compared the presence and extension of vascular calcifications by PET/CT scan of whole body in 178 modern Egyptians for cancer stadialization, and CT scans in 76 mummies (3100 î. H. – 364 d. H.), respectively.
In this setting there is an underlying pathophysiologic continuum from coagulation balance to thrombosis determinants in coronary arteries atherosclerotic plaques.
The scientific discoveries in coagulation field started with Hyppokrates, Aristoteles, Celsus and Galenus knew that fresh blood coagulates in a couple of minutes. They have been described exhaustively several types of bleeding, internal and external. However, they did not associate blood coagulation with haemostasis.

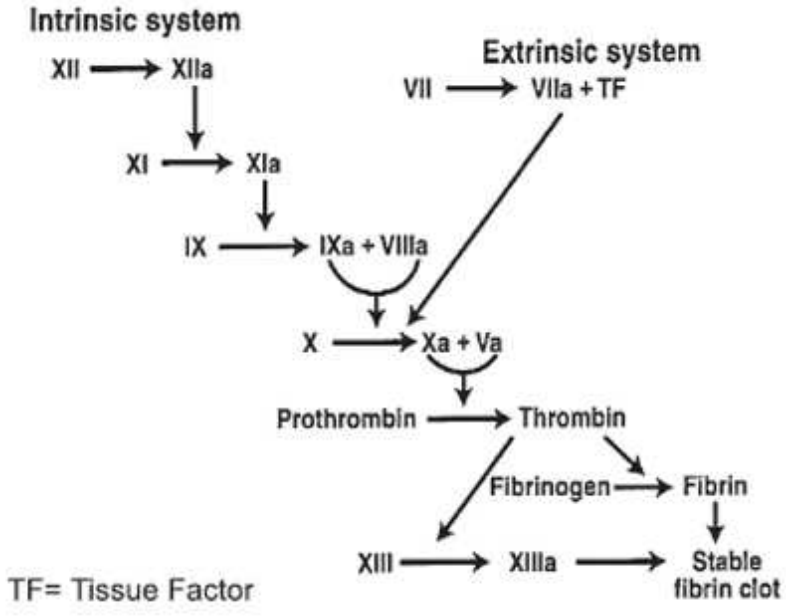

Figure 1. Coagulation waterfall

Two millenniums passed away till surgeon Jean-Louis Petit from Paris reported that haemostasis after a limb amputation was the result of clots formed inside blood vessels. In the meantime (1619), William Harvey discovered the blood circulation, and Anthony van Leeuwenhoek the microscope. In 19th century, Rudolf Virchow clearly described thrombi inside inferior limbs veins, and their trend to embolize. In short time platelets were also discovered.
A bit more than a century ago, Paul Morawitz convincingly assembled into a scheme the four known coagulation factors: in presence of calcium and thromboplastin, protrombin is converted into thrombin. In turn, thrombin converts fibrinogen into fibrin clot. Then, roman numbers were allocated to coagulation factors, from I to XIII.
Armand Quick is known by protrombin time. Once anticoagulant agents developed, other parameters became available in order to adjust drug dosages.
The intrinsic and extrinsic systems converge by activating factor X which, together with activated factor V, catalyses the transformation of prothrombin in thrombin which, in turn, catalyses the transformation of fibrinogen in fibrin. Finally, activated factor XIII intervenes in clot stabilization (figure 1).
The coagulation system coordinates with platelets in generating the fibrino-platelet thrombus. The vascular injury simultaneously triggers the activation and aggregation of platelets setting the

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coagulation system. The platelet activation is initiated by subendothelial collagen and von Willebrandt factor (vWF) exposure, upon thrombin platelets adhere. The adherent platelets become activated and deliver ADP and thromboxane A_2, platelet agonists which activate ambiental platelets and recruit them at lesional level. Starting with platelet activation, glycoprotein IIb/IIIa undergoes a conformational surface change which allows fibrinogen binding and platelet aggregation mediation. The coagulation is triggered by the tissue factor exposed at injury site, which triggers, in turn, thrombin generation. As a potent platelet agonist, thrombin amplifies platelet recruitment at injury site. Also, thrombin converts fibrinogen into fibrin, which models platelet aggregates into fibrino-platelet thrombus.

