Quantum Biophysical Semeiotic Microcirculatory Theory of Arteriosclerosis

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Abstract.

For the first time the Authors describe Quantum Biophysical Semeiotic Microcirculatory Theory of Arteriosclerosis, based on Congenital Acidosic Enzyme-Metabolic Histangiopathy-Dependent Arteriosclerotic Constitution. Allegra's Syndrome plays a central role in both bedside diagnosis and pathogenesis of the predisposition to ATS, highlighting the underlying micro-vascular patho-physiological mechanisms. The original and remarkable insights, physicians are given by this new theory of ATS into its complex pathogenesis, allow to understand the real nature of CVD, and to perform its Pre-Primary and Primary Prevention on large scale in individuals rationally enrolled.

Introduction.

In 2005, one of us has suggested a new theory of atherogenesis based on original data of a long clinical biophysical semeiotic research (1). This theory, recently up-dated with the data regarding inherited real risk of CVD, proved to be really useful in subsequent researches, proving to be efficient in the Primary Prevention of ATS (2-18).
A large number of Authors have emphasised earlier the important role played by *vasa vasorum* in atherogenesis. However, the difficulties of investigating these vascular microvessels kept them from convincing the physicians about the real value of such a theory. In addition, sophisticated semeiotics, as minimal 3 D. computerized tomography, that cannot be utilized on large scale and in therapeutic monitoring, cannot allow physicians to assess *in vivo* deeply structure and function of arteriolar-venular anastomoses (AVA), including Endoarteriolar Blocking Devices both physiological and newborn-pathological, discovered by one of us (3, 7, 10, 11, 18-20).

The *vasa vasorum* are necessary to maintain normal vessel wall homeostasis. As a matter of facts, inadequate perfusion of the related vessel wall, as deficiencies of these vasa, has been shown to lead to intimal hyperplasia (21).
The initial hypothesis relating atherosclerosis to increased development of the vasa vasorum was made by Barger et al. in 1984 (22). Since then, it has been shown that coronary vasa neovascularization takes place early after induction of experimental hypercholesterolemia, suggesting a role for neovascularization in atherogenesis (23). This neovascularization has been shown to favor second order vasa (24).
Apolipoprotein E-deficient mice given the angiogenic factor vascular endothelial growth factor (VEGF), which leads to increased angiogenesis, show a subsequent increase in plaque area while mice administered the anti-angiogenic factors endostatin and TNP-470 show decreased intimal hyperplasia.

A decrease in intimal hyperplasia was also observed in a murine study following chronic endothelin receptor antagonism, which decreases VEGF expression and decreases vasa neovascularization.
These studies provide evidence that neovascularisation of the arterial wall (i.e., impairment of vasa vasorum!) is a crucial part of the atherosclerotic process.
Abnormalities of the vasa vasorum have also been implicated in the development of neointimal hyperplasia after balloon angioplasty and stenting. In two animal models, local injury to the vascular wall stimulated intimal hyperplasia and adventitial neovascularisation, that was increased by VEGF and PR39 and tempered by the inhibition of VEGF and fibroblast growth factor, leading Khurana et al. to hypothesize recently that intimal hyperplasia has both angiogenesis-dependent and -independent phases (25).

Indeed, it has previously been shown that following angioplasty injury, the number and the density of adventitial microvessels increase in the initial three post-procedural days, then regress.
Kwon et al. evaluated the spatial pattern of neovascularisation, showing that although number and diameter of the vasa, increased after injury, the total vascular area was lower in injured vessels than in control vessels (26)
Deployment of an intravascular stent leads to arterial wall compression and increased resistance within the vasa vasorum, resulting in vascular wall ischemia and subsequent neo-intimal proliferation (27). Vasa vasorum provided with newborn-pathological, type I, subtype b), aspecific EBD bring about type II and III dissociated microcirculatory activation of vasa vasorum and thus wall ischemia, and subsequent neo-intimal proliferation (28), we shall explain later on.

Proliferation studies have shown that a tyrosine kynase inhibitor inhibited both neovascularisation and neo-intimal proliferation after coronary stenting, and that the neo-intimal proliferation was proportional to the number of adventitial microvessels present (29).

With the established importance of the coronary vasa vasorum on neo-intimal proliferation in atherosclerosis, angioplasty injury, and arterial stenting, accurate quantification of vasa vasora number and volume (from QBS point of view, O2, pH, and so on!) is a fruitful area of research.
The traditional method of vasa vasorum quantification uses histology, but this approach requires staining for vasa vasora endothelial cells and suffers from difficulties such as cutting through metallic stents, inaccuracies due to unperfused vasa, and incorrect data due to a limited number of measured cross-sections.
An *in vivo* human method is not plausible, as the coronary microcirculation begins at the level of arterioles of 50μm in diameter and progressively branches into capillaries, 5μm in diameter; these blood vessels are too small to visualize using currently available methods. Three-dimensional microscopic computed tomography (micro-CT) has emerged as an accurate and accessible method (30).

Brief History of Atherosclerosis Theories

Aristotle, IV sec. a. Ch., 384-322, observed “bone in the heart”. In the 1500 two Italian physician Antonio BENIVIENI and Gabriele FALLOPPIO described artery wall heartening. In the 1600 Lorenzo BELLINI noticed in a 90 year-old woman artery calcification, nowadays termed Moenckberg’s mediocalcinosis.
At the beginning of 1700, Herman BOERHAAVE (1668-1738) noticed artery calcification, too, but in a genius manner have suggested for the first time the patho-physiology of ATS: *Vasa Vasorum* are not able to provide sufficient amount of blood to artery wall, using rudimental microscope in investigating conjunctiva microcirculation !
In the 1800 Morgagni emphasised that ATS is not dependent from the age!

In the year 1883 Johan Friedrich LOBSTEIN termed the artery wall heartening as "Arteriosclerosis", whereas in 1904 Felix Jacob MARCHAND spoke of "Atherosclerosis".

Regarding ATS pathogenesis, according to all pathogenetic theories of atherogenesis, endothels, poly- mono-nucleated leucocytes (monocytes and T lymphocytes), smooth muscle cells, and platelets play a central role. In addition, a fundamental role is played by lipid and protein infiltration of arterial wall, as well as by mechanic action of blood-flow on such a wall, i.e., *shear-stress* and *shear rate*.

