Coronary Artery Disease and CAD Inherited Real Risk

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ABSTRACT

The genetic alteration of mit-DNA affects the mitochondrial activity, main responsible of cell respiration in biological systems. The chance to investigate, indirectly and through bed-side evaluation, the mitochondria functionality, with the support or chaos theory, opens new ways to understand and face the very beginning states of Coronary Artery Disease – CAD, even silent and not yet clinically diagnosted, and of the inherited real risk of CAD.

Introduction

This paper highlights the central role of mitochondria and mitochondrial DNA (mit-DNA) in the process that underlies the ischemia of myocardial cells. For this purpose is useful the Quantum Byophysics Semeiotics - QBS, extension of the classical semiotics with the support of quantum and complexity theories, a scientific approach first described by Stagnaro et al. (Manzelli, 2007b) based on the Congenital Acidosic Enzymo-Metabolic Histangiopathy – CAEMH (Stagnaro, 1985), a unique mitochondrial cytopathy, present at birth and subject to medical therapy.

We will see how the presence of deterministic chaos is crucial for understanding the diagnosis, prevention and therapy of Coronary Artery Disease - CAD, and especially to reveal the Inherited Real Risk of CAD (Stagnaro, 2004a).

According to Stagnaro works, today the doctor could be able to evaluate, simply using the stethoscope (Stagnaro, 1978), the mitochondria functionality of his patients, bed-side, as well as in all biological systems. It is possible, since birth, to make a diagnosis in order to detect the presence of Inhereted Real Risk of CAD linked to specific QBS constitutions (Stagnaro, 2009), so that an intelligent prevention just on subjects with Real Risk can be implemented, without spending for NHS[1]. On the basis of QBS constitutions -

i.e. Oncological Terrain, Diabetics Constitution (Stagnaro, 2004c), etc. – is possible to prevent the onset of more serious diseases that human being is suffering today, as for example, cancer, diabetes, ischemic heart diseases, including myocardial infarction.

1. State of the art

Coronary artery disease (CAD)

Coronary Artery Disease (CAD) is the end result of the accumulation of atheromatous plaques within the walls of the coronary arteries that supply the myocardium (the muscle of the heart) with oxygen and nutrients and is the leading cause of death worldwide. While its symptoms and signs are noted in the advanced state, most individuals with CAD show no evidence of disease for decades as it progresses before the first onset of symptoms, often a "sudden" heart attack, finally arises. After decades of progression, some of these atheromatous plaques may rupture and start limiting blood flow to the heart muscle.

The disease is the most common cause of sudden death. As the degree of CAD progresses, there may be near-complete obstruction of the lumen of the coronary artery, severely restricting the flow of oxygen-carrying blood to the myocardium. Individuals with this degree of CAD typically have suffered from one or more myocardial infarctions[2] (heart attacks), and may have signs and symptoms of chronic coronary ischemia[3], including symptoms of angina at rest and flash pulmonary edema. Limitation of blood flow to the heart causes ischemia[4] of the myocardial cells, which may die from lack of oxygen and this is called a myocardial infarction. It leads to heart muscle damage, heart muscle death and later myocardial scarring without heart muscle regrowth. Chronic high-grade stenosis of the coronary arteries can induce transient ischemia which leads to the induction of a ventricular arrhythmia, which may terminate into ventricular fibrillation leading to death.

There is a term in medicine called *"Cardiac Syndrome X"*, which describes chest pain (Angina pectoris) and chest discomfort in people who do not show signs of blockages in the larger coronary arteries of their hearts when an angiogram (coronary angiogram) is being performed. No one knows exactly what causes "Cardiac Syndrome X" and it is unlikely to have a single cause. Today, it is speculated that the major contributing factor to "Cardiac Syndrome X" is *"microvascular[5] dysfunction"*.

CAD and non-linear dynamics

In literature there are several researches aimed to test the non-linear behavior of heart muscle. Dynamic analysis techniques may uncover abnormalities in heart rate (HR) behavior that are not easily detectable with conventional statistical measures. The short-

term fractal scaling exponent performed better than other heart rate variability parameters in differentiating patients with CAD from healthy subjects. Patients with stable angina pectoris have altered fractal properties and reduced complexity in their RR interval dynamics relative to age-matched healthy subjects (Ristimäe, 1998).