Figure 2 illustrates a "two-state" model of atherotrombosis. The high risk atheroma has a thin fibrous cap over a large lipid nucleus containing tissue macrophages. When fibrous cap fractures, coagulation proteins from blood fluid phase arrive at macrophages associated to tissue factor and microparticles derived from apoptotic cells from solid part of plaque. These events trigger thrombus formation on ruptured plaque.

Among the multiple factors in figure 2, we mention thrombomodulin and t-PA. Thrombomodulin is the natural anticoagulant of human body. Despite the remarkable progresses in thrombopharmacology, thrombomodulin seems to remain still an untangible standard. Japanese researchers investigate the possibility to use monkey or rabitt thrombomodulin to human subjects. On the other side, endogenous t-PA, fibrinolytic delivered by the vascular endothelium in blood torrent during aerobic physical activity, was synthetised in a recombinant form; rt-PA is used in the clinical arena in acute myocardial infarction. In our clinic of cardiology, there is an experience of over 12 years with rt-PA in ST segment elevation myocardial infarction (STEMI).

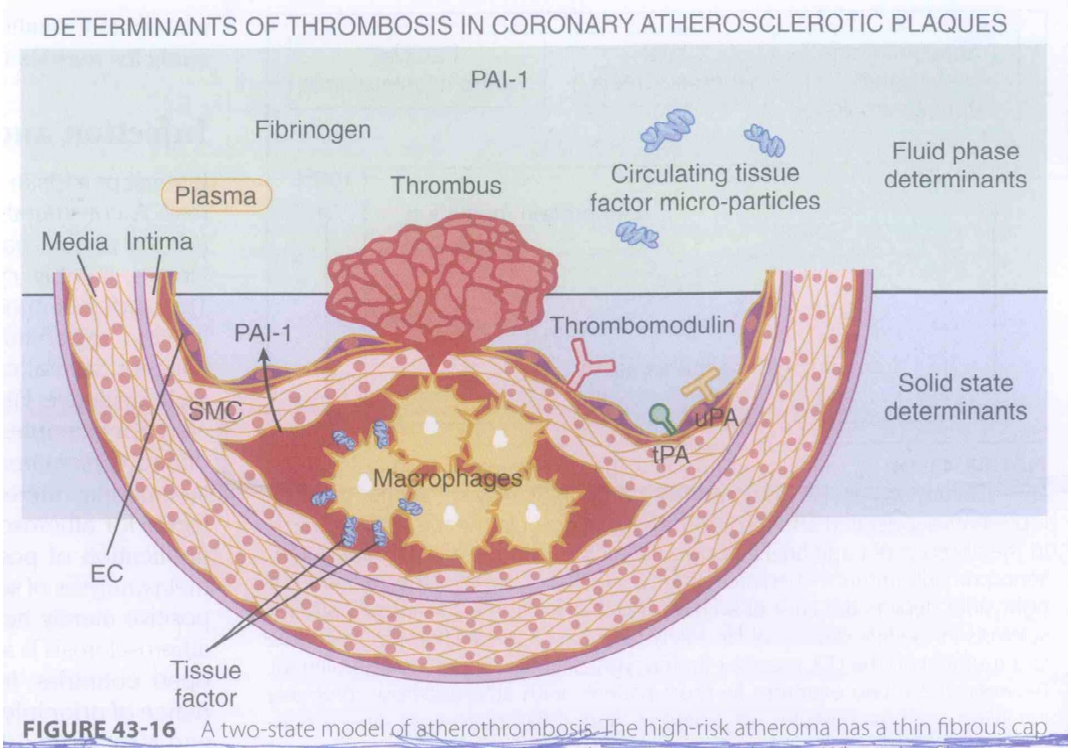

Figure 2. Thrombosis determinants in coronary atherosclerotic plaques (Libby, 2005)

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3. RESULTS AND DISCUSSION

Mean ages in HORUS were 52,3 years in actual Egyptians, and 36,5 years in antique Egyptians, respectively. Here we need to make some demographic considerations:

- during the first period of life, in antique Egyptians occurred considerably more deaths than in modern Egyptians, because childhood diseases, infections and trauma
- die oldest mummy has 60 years old, while in modern Egyptians there are survivors till the age of 84 years old.

Thus, between 30 and 60 years, the prevalence of atherosclerosis was quite similar in antique and modern Egyptians, respectively (figure 3).

The results are interesting. However, we have to take into consideration some statistical limits (number of patients, age groups repartition, etc.). Pharaohs were the elite of antique society, modern patients are mainly low-income. Probably the levels of physical activity are different into the two groups. The reactivity of atheroma plaques and their ability to generate patent vascular diseases is hard to get compared between the two populational groups.