Such a unified theory of ATS is the end of an awful number of pathogenetic theories, that emphasises - from time to time - one of these multiple pathogenetic factors, beginning with Virchow's (1856), Anitchkov's and Chalatov's (1913) theories. It is impossible to overrate Virchow's inflammation theory of artherosclerosis and his great contribution to the concept of artery insudation and thrombosis process. But even Virchow did not expressly stress the concept of atherosclerosis as an autonomic non-inflammatory entity; he called the condition chronic "endoarteritis deformans" (31).

The most recent theories, for instance the well-known "*To insult response theory*" (Ross e Glomset, 1973 e 1986), and "*To retention response theory*" (K. J. Williams e I. Tabas 1995), according which the initial phenomenon is represented by endothelial lesion, structural and respectively functional, rather than LDL depot in arterial wall, cannot explain neither the real nature of ATS beginning, nor the extremely location of initial endothelial lesion.

In fact, contrary to the first hypothesis, "To insult response theory" was based on (Ross e Glomset,1973), Authors agree nowadays with ATS beginning brought about by functional endothelial lesion, rather than focal endothel loss, with intimal cell deprivation, and subsequent platelet adhesion.

Really, the early event in atherogenesis is considered now the functional impairment, dysfunction of endothels, caused by an awful number of pathogen agents, despite the difficult understanding of local lesion, explained exclusively by insights provided by Quantum Biophysical Semeiotic Theory of Arteriosclerosis, later illustrated.

Accordingly, functional endothelial impairment brings about over production of VCAM1 and ICAM1, i.e., adhesion molecules of cell surface, as well as increased secretion of biologically active substances (cythochines, growth factors, free radicals, a.s.o.), which causes leucocyte adhesion to endothels and derangement of endothelial hemostatic balance, capillary permeability of plasma proteins and lipids, and vassal tone control (32-34).

QBS Evaluation of Arterial Abnormalities in Offspring of Patients involved by CVD, even premature.

Among the various and important risk factors for cardio-vascular events we have to consider the frequency of coronary heart disease in family history (35, 36).

Regarding our microcirculatory theory of ATS, these relations, one of us has observed "clinically" by means of Biophysical Semeiotics, are of paramount importance, since they represent a relevant introduction to both the explanation of our theory on arteriosclerosis and its understanding (1).

The numerous theories on arteriosclerosis pathogenesis clearly demonstrate present short knowledge of this really important topic, in spite of the progresses of sophisticated semeiotics, including image semeiotics. Recently, authors agree generally on the "initial" lesion of endothelial cells, whose action mechanisms we will discuss later on.

With regard to the role played by endothelial cells under physiological and pathological situations, as reader can see in our large Bibliography in www.sisbq.org and www.semeioticabiofisica.it, over a large number of years we have tried hardly, from the clinical point of view, to attract the attention of colleagues on the primary role played by *endothelial cells*, showing mitochondrial impairment, for the first time examined at the bed-side by quantum biophysical semeiotic method (32, 37-39).

At this moment we remember three important risk factors, which play a primary role in atherogenesis: tobacco smoking, dyslipidaemia and arterial hypertension. However, these factors not in all cases can provoke atherogenesis. Moreover, when present, the artheriopathy shows a different seriousness in relation to the genetic factor surely present, e.g., CAD Inherited Real Risk, which represents the *condition sine qua non of* heart coronary disease (32, 37-39).

Interestingly, ischemia risk, as ECG shows, is about 40% higher and death risk due to cardiac cause is 2,5-7 % greater in individuals with family history "positive" for *premature* coronary heart disease in comparison to people without such family history (40).

Among the present numerous papers about this topic, we remember that arteriosclerotic lesions have been observed by autopsy in coronary arteries of very young individuals with family history positive for coronary artery disease (41).

Over the last decades, B-mode ultrasonography at high resolution proved to be a reliable and valid method in recognizing initial arteriosclerotic abnormalities in arterial walls (41). Intimal and media thickening of the carotid artery has been observed in individuals with risk factors for cardiovascular disorders, proving to be a remarkable sign of the presence of coronary arteriosclerosis as well as of its complications.

The reader, skill in the original diagnostic method, knows certainly that Quantum Biophysical Semeiotics allows to recognize, at the bed-side, these macrovascular lesions directly (artery-gastric aspecific and -caecal reflex; pathological *preconditioning*), as well as indirectly with the aid of analysing local *vasa-vasorum* (= at birth, activation type II, dissociated), we will describe in following, illustrating QBS arteriosclerotic constitution.

With the aid of ultrasonography doctor can evaluate finally, with non-invasive method, endothelial function by observing diameters modifications of brachial artery, brought about by insufflation and deflation of elastic arm-band (43). Finally, we remember that the brachial artery reactivity, e.g. to blood-flow, is abnormal in individuals with overt arteriosclerosis and in asymptomatic subjects with coronary risk factors (44).

It is now a lot of years that, in a clinical research, we have demonstrated the reduced reactivity of brachial artery in arteriosclerotic patients and their offspring (45).

As far as the application of QBS easiest method is concerned, doctor must assess "in toto" ureteral reflex intensity (= ureter dilation, Fig.1) caused by intense (non occlusive) digital pressure on the brachial artery (or on whatever other artery, of course), evaluating precisely the intensity in

cm. Contemporaneously, appears artery-gastric aspecific reflex, more easily detected than the ureteral one, when the knowledge of the method is not yet steady.

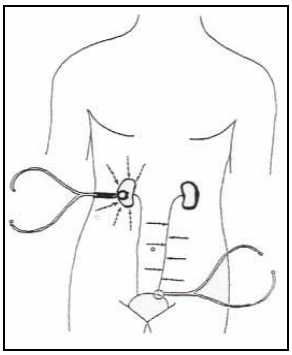

Fig.1

Figure shows the location of the bell-piece of stethoscope and lines on which digital percussion has to be applyed, gently and directly, in order to outline skin projection area of kidneys and ureters

Thereafter, the subject to be examined is invited to perform Valsalva's manoeuvre (increase of acethyl-choline) for about 10 sec.; then, doctor assesses the value of same parameter for a second time. In healthy, the intensity of both "in toto" ureteral reflex and gastric aspecific reflex doubles or augments significantly.

Clinical evidence shows that the severity of arteriosclerosis and decreased intensity of "in toto" ureteral and gastric aspecific reflex during Valsalva's manoeuvre are inversely related.