Major untoward events, such as life-threatening arrhythmias and acute coronary events, have been suggested to be triggered by the activation of the autonomic nervous system in patients with CAD. Heart rate variability analysis methods, such as fractal and complexity measures as well as conventional techniques, give valuable clinical information among patients with ischemic heart disease (Huikuri, 2001).

The challenges posed by chronic illness have pointed out to epidemiologists the multifactorial complex nature of disease causality. It is time to add to the epidemiologic research agenda the notion of nonlinearity and its relevant form of analytical approaches that are being tested in other disciplines (Philippe, 2004).

Processing the database with RR-intervals of patients suffering from CAD has shown that the largest Lyapunov exponent can be a diagnostic criteria allowing one to distinguish between different groups of patients with more confidence than the standard methods for time series processing accepted in cardiology (Pavlov, 2008).

A computerized approach of nonlinear dynamics analysis of electrocardiogram (ECG) signals has been applied for the detection of CAD. The well-known nonlinear dynamics descriptors, recurrences percentage, mutual information, fractal dimension, and a new descriptor, next embedding dimension error, are good quantitative descriptors of fluctuations (Antanavičiusa, 2008).

These pioneering works, even if corroborating the correlation between deterministic chaos and the presence or absence of CAD, still leave many open questions and unresolved issues. First, these are purely statistical approaches, based on clinical test's time series (e.g., ECG) studying the changes taking place in heart rate in healthy (physiological, white area) and patient (pathological, black area): downstream diagnosis of CAD. Second, they do not address the underlying problem, namely investigating the causes of CAD, for example by analyzing the lifelong behavior of coronary parenchymal cells, microvascular tissue or blood flow in microvessels. Furthermore, CAD is a growing epidemic, and it should be noted that often a subject unaware of being affected by CAD does not undergo clinical trials and cardiology visit, and anyway often the tests performed are not sufficient to diagnose the disease, as evidenced by the numerous deaths of young athletes for heart attack, although they undergo regular cardiac monitoring.

For all these reasons it needs to explore new approaches, such as that introduced by Quantum Biophysical Semeiotics – QBS – (Stagnaro, 2007b) which through bed-side evalutation, not only can diagnose the presence or absence of CAD, even silent, but can also assess the existence of pre-metabolic syndrome[6] that can last for years or decades, pre-clinical stage of the disease still potential or on training (evolution to pathology, pre-morbid state or gray area), so allowing an effective prevention.

Genetics, mit-DNA and chaotic dynamics

Several works of the last decades evidence the importance of deterministic chaos and fractals in genomics, genetics ed epigenetics (Capra, 1997).

By studying the complexity the focus had shift from the structures to the processes of their emergence. In the past there was the view of genes as stable and clearly distinct units that transmit hereditary characteristics. Genetic stability is instead an emergent property that stems from the complex dynamics of the whole cellular network and we expect that our understanding of these processes of emergence will increase significantly with the application of chaos theory to the new discipline of epigenetics.

The stability of genetic structure is the result of a well-orchestrated dynamic process that requires the participation of a large number of enzymes, those organized in complex metabolic networks that regulate and ensure both the stability of DNA molecules, and the accuracy of their duplication. The stability of genes is not an intrinsic property of DNA molecules, but a result of complex dynamics of cellular processes.

What emerges from recent studies is the deeper understanding that biological processes involving genes are all regulated by the cellular network in which the genome is integrated. This network is a highly non-linear reality, a reality that contains multiple chains of feedback, so that patterns of genetic activity change constantly in response to changing circumstances. Natural selection does not operate on individual genes but on the scheme of self-organization bodies. It is possible to represent the whole process of biological evolution as a trajectory in a phase space that moves within a basin of attraction to an attractor (Medio, 1992) that describes the functioning of the body in the stable form that characterizes his adulthood. Complex systems exhibit nonlinear structural stability. A basin of attraction can be distorted or disturbed without changing the fundamental characteristics of the system. In the case of an embryo during evolution, it means that it is possible to change, to some extent, the initial conditions of the process without seriously damaging the development of the whole organism. Therefore, the stability of development, which remains a mystery from the perspective of genetic determinism, is clearly a consequence of basic properties of complex nonlinear systems.

DNA mutation and recombination are the two main way of bacterial evolution, but Margulis (1993) discovered a third way: the symbiosis. The most remarkable evidence of evolution through symbiosis - the tendency of different organisms to live in close association with each other, as the bacteria in our gut - is offered by mitochondria[7], the power plants that are found within most nucleated cells.