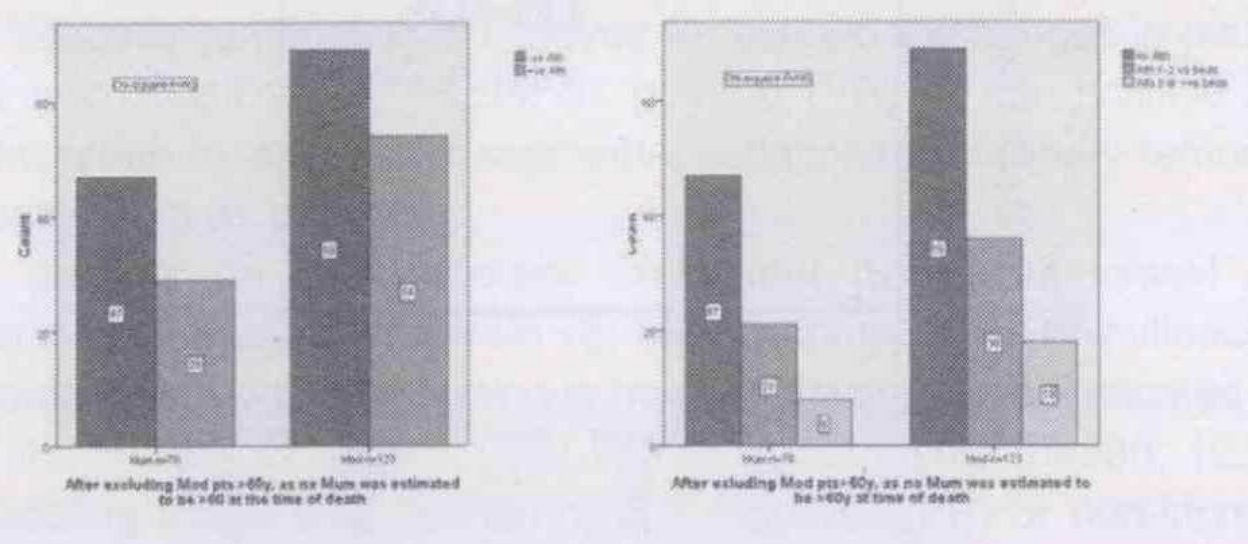

Figure 3. Results

The anthropological evolution of human body modulates the fluido-coagulant balance. During his long evolution, the human being became more and more sedentary. (figure 4). As a consequence, blood fluid tends to become more viscous and, subsequently, the risk of cardiovascular disease raises.

The chronological evolution of the human being tends to repeat the anthropological evolution into a miniatural temporal scale. Thus, children are, as a rule, more physically active than adults and, subsequently, more exposed to bleeding. Under the burden of cardiovascular risk factors, the vulnerability at thrombosis displays in younger ages.

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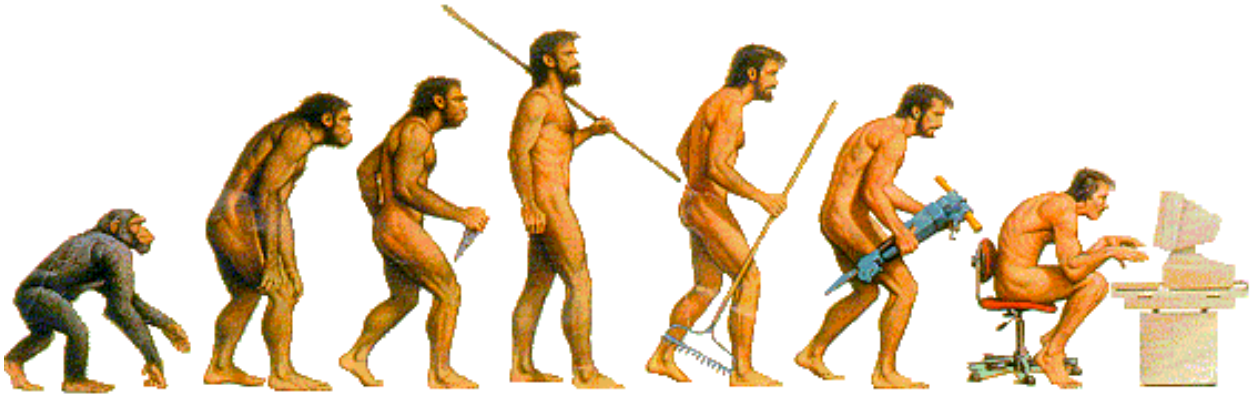

Figure 4. Evolution of Man

More than a half century ago, during Korea and Vietnam wars, anatomopathologist researchers observed atheroma plaques in american soldiers coronary arteries. Taking into account that sedentarism appears at younger ages, it is presumable that atherothrombosis will appear earlier in lifespan.