A further easy evaluation of this event is the comparison of basal parameters values of the same reflexes and those observed during "*boxer's test*", which brings about vessels dilation, due to increase of the peripheral arterial resistance, increasing contemporaneously both vasomotility and vasomotion of related *vasa vasorum*, quantified by QBS, as well known to skilled reader: the intensity of artery-"in toto" ureteral reflex appears practically doubled, in healthy, and latency time of artery-caecal reflex clearly extended (= temporaneously decreased tissue acidosis, due to Valsalva's manoeuvre).

In fact, showing coherence, latency time of both caecal and gastric aspecific reflex at basal line results, in healthy, the half of that observed after acethyl-choline secretion due to Valsalva's manoeuvre and, in second experiment, after physiological endothelial secretion of radical NO.

In healthy, identical results are observed by the *test of acute pick of insulin secretion* (See in the site: Diabetes mellitus), applied after assessing the various basal parameters values (46, 47).

On the contrary, all these data, collected by dynamic tests, are abnormally modified in individuals, even in the two first life decades, at "inherited real" risk of arteriosclerosis, as we demonstrated in previous papers (3, 44-51).

These facts, observed in a long, well established experience, on which all doctors must agree, corroborate our microangiological theory of arteriosclerosis, because they show clearly the very early *functional-structural* disorder of macrovascular wall, however, preceded, as we shall illustrate later in details, by Endoarterial Blocking Devices (EBD) abnormalities of related microvessels, *which has to be considered, in our opinion, the first and essential alteration* (6).

As a matter of fact, it has been notoriously demonstrated that family history of coronary artery disease represents an independent risk factor for cardiovascular pathology, showing clearly heritable component, we recognized as CAEMH. This anamnestic datum has been included in prevention guide-lines of CAD, and, at the moment, is used in paediatric cardiology as important indication in the screening of lipids blood concentrations, beside genetic assessment of mutations of

genes, which codify lipoproteins receptors, that is obviously an a wearisome and dispensive research, certainly not suitable for a large scale prevention.

Since we do not know, at the moment, when originate precisely the first vascular abnormalities (and those of related *parenchyma*), it appears to be an important and essential event the use of a "clinical" tool, reliable in detecting the presence as well as in quantifying the severity of such arterial structural abnormalities.

Our researches corroborate, from the "clinical" point of view, those of other authors, performed with sophisticated methods, because they indicate, as markers of early arteriosclerosis, the association between decreased reactivity of brachial artery and intimal-media thickening of carotid artery, present in young people with family history positive for *premature* myocardial infarct. This association is interesting, because the abnormal vasodilatory response to achethyl-choline (Valsalva's Manoeuvre) and endogenous insulin can be easily evaluated at the bed-side, as above referred, in individuals earlier involved by microvascular dysfunctions, including *"in primis"* Arterious-Venous Anastomoses (AVA), functionally speaking, i.e. including EBD (6, 44-51).

In other words, the very first arteriosclerotic arterial abnormalities are "pre-clinical", the so called *pre-clinical lesions,* and precede by decades the *fatty-streaks*.

For the first time, nowadays, by means of the original semeiotics doctor is able to recognize clinically these modifications, almost functional, even by the bed-side evaluation of analogous abnormalities of haemoderivative structures, including EBD, and the reduced arterial vasodilation, brought about by different manner, always associated to intimal-media thickening, based on endothelial insufficiency, which plays a primary role, in our opinion, in the most important alterations of *vasa vasorum*, CAEM-α dependent.

At this point, it is necessary to remember that arteriosclerosis is notoriously a systemic, degenerative-inflammatory process, which involves circulatory tree and, interestingly, is associated, sooner or later, to other disorders. Consequently, functional and structural abnormalities, observed *in loco,* are present also in other districts in young individuals without clinical symptomatology. Moreover, the association abnormal vascular reactivity-intimal-media thickening, noticed by a large number of authors, starting from the old ages, has been corroborated by us, for the first time with the aid of a stethoscope.

Such statement is valid also for hypertensive and/or diabetic patients and individuals with suspected CAD (56, 57).

These noteworthy facts, about which a large number of authors agree, are referred and discussed extensively, since they provide further evidences in support of *qbs microcirculatory theory of arteriosclerosis*: endothelial impairment, caused by CAEMH and worsened by a lot of environmental risk factors, only partially known, bringing about lowering synthesis of radical NO, increased secretion of vasoconstrictors substances, and endothelial-dependent haemostatic unbalance, can predispose these individuals to monocytes and platelets adhesion, medial smooth muscle cells proliferation and subsequently their migration to the intimae, monocytes-derived macrophages as well as lipoproteins storage in the arterial wall (foam cells).

Certainly, a large variety of other factors, as inflammation, intervene, in our opinion, only in a subsequent stage, in arteriosclerosis pathogenesis, but *genetic factor*, bedside recognized easily, as we shall describe later on, is really dominant, primary and necessary to explain completely the diverse phases of arteriosclerosis natural history, enlightening what accounts for the reason of well localised *minimal lesion.*

To conclude, apart from practical aspects, as early *clinical* recognizing initial functional and, thus, structural, abnormalities of arterial wall, in asymptomatic subjects, unavoidable in defining **qbs arteriosclerotic constitution,** previous discussion about the relation between abnormal reactivity of arterial wall and intimal-media thickening introduces the illustration of our "intuition" on the existence of a singular, characteristic constitution, arteriosclerosis is based on, which allows

to give satisfactory answers, lacking until now, and unavoidable to *primary prevention*, hopefully efficacious when applied on very large scale, Quantum Biophysical Semeiotic Microcirculatory Theory of Arteriosclerosis is based on.

QBS Arteriosclerotic Constitution.

Clinical evidence suggests the existence of **arteriosclerotic constitution**: acute myocardial infarction can involves an individual without significant environmental risk factors, among those we know today, but in presence of CAEMH-positive (*as indicates the personal case of one of us*); not "all" dyslipidaemic and/or diabetic and/or hypertensive, a.s.o., patients die from ictus, myocardial infarction, or other arteriosclerotic complications; not "all" hypertensive patients die for generalized or localized arteriosclerosis (CAD).
On the contrary, there are acknowledged cases of dead due to arteriosclerotic complications over the first two decades of life, without well-known environmental risk factors (1, 3, 4)

Thus, **arteriosclerotic constitution** exists as the diabetic, osteoporotic, rheumatic, arthrosic, hypertensive, glaucomatous, oncological, dyslipidaemic, a.s.o., constitutions. In the same individual can be associated diverse constitutions, originated on the common inherited base, i.e. CAEMH.