These fundamental components of all animal and plant cells that perform cellular respiration, contain their own genetic material and reproduce independently and at different times than the rest of the cell, and in fact have their own DNA, mitochondrial DNA[8].

Deterministic chaos and non-local reality

Deterministic chaos has been defined[9] as the 'stochastic or probabilistic behavior occurring in a deterministic system' and its main characteristics are the uncertainty and unpredictability, but is possible to detect and investigate it and to get qualitative information through invariant statistic measures such as LCE[10], fractal dimension[11] and entropy[12] (Medio, 1992).

Entropy represents the rate of uncertainty, or equivalently, the rate of variation of qualitative information of dynamical systems, and is important in the causal interpretation of quantum theory (Bohm, 1980), which supposed the electron to be a certain kind of particle which follows a causally determined trajectory[13]. In addition to the Newtonian classical potential, the particle[14] moves according to a new potential, called Quantum Potential – QP – which is determined by the quantum wave field[15], or wave function. QP is independent of the strength, or intensity, of the quantum field but depends only on its form, so that the information in the form[16] of the quantum wave directs the energy of the electron and even distant features of the environment can effect this movement in a deep way.

The feature, in which very distant events can have a strong influence, is what is meant by a nonlocal interaction. Non-locality implies an instantaneous connection between distant events and does operate in nature, as proved by Aspect et al. (1982), who provides strong evidence for a nonlocal form of interaction. This result follows in a natural way, within the causal interpretation, as a result of the nonlocal QP that directly connects distant particles.

Sub-quantum behaviors and biological systems dynamics are usually considered as separated and different worlds, but there are some interesting works as Lory's experiment (Stagnaro, 2008) that open new perspectives about the presence of non-local reality in biological systems. Furthermore, since life system is based on the communication system, DNA functioning can not only be seen as a storage of genetic information. We can consider DNA/RNA dynamic system as an Information Energy – EI – catalyst (Manzelli, 2009) able to transmit and receive bio-physical quantum signals to and from the proteins in the living cells, so DNA can be thought as an "antenna" transmitting nonlocal information[17] through 'gene quantum signals'.

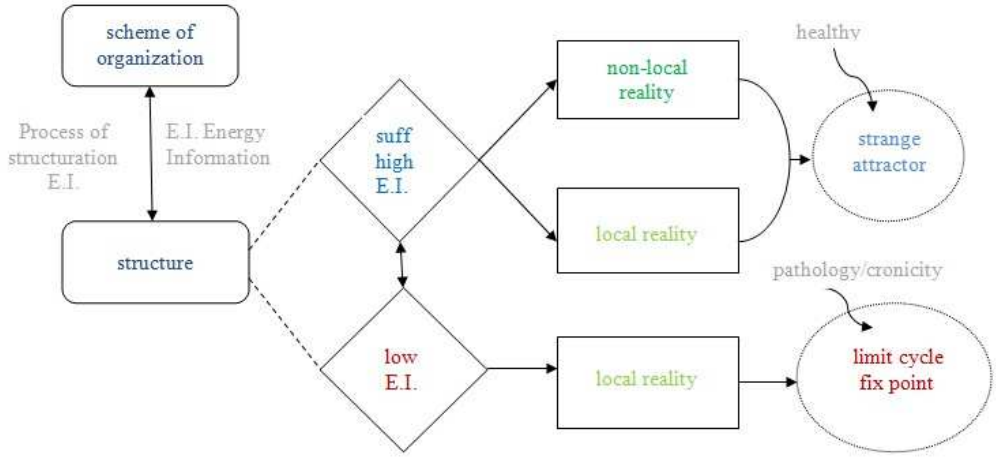
In biology, Varela et al. (1974) proposed the theory of autopoiesis, useful to understand the connection between organization and structures in living systems. An autopoietic system, so as described by Maturana and Varela, is based on a scheme of autopoietic organization through a process of structuring which can lead to different structures. The autopoietic organization is conservative and always acts on itself: self-production, self-regulation, self-referential, recursion, circularity. The scheme of organization works relentlessly to achieve the autopoiesis through a continuous process of structuring, generating dissipative structures with non-linear dynamics (Prigogine, 1967).

There is structural coupling between organization (conservative) and structure (dissipative) to achieve always the autopoiesis. If there was a tendency to disease (or if there is pathology), the organization would always be orientated towards the survival,

materializing and engaging compensatory mechanisms to restore groped the simultaneity and synchronicity.