Table 1

	Acute Myocardial Infarction	Acute Ischaemic Stroke
Similarities		
Pathophysiology	Arterial occlusion + ischaemic necrosis in nearly all cases	Arterial occlusion + ischaemic necrosis in nearly all cases
Clinical picture	Acute onset	Acute onset
Prognosis	High mortality (if untreated by reperfusion)	High mortality and permanent disability
Effective treatment	Reperfusion therapy	Reperfusion therapy
Differences		
Aetiology	Uniform plaque rupture + thrombosis in situ in 90-95%	Multifactorial: cardioembolic, arterioembolic, thrombosis in situ, lacunar, cryptogenic
Arterial occlusive thrombus feasible for catheter-based intervention	Found in 90-95% of acute coronary angiograms	Found only in ≈ 40-50% of acute CT-angiograms
Time window symptom onset – intervention start (to offer benefit and not harm)	24 h (48 h in some patients)	3 h (8 h in some patients)
Reperfusion damage	Only theoretically, clinically is reperfusion beneficial	Reperfusion damage (parenchymal bleeding) is a real clinical problem
Clinical picture	Pain (dyspnoea) alerts most patients to call early for help	Neurological dysfunction and absence of pain frequently results in late medical contact
Diagnostic method before reperfusion therapy indication	ECG (fast, simple, cheap, at the site of first medical contact)	CT (takes more time, expensive, in-hospital)
Diagnostic biomarker	Troponin (although not needed for the initial decision in ST-elevation myocardial infarction)	Not yet available
Contraindications for catheter-based therapy	None	Intracranial bleeding or advanced ischaemia on CT
Percentage of hospitalized patients who undergo reperfusion therapy in well-functioning health-care systems	>90%	<10%

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Which is better tolerated: bleeding or thrombosis? In contemporary medical practice, severe patient survival could depend upon a choice between hemorrhage or thrombosis treatment, between Scylla and Charybdis. Of course that, on-site, every doctor takes the appropriate decision, having at disposal a therapeutical armamentarium to modulate fluido-coagulant balance into one direction or another. Interestingly, the "therapeutical bleeding" was used to treat acute pulmonary oedema.
Acute myocardial infarction and ischemic stroke have in common many similarities, but also differences which modulate antithrombotic drug administration using measurable parameters like INR (table 1).
Atrial fibrillation confers a higher thrombotic risk, especially in patients that already underwent a myocardial infarction. The therapeutic strategies in these cases include the new oral factor-specific anticoagulants, eventually associated with antiplatelet agents. The trials RE-LY with dabigatran, ROCKET-AF with rivaroxaban, AVERROES and ARISTOTLE with apixaban provide evidences for the use of new oral anticoagulants to this complex segment of patients.

4. CONCLUSIONS

The complex physiological systems that control blood fluidity are governed by the laws of time (inexorable) and change (continuous).
In normal settings, the fine balance between coagulation and fibrinolysis prevents both bleeding and thrombosis. The accelerated urbanization of the last decades modifies the original environment, leading to biochemical and metabolic remodeling of humans. The alteration of this balance in favour of coagulation leads to thrombosis, the major challenge of the 21st century medicine. There are interesting changes not only from anthropological perspective, but also from birth to death. A third evolutive line is the history of scientific discoveries in atherothrombotic field.
In modern world the risks for vascular dramas, like myocardial, brain or lung infarctions are higher than the risk for bleeding. To reduce the aferent risks, the mass administration of some antithrombotic is performed as follows:

- oral anticoagulant in atrial fibrillation
- antiplatelet in ischaemic heart disease

As the human body seems to be unable to reset the fluido-coagulant system, medicine acts. The primary and/or secondary prevention of devastating cardiovascular diseases is performed pharmacologically, administering antithrombotic drugs to high risk population in mass and routinely. The development of these drugs is impressive.

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