In following, easy methods necessary reliable in bedside recognizing, in a "quantitative" manner, starting from the first life decades, CVD inherited real risk by **Quantum Biophysical Semeiotics,** are described. Surely, a thoroughly examination need a steady knowledge of this original diagnostic method.

1) The mean-intense, but not occlusive, digital pressure, applied upon an artery (e.g. brachial, radial, phemoral, carotid artery) of an healthy subject, lying down psycho-physically relaxed in supine position, provokes the gastric aspecific reflex (Fig. 2) after a latency time (lt.) of 10 sec. exactly. In addition, after the *preconditioning* (doctor performs for the second time this evaluation after an interval of exact 5 sec.) lt. increases to 20 sec.: doubled value

Interestingly, in health, the "intense" digital pressure upon an artery does not cause *simultaneously* the gastric aspecific reflex, which appears after 16 sec., as in case of Caotino's Sign (32)

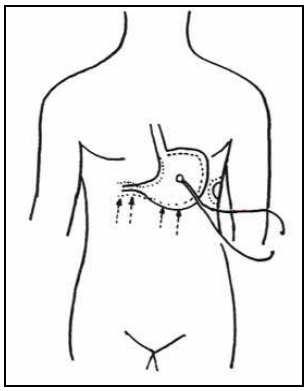

Fig.2

The figure indicates the correct location of the bell-piece of stethoscope and lines on which digital percussion, directly and gently, must be applied, in order to outline skin projection area of great gastric curvature: in practice, it is enough to recognize a small tract of gastric great curvature. Gastric aspecific reflex: in the stomach, both fundus and body are dilated, while the antral-pyloric region contracts.

On the contrary, in an individual at inherited real risk of arteriosclerosis and obviously in arteriosclerotic patient, under mean-intense digital pressure, artery-gastric aspecific reflex shows a lt. ≤ 10 sec., in inverse relation to the severity of the risk itself, as well as of the disease severity.

Interestingly, under "intense" digital pressure, *simultaneously* the gastric aspecific reflex appears (32).

Really useful from diagnostic view-point, the arterial *preconditioning* results pathological: the second evaluation, performed after 5 sec. exactly from the previous investigation, i.e., at basal line, shows lt. either unchanged, 10 sec., or clearly decreased in comparison to basal value, and in relation to the seriousness of **arteriosclerosis constitution**, in inverse relation to the severity of underlying disease.

Identical results to those collected by *preconditioning*, are those observed by Valsalva's manoeuvre (acethyl-choline increase), outlining internal and external coherence of biophysical semeiotic theory.

It is easy to understand that, after such a assessment physician can evaluate separately the condition of diverse arterial vessels, e.g., coronary arteries (54).

2) The subject to examine clenches his fists intensively: *boxer's test*. In health, after lt. of 10 sec., appears the gastric aspecific reflex (Fig. 2), while in presence of **arteriosclerotic constitution** or in case of overt arteriosclerosis, once more, lt. results ≤ 10 sec. The second test performance, after an interval of exact 5 sec. (*preconditioning*), shows results identical to those referred at the point 1.

In conclusion, the two easy methods, applied also in dynamic way, are sufficient to give prominence to **arteriosclerotic constitution**, easy quantifiable on the ground of above-described parameters, on both static and dynamic tests.

Without deepening into a patho-physiological argument, really interesting, but out of our concern, the illustrated biophysical semeiotic examination allows to collect, at the bed-side, useful information on both function and structure of the adventitial vessels, directly related to nutritional state of the local arterial walls, i. e. to Microcirculatory Functional Reserve.

It is easy to understand that the steady knowledge of the new physical semeiotics allows to recognize a large variety of clinical microangiological signs.

In following we summarize only some of them, which permit to assess, in a refined way, microvessels function and structure, including the so-called *vasa vasorum*:

1) the mean-intense (*not maximum*) digital pressure, applied upon a finger-pulp of an individual psycho-physically relaxed and in supine position, brings about upper ureteral reflex (= the upper ureteral third dilates), which informs about Arterio-Venous Anastomoses (AVA) type II, group B, according to Bucciante. At this moment, if digital pressure increases *maximally*, in healthy, the reflex disappears completely, showing the structural-functional normality of these haemoderivative components, essential in regulating microcirculatory blood-flow.

On the contrary, in diseased patients the reflex intensity lowers, without disappearing;

2) analogously, the mean ureteral reflex (the mean ureteral tract dilates) shows an identical behaviour under the same experimental conditions, as far as EBD are concerned;

3) the mean-intense pressure – as above described - brings about the upper ureteral reflex (See point 1), which indicates the opening of AVA type II, group B. However, if the individual, at this point, raises his arm to vertical position, reflex rapidly disappears physiologically: closure of haemoderivative formations and consequently increase of blood supply to capillaries and post-capillaries venules, aiming to preserve the physiologic histangic pH;

4) under identical conditions, in health, if the subject to examine lowers his arm vertically, the upper ureteral reflex intensity increases promptly: AVA type II, group B, dilates further and, then, their haemoderivative function increases, once more aiming to keep microcirculatory blood-flow supply in normal, physiological ranges. These physiological reactions give prominence to the normality of venous-arteriolar reflex (VAR);

5) the mean-intense digital pressure on a finger pulp, under above illustrated condition, causes gastric aspecific reflex after latency time of about 10 sec.

In health, this parameter value persists unchanged in all three positions (horizontal, high vertical and low vertical), due to above-illustrated reasons.

All these dynamic tests result abnormal, and of different degree, of course, in case of arteriosclerosis, starting from the very initial stage: i.e., arteriosclerotic constitution as well as its dependent Inherited real Risk.

Arteriosclerosis QBS Microcirculatory Theory. Microvascular/microcirculatory remodelling.