In a previous work (Caramel, 2010) we tested in biological systems the hypothesis of the correlation between nonlocal reality and deterministic chaos, of the co-presence of local reality and non-local reality in physiological states, and of a sufficient high amount of information energy – EI – as catalytic process to maintain nonlocality in the autopoiesis.

If the system was fully healthy, there would be actually a non-local reality (parallel to the local reality) - simultaneity and synchronicity - and the presence of deterministic chaos (chaotic or strange attractor). If there was disease, the autopoiesis would still be present, but the non-local reality and the correlated strange attractor equlibria, corroborating the presence of deterministic chaos, would disappear so that we would observe just limit cycle equilibria in the case of pathology, and fixed points in case of chronicity.



Scheme 1. Autopoiesis and Energy Information

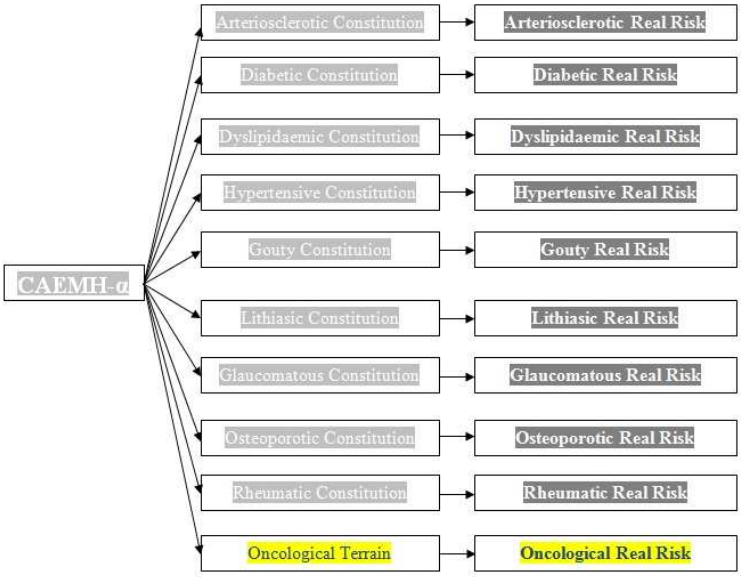
Most of metabolic processes are catalyzed by enzymes and receive energy through special molecules known as organic phosphate or ATP, of mitochondrial origin. All cellular structures exist in conditions far from thermodynamic equilibrium: they are dissipative, far from equilibrium with their own stability, spontaneous emergence of new forms of order. As the flow of energy increases it is possible that the system encounters an instability - fork - at which the system itself can enter into a completely new state, where new structures and new forms of order can emerge - emergences - or self-organization.

Creativity is a key property of all living systems, and if cell metabolism does not use a constant flow of energy to repair structures as soon as they damage, fastly they would decay to steady-state: the cell would die (from chaotic attractor to limit cycle to fixed point). If it is reduced the blood flow in an artery, the microcirculation would activate itself, but the fractal dimension would be reduced. We then describe the cell as an open system. Living systems are closed at the level of organizational structure (they are autopoietic networks), but open in terms of materials and energy. "*The cell enter in connection automatically with other bodies. If it expels something, there will be any other body that will absorb it*" (Lynn Margulis)

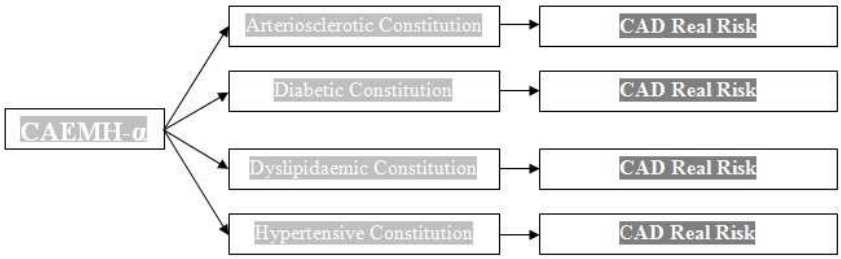
2. **Inherited Real Risk of CAD**

According to Stagnaro (2007), genoma's information are transmitted simultaneously both to parenchyma and related microvessels, so that mutations in parenchimal cell n-DNA and mit-DNA are the *the conditio sine qua non* of the most common human disorders, like diabetes and cancer, today's epidaemics. In fact, all these diseases are based on a particular congenital, functional, mithocondrial cytopathy, mostly transmitted through mother, and defined Congenital Acidosic Enzyme-Metabolic Histangiopathy, CAEMH (Caramel, 2010). In addition, parenchymal gene mutations cause local microcirculatory remodeling, so doctor can evaluate it at the bedside in a reliable manner, gathering indirect information on inherited modifications of relative parenchymal cell, since biological system functional modifications parallel gene mutation, according to Angiobiopathy theory (Stagnaro, 2004).