For the first time, at the beginning of XVIII century, Herman Boorgrave spoke of the primary role played by vasa vasorum impairment in ATS pathogenesis.
Analogously in the past century (http://www.medicina.unict.it/Public/Uploads/links/A.pdf) S.B. Curri and A. Belcaro have suggested a fascinating theory of chronic venous insufficiency, based on vasa vasoum heritable alterations. According to these Authors, venous external layers, whose nutrition is provided by malfunctioning vasa vasorum, are suffering due to insufficient flow-motion along these microvessels.
In a lot of previous articles, we have illustrated structural-functional bases microcirculatory/microvascular remodelling, including that of vasa-vasorum, CAD Inherited Real Risk is based on (1-19, 31, 32). In truth, both definitions of microvessel remodelling are valid to an equal extence, the first emphasising hemodinamic aspect and the later the morpho-functional aspect of the same reality.
Functional microcirculatory alterations of both artery wall vasa vasorum, and parenchimal microvessels (for instance, epicardial coronay arteries and heart muscle cells microvessels), i.e., arterial, vaso parietal type of microcirculatory remodelling, and that parenchimal-tissue, are accurately analyzed with the Psychokinetic Diagnostics (33, 34), that allows physician to bedside assess every, small, single segment of *vasa publica* and *vasa private*, according to M. Ratschow (58).
Regarding the heart, AMI can be caused only by the first type, i.e., coronary artery-wall of microcirculatory remodelling (*vasa vasorum*),
On the contrary, the second type of Inherited Real Risk of CAD, i.e., the parenchymal one, can cause cardiomyopathy with amyloid deposit, Tako Tsubo cardiomyopathy if the remodelling is located at the level of left ventricular apex, *so-called* X Syndrome, Arythmia, a.s.o., but not acute myocardial infarction.

To summarise, mit-DNA andn-DNA mutations in parenchymal cells, e.g., in the heart muscle cells (40% of total cardiac cell volume is represented by mitochondria!), and in microvessel wall cells, cause CAD Inherited Real Risk if microcirculatory remodelling is vaso-parietal in nature, as referred above, while the second type of remodelling can bring about other numerous heart disorder, but not AMI.

At this point, we describe, as example, the CAD Inherited Real Risk (IRR) of epicardial coronary wall, namely the first type of microcirculatory/microvascular remodelling.
With the aid of Psychokinetic Diagnostics, unavoidable to clinical investigation of a biological system, even in localized part of it, e.g. myocardium, physicians can assess in quantitative way so called pa5thological spatial dysomogeneity, according to Schmidt Scoembein (55), in every area of a tissue, caused by microcirculatory/microvascular remodelling, indicating that strcture and function are two poles of identical equation (Leukardt). Such a spatial disomogeneity brings about localised tissue acidosis, increasing the blood-flow along Arterio-Venous-Anastomoses (= fluctuation of the middle ureteral reflex) and thus causing the augmentation of pressure in post-capillary venules
Finally, one has to remember the presence of CAD vaso-parietal, coronary type, Inherited Real Risk can be bdside recognized in one second by Caotino's Sign (32). On the contrary, the type parenchymal, microvascular remodelling is not detected with the aid of Caotino's Sign.

No Author has considered accurately the slow evolution of CAD IRR towards heart coronary disorder, under unfavourable conditions, i.e., in presence of some among 300 environmental risk factors. I refer to the quantum biophysical semeiotic reflection on AMI pathogenesis, in the light of

ATS Microcirculatory Theory, which proved to be, in our clinical experience, a efficient tool in CAD primary prevention.
In following, we illustrate the microcirculatory point of view of the shaping atheromatous plaque in epicardial coronary arteries, as well as in transit coronaries, when involved by microcirculatory remodelling.
An awful number of experimental and clinical evidence outline the central role of QBS theory of coronary artery disease in individuals involved by CAD IRR, according to Microcirculatory Theory of Arteriosclerosis. In fact, the heritable, initial alteration, ICAEM-dependent, is to be find in the *vasa vasorum* of coronary, involved by CAD IRR, always present at birth, *conditio sine qua non* of ATS, rather than in blood alteration associated to endothelial lesion, according to the theory *To Insult Response Theory* of Ross e Glomset.
To understand at the best *Sinn u. Bedeutung* of Microcirculatory Theory of Arteriosclerosis , some information on mitochondria biological properties are unavoidable.

In cell biology, a mitochondrion (plural mitochondria) is a membrane-enclosed organelle found in most eukaryotic cells.[1] These organelles range from 0.5 to 1.0 micrometer (μm) in diameter. Mitochondria are sometimes described as "cellular power plants" because they generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy.[2] In addition to supplying cellular energy, mitochondria are involved in a range of other processes, such as signaling, cellular differentiation, cell death, as well as the control of the cell cycle and cell growth.[3] Mitochondria have been implicated in several human diseases, including mitochondrial disorders[4] and cardiac dysfunction,[5] and may play a role in the aging process. The word mitochondrion comes from the Greek *μίτος mitos*, thread, + *χονδρίον chondrion*, granule.

Several characteristics make mitochondria unique. The number of mitochondria in a cell varies widely by organism and tissue type. Many cells have only a single mitochondrion, whereas others can contain several thousand mitochondria. The organelle is composed of compartments that carry out specialized functions. These compartments or regions include the outer membrane, the intermembrane space, the inner membrane, and the cristae and matrix. Mitochondrial proteins vary depending on the tissue and the species. In humans, 615 distinct types of proteins have been identified from cardiac mitochondria, whereas in Murinae (rats), 940 proteins encoded by distinct genes have been reported. The mitochondrial proteome is thought to be dynamically regulated. Although most of a cell's DNA is contained in the cell nucleus, the mitochondrion has its own independent genome. Further, its DNA shows substantial similarity to bacterial genomes.

Regarding the insight the real nature of localised initial arteriosclerotic lesion of arteries is the eteroplasmia: Heteroplasmy is the presence of a mixture of more than one type of an organellar genome (mitochondrial DNA (mtDNA) or plastid DNA) within a cell or individual. It is a factor for the severity of mitochondrial diseases, since most eukaryotic cells contain many hundreds of mitochondria with hundreds of copies of mtDNA, it is possible and indeed very frequent for mutations to affect only some of the copies, while the remaining ones are unaffected. Microheteroplasmy is normally found as hundreds of independent mutations in one organism, with each mutation usually found in 1–2% of all mitochondrial genomes.

In health, the dynamics of single components of small arteries and arterioles, according to Hammersen, e.g. a coronary artery *vasa vasorum*, with a diameter less than 50 μ., analogously to what happen in every healthy greater artery, both elastic and muscular, i.e., *Vasa Vasorum*, according to Ratscow (58), shows arterial *systole* and *diastole*: Peripheral Heart, *according to Claudio Allegra*. The duration of both at rest is 6 sec.: arterial dilation – *diastole* – realises rapidly in $\leq$ 2 sec.

Vessel response (= the diverse receptors of local smooth muscle cells) is “simultaneous” to Insulin, Adiponectine, Melatonin, Valsalva’s Manoeuvre, a.s.o., secretion, brought about by “intense” stimulation of respective trigger-points, associated to simultaneous type I, associated microcirculatory activation, wherein the *diastole* (= dilation: quick inceasing of third upper ureter) rises to 11 sec., whereas the *systole* (= contraction: disappearing of reflex, i.e., the third upper ureter becomes virtual), lowers to 1 sec. obviously.
At rest, under physiological condition, the period of these oscillations is 12 sec., but it may rises to 14 sec. or more under “intense mitochondrial stimulation, physical and chemical in nature (Cem-Tech, Russian device, sulphydric thermal water, e.g. Porretta Terme-Bologna, Italy), aimed to highest supply of blood, namely material-information-energy, to tissue.
In fact, structure and function are the two pole of the same equation: modifying the first, even slightly, one alters the second, according to Leukhardt, 1822-1898 (in 59)

The physiological functional behaviour of artery wall dynamics, e.g., coronary artery oscillations, bedside evaluated in single part of the vessel with the aid of Psychokinetic Diagnostics (34), demonstrates that local cell membrane, glycocalyx, n-DNA and mit-DNA are perfectly structured, indicating thus the physiological condition of related cells: pH about 7,4 (60, 61).

On the contrary, at rest, for instance, in presence of CAD IRR, though well-localised, due to the alteration of *vasa vasorum* - *Vasa Privata*, according to Ratscow (58) – this segment of artery, predisposed to plaque formation, CAEMH-dependent, fluctuates according to slightly dissociated, type 2, microcirculatory activation, showing diastole and systole parametric values of 6,5 sec. and respectively 5,5 sec. Such as diastolic slowness is in direct relation to the local impairment of flow-motion, reducing the material-information-energy to coronary vessel wall (related media and adventitia).In fact, the outer 2/3 of artery wall are fed by *vasa vasorum*.
Interestingly, diastole realizes slowly in 2 sec. or more, as it occurs in initial phase of myocardial ventrical insufficiency, when the systole is yet efficient.

From the above remarks it is easy to understand that the segment of artery, involved by microcirculatory remodelling, i.e., site of CAD IRR, reacts pathologically to stress tests, as Insulin Acute Pick Secretion Test, Adiponectine Test, Melatonine Test (62-66): its slowness is 2-3 sec. or more, in relation to underlying alteration of local cell membranes, glycocalices, mit-DNA, and n-DNA.
Such a initial vessel alteration, i.e., CAD inherited Real Risk, will end slowly , after decades, in the ATS plaque formation, followed by the known complications.
In our opinion, in the first decade of life, the QBS Stage of media-intimal thickening, both micro- and macrovascular, namely before the generally admitted I Stage of natural history of ATS, for instance, according to To Insult Response Theory of Ross and Glomset, is brought about by smooth muscle cell proliferation, due to the production in hypoxic tissue of Cadaverine, which is also known by the names 1,5-pentanediamine and pentamethylenediamine, as well as Putrescine, 1-6 diamino-butane, starting from the catabolism of Ornithine, an amino acid that plays a role in the urea cycle.
Putrescine reacts with diverse factors, like NF-kb and other numerous citochines, causing cell proliferation after binding to their nucleous.
Regarding stimulating cell proliferation, Let’s remember the primary role played by Jaluronic acid, either modified during its synthesis – there are three way of Jaluronate synthesis – or partially metabolised into smaller molecules, that binds less water so that bound water/free water relation worsens, bringing about artery media layer enlargement.
Finally, among other action mechanisms, Jaluronic acid binding itself to one among three receptors, CD14, stimulates cell proliferation.

Regarding the "initial, preclinical lesions", from a lot of decades the Authors, including myself, are speaking of Hp and LP endothelial areas, at high and respectively low probability to initiate atherogenesis (67). Until now the study of these areas were devoted exclusively to endothelial morphology. In fact, HP areas show a great polymorphism of endothels, in the sense that giant endothels and plurinucleate endothels are near to small endothelial cells and local accumulation of blood cells, including *Colony Forming Units* (CFU), possible retro-viruses, a.s.o.
QBS allows doctor to ascertain, since birth, HP areas by means of functional evaluation, illustrated in following.
In health, applying with thought mean-intense digital pressure, according to Psychokinetic Diagnostic (34), upon a coronary artery segment - e.g., posterior descendent right coronary artery, in its middle area - "in toto" ureter, stomach, and choledocus do not augment their size, i.e., persist unchanged, revealing that artery wall is not thickened.
Interestingly, if digital pressure become of "mean" intensity, "in toto" ureteral reflexes and choldocus reflex appear quickly in 1 sec. (NN = 2 cm. under this assessment!): physiological dilatino of vascular wall, nemely its compliance is normal.

Interestingly, these reflexes increase in significant way (3 cm. or more "simultaneously" to pressure increasing on the artery), as well as at beginning of stress tests, above cited, demonstrating physiological coronary artery compliance, evaluated in a precise point.

On the contrary, in case of localized coronary disorder, even initial, "small" digital pressure upon the artery, brought about with thought, as above referred, causes the first ureteral reflex and choledocus reflex, indicating the pathological wall thickening: 1 cm. or more, in relation to intimal-media alteration.
When digital pressure become of "mean" intensity, parameter value appears less than the normal one (NN = 2 cm.) and it realises slowly in 2 sec. or more, due to artery wall rigidity.
Finally, stress tests and "intense" digital pressure, applied on the artery, cause non significant increase of both reflexes, related to the seriousness of underlying coronary disorder, showing the lowered compliance of local coronary artery.
Interestingly, *nail* pressure, applied on a small segment of diseased coronary artery, even in the first stages, unavoidable to bedside demonstrate the presence of cythochines, brings about gastric aspecific reflex, after a latency time of 3-5 sec. (NN $\geq$ 10 sec.), in relation to the seriousness of disorder, as it occurs in AMI!
In the light of above remarks on understand the statement of one of us "The Death of Clinical Medicine parallels Medicine End" (Stagnaro Sergio. *Canadian Medical Association Journal*, CMAJ 2008; 178: 1523-1524, 10 June 2008. http://www.cmaj.ca/cgi/eletters/178/12/1523).

In a large Literature the anatomo-functional bases of microcirculatory remodelling at level of *vasa vasorum*, characteristic of CAD Inherited Real Risk, are fully illustrated. Really, both definition, i.e., microcirculatory and microvascular remodelling are equally valid, since the first refers to *functional-haemodynamic* aspect, while the second emphasises *morphological-structural* property of the same reality.

Microcirculatory remodelling functional alterations, both parietal-vascular (e.g., epicardial coronary) and parenchymal ones (e.g., heart myocardial cells), Inherited Real Risk is based on (e.g., CAD IRR), almost always associated, can be subdivided in vaso-parietal (coronary) and parenchymal (myocardial) variants. Thy are accurately analysed in every biological system with the aid of Psychokinetic Diagnostics, which allows physician to bedside assess single segments of *vasa publica* and *vasa privata*, in this case *vasa vasorum*, according to M. Ratschow (58), as well as parenchymal microvessels, and obviously the related, well-localised, cardiac parenchyma.

AMI and Peripheral Obstructive Arteriosclerotic Disorder, due to ATS plaque, are caused exclusively by the first variant of microcirculatory remodelling, namely artery wall type, associated almost always with parenchymal microcirculatory remodelling.
Regarding the heart, in the first 40 days of embriogenesis mesenchymal primitive cells form vessels and myocardial cells of single part of myocardium. As a consequence, the first alterations of coronary artery wall have to be early, so that CAD IRR is fully explained.

On the contrary, the microvascular Inherited Real Risk of the II type, i.e., parenchymal variant, can bring about the cardiomyopathy secondary amyloid deposit,Tako Tsubo Cardiomyopathy, when localised in the apex of left ventricle, to *X Syndrome*, to Arythmia, an do on, but not to CAD and AMI!

To summarise, genetic mutations of mit-DNA and n-DNA in parenchymal cells, in our case heart muscle cells,,wherein 40% of the volume is represented by mitochondria, as well as in microvessel cells cause IRR of coronary artery (CAD) if the remodelling is vaso-parietal in nature, whereas the parenchymal microvascular remodelling may bring about above mentioned heart disorders, but not AMI.
At this point, it is extremely necessary to analyse CAD IRR at the level of epicardial and transitory coronary artery wall, which represent the first type of *microvascular/microcirculatory remodelling.*
As referred above, Psychokinetic Diagnostics (33, 34) allows doctor to study single, localized part of every tissue and well defined, pathological "spatial disomogeneity", really different from the physiological "temporal disomogeneity", according to Schmidt Scoembein (68).
Pathological "spatial disomogeneity" is present since individual's birth, is secondary to IRR, precisely speaking, to microcirculatory remodelling, causing localized tissue acidosis, because it is associated with AVA hyperstomy.
Physician can bedside recognise CAD IRR coronary parietal remodelling type, in only one second by means of *Caotino's Sign* (32), that cannot diagnose the parenchymal microcirculatory remodelling.

We must pay accurate attention to the analysis of the slow evolution from CAD IRR, both of I and II microcirculatory remodelling type, ending after decades to coronary damage, plaque formation, under unfavourable environmental risk factors (about 300!).
We refer, for instance, to quantum-biophysical-semeiotic investigation on AMI pathogenesis, in the light of Microcirculatory Theory of ATS, unavoidable in hinder CAD epidemics, considering in original way the new microcirculatory pathogenesis of atheromatous plaque formation in epicardial coronary as well as in those of transition among cardiac musculature, in presence of local microcirculatory remodelling, always associated with the parenchymal one, though of different severity.

Microangiological Clinical Amalysis of Vasomotility and Vasomotion in CAD Inherited Real Risk during Stress-Tests

At rest, in an individual, aged 20-30 years, involved by CAD Inherited Real Risk, physician observes slight dissociated, type 2, activation of arterioles oscillations: *vasomotility* (= duration of upper ureteral reflex lasts about 6,5 sec.; NN = 6 sec.), aiming to maintain the physiological level blood supply to nutritional capillaries, who's fluctuations, i.e., *vasomotion*, despite the obstacle to flow-motion, due to newborn-pathological, type I, subtype b), Endoarteriolar Blocking Devices, located in small artery, according to Hammersen, show physiological parameter value: venular capillary dilation is yet normal, namely 6 sec. (Fig 3)

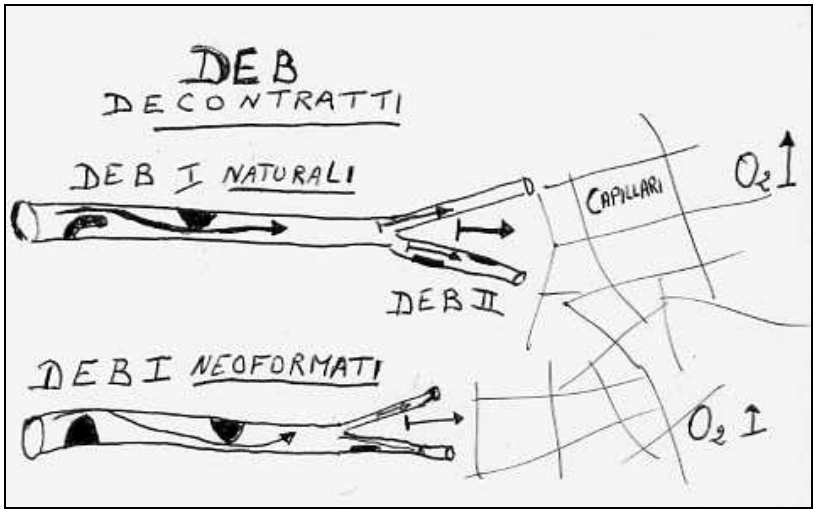

Fig 3
The figure shows the different flow-motion and thus tissue oxygenation under normal (upper small artery) and pathological conditions, caused by newborn-pathological EBD (= Italian DEB).

As a consequence, at rest, artery (e.g., coronary) microcirculation, precisely in the site of IRR, is small dissociated and the Latency Time of related gastric aspecific Reflex (e.g., heart-gastric aspecifi Reflex) appears physiological: 8 sec. under digital pressure of mean intensity (Tab.1.

Importantly, below ten years of age, in health at rest, there is a physiological, type I, associated, activation, so that both *vasomotility* and *vasomotion* show diastole duration of 7 sec. (NN above 10 years = 6 sec.), due to heart lasting structuring. Such a type I, associated, microcirculatory activation accounts for the reason latency time of heart-gastric aspecific reflex is 10 sec. (NN above 10 years = 8 sec. during small digital pressure on the precordium). The reflex duration is > 3 sec. < 4 sec. Glycocalixes are normally functioning, like AVA (type A group I e II, according to Bucciante).

On the contrary, in case of ATS Inherited Real Risk, e.g., CAD IRR, since the first day of life physiological microcirculatory activation is altered and one observes the type II dissociated: *vasomotility is 6,5 sec.* as diastole and *vasomotion* 6 sec. ; AVA (type A group I e II) overt, " flow-motion centralization". In a few words, there is Allegra's Syndrome (27).
As a consequence, in health, in the first life decade, latency time of artery-gastric aspecific reflex is 10 sec., while in tissue areas involved by ATS IRR latency time lowers to 8-9 sec. (NN = 10 sec.). In addition, glycocalixes are malfunctioning, demonstrating structural alterations of mit-DNA, n-DNA and interstitium.
Interestingly, if the subject, showing very slight type II, dissociated microcirculatory activation in *vasa vasorum* of whatever artery segment , undergoes stress tests, as *insulin acute pick secretion test, Endogenous Adiponectin Test, Endogenous Melatonin Test, Effort Test,even simulated, a.s.o.,* the predisposition to CVD, including CAD, becomes significantly more intense, and thus easier o be recognised, due to microcirculatory events, very fascinating, playing a paramount role in the interpretation of patho-physiology of both CAD and its complications, AMI and Angina.

In health, during above-mentioned stress test, caused by "intense" stimulation, necessary to provoke non local realm in biological systems, e.g., in the heart, the physician observes "simultaneously"

highest activation of both *vasomotility* and *vasomotion*, showing a dilation (= diastole) duration of 11 sec., that is the most intense value of microcirculatory dilation.
As a consequence, the related parenchyma, e.g., myocardium during its structuring, receives elevated amount of material-information-energy. Under this condition, gastric aspecific reflex latency time is prolonged during stress tests, rising from about 10 sec. to 20 sec., namely doubled, as one notes in the Preconditioning.

On the contrary, in individual with IRR, e.g. CAD IRR, under identical conditions, cited above, the activation of *vasomotility* occurs later , i.e., after about 3 sec., it is less intense, and the duration of the *slow* dilation lasts more than 6 sec., but never at its highest value (NN = 11 sec.). All QBS parameter values parallel the seriousness of underlying predisposition to CVD, in our example to CAD. Therefore, beside small artery segments, involved by parietal CVD IRR, e.g., CAD IRR, physicians observe that the related parenchymal areas, e.g., myocardial zones, involved by parenchymal microcirculatory remodelling, as illustrated above, show a worsened oxygenation, more or less intense: ischemia and acidosis can bring about Ventricular Fibrillation!
These events indicate the initial suffering of small artery and arterioles, according to Hammersen, *smooth muscle cells*, associated with alteration of related glycocalices in zones embriologically identical.
Regarding the *vasomotion*, caused by *vasomotility*, as clinical experience demonstrates (in the skin on the rotula and inferior lip, where arterioles are absent, there is no *vasomotion*), it results increased but typically in less intense manner than the *vasomotility*, realising the type II intermediate microcirculatory activation (*vasomotility* lays generally less than 10 sec.), due to newborn-pathological, type I, subtype b) Endoarteriolar Blocking Devices.

In summary, QBS Microcirculatory Theory of Arteriosclerosis is based on some Principles, which proved to play a central role, as demonstrates a long clinical experience. CAEMH is the condition sine qua non of every disorder and it modifies parenchymal mit-DNA. The reduced blood supply in parenchymal genetic altered cells as well as in altered Vessel Wall cells brings about Vasa Vasorum microcirculatory remodeling causing newborn-pathological EBDs. As a consequence, AVAs are continuously open and they induce Tissue Acidosis, SMC proliferation and migration. Due to embryological reasons, is present more or less dysfunction of local endothels (Table 1).

Principles of ATS QBS Microcirculatory Theory

1) CAEMH *conditio sine qua non* of every disorder.
2) CAEMH modifies mit-DNA of Parenchymal, as well as Vessel Wall cells, including those of *VasaVasorum*.
3) According to Angiobiopathy Theory, parenchymal alterations parallel Vessel Wall cell alterations.
4) Parenchymal cells need less blood supply than the normal ones, bringing about *Vasa Vasorum* microcirculatory remodelling: type I, subtype b) newborn-pathological Endoarteriolar Blocking Devices.
5) As a consequence, A.V. Anastomoses are persistently open, causing Tissue Acidosis, and thus SMC Proliferation and Migration.
6) Local Endothels are similarly altered due to Embriological reason. As a consequence cell infiltration, lipid and protein deposit may occur at this level, contributing to media-intimal thickening.

Tab. 1

In our opinion, the related histangic hypo-oxygenation can provoke the production of poli-diamine, that stimulate notoriously *smooth muscle cells* proliferation, e.g. Cadaverine and Putrescine, NH2 1-6 butane, i.e., NH2-CH2 –CH2-CH2-CH2-NH2, ornythine catabolites. Therefore, both cell proliferation and media-intima thickeness could begin in earlier period than till now admitted, according to present theory, as To insult response theory of Ross and Glomset and that of response to endothelial dysfunction, according to Williams and Tabs.
The *smooth muscle cells* of newborn-pathological type I, subtype b), aspecific, EBD are more efficient and less reactive, as Clinical Microangiology demonstrates: "simultaneously" to the beginning of stimulation under stress tests, midle ureteral refex, characteristic of EBD, increases significantly, and realises quickly, obstructing intensively arteriolar flow-motion, partially hindering the increased work of small arteries. As a consequence, in presence of CVD IRR, e.g. CAD IRR, during stress tests, local myocardial oxygenation augments but showing reduced increase than in healthy subjects, and it worsens paralleling the CAD predisposition increasing.

In conclusion, artery occlusion caused by atheromatous plaque, localised in the zone since birth involved by CVD Inherited Real Risk, hinders the blood flow to related parenchymal areas, which are suffering since ever from insufficient supplying of material-energy-information, also due to parenchymal type microcirculatory remodelling (Tab. 2)

Quantum-Biophysical-Semeiotic Microcirculatory Theory of Arteriosclerosis

Stage I: at Birth→First Year.
Vasa Vasorum with Inherited Real Risk of ATS.
Type II "small", dissociated Microcirculatory Activation, Allegra's Syndrome: at Rest, pH NN.

Stage II: after 1 Year → 5 Years.
Type II "intense", dissociated Microcirculatory Activation, present even at Rest → pH ↓ → Poly-diamines and Jaluronic Acid Fragments↑ → Cell Proliferation-Migration Stimulation → Artery Intimal Thickening.

Stage III: after 5 Years → 10 Years.
Type III dissociated Microcirculatory Activation → growing Endothelial and Tissue Damage → cellular Infiltration and initial Plaque Formation → subsequent artery Lumen Narrowing

Tab. 2

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