The presence of intense CAEMH – termed CAEMH-α - in a well-defined myocardial area, involved by gene mutations in both n-DNA and mit-DNA, is the ground for one or more biophysical semeiotics constitutions[18] (Stagnaro, 2004c) which could brings about their respective congenital Real Risks - RR (scheme 2) and / or CAD Real Risk[19] (scheme 3) characterized by microcirculatory remodeling from biophysical-semeiotic viewpoint, especially intense under environmental risk factors. Such as congenital microvascular remodeling, including also vasa vasorum of large coronary arteries, shows since birth interesting structures, i.e., newborn-pathological, type I, subtype b), Endoarteriolar Blocking Devices, EBD, localized in small arteries, according to Hammersen (1968). Interestingly, CAD Inherited Real Risk is associated to endothelial dysfunction[20] (there are mitochondria also in endothels, although in small amount), which doctor can bed-side assess in easy and reliable way, at rest as well as under stress tests[21]. As a consequence of above, briefly referred remaks, physicians are able nowadays to demonstrate the presence of typical pathological EBD in coronary microvessel, which play a central role in CAD Inherited Real Risk.



Scheme 2. CAEMH-α, biophysical semeiotcs constitutions and associated real risks

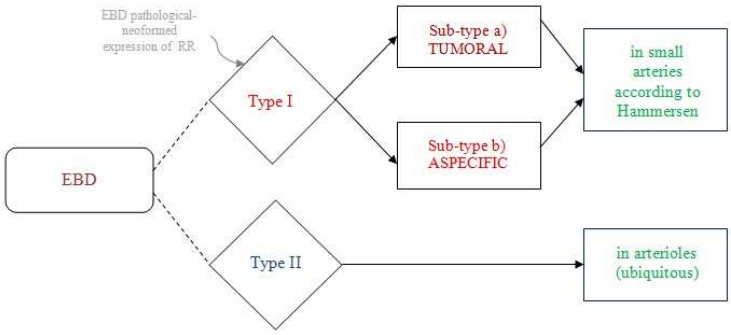


Scheme 3. CAEMH-α, biophysical semeiotcs constitutions and inhereted real risk of CAD

Through the objective semeiotic biophysics examination in a few minutes, it is possible to recognize and quantify if a patient has got any congenital Real Risk (RR) to have a disease by mean the observation of EBD, type I, subtype a) cancerogenous (scheme 2, in yellow) b) nonspecific (scheme 2, in gray, present in all the other more frequent and severe disease).

The EBD is a kind of dam which opening or closing itself regulates blood flow in microvessels directed to the parenchyma (tissue, substance of a body). With a simple stethoscope it is detectable if there is a clear genetic predisposition to have a disease such as cancer, diabetes or CAD, and it is possible to quantify and monitor it over time since birth. So there is the possibility of implementing a prevention on a huge hall in individuals clinically finally selected in a rational way. This new way of prevention will not allow to materialize physical illness, which can be anyway potentially present (or be RR as "residual") at potential level. As similarity we can think of butterfly valves that regulate the flow and mixture of air and gasoline in car engines, since the EBD are dams that are simply regulating blood flow to the parenchyma[22], precisely cells of various tissues. If these DEB are tough, rigid, inelastic, there is RR.

There are EBD Type I - located in small arteries, according to Hammersen - and Type II – they can be found in the arterioles that are, according to Hammersen, between small arteries and capillaries -: only type II is ubiquitous, in the sense that it is observed everywhere, in all arteries (scheme 12). Even these physiological types get sick or old. However, the other types, pathological-neoformed, are expressions of the RR, of potential disease, they occlude more, but through therapy they can be transformed from the subtype a) tumoral, to subtype b) aspecific, and then in "physiological" type, decreasing gradually their amount[23].



Scheme 4. Endoarterial Blocking Devices (EBD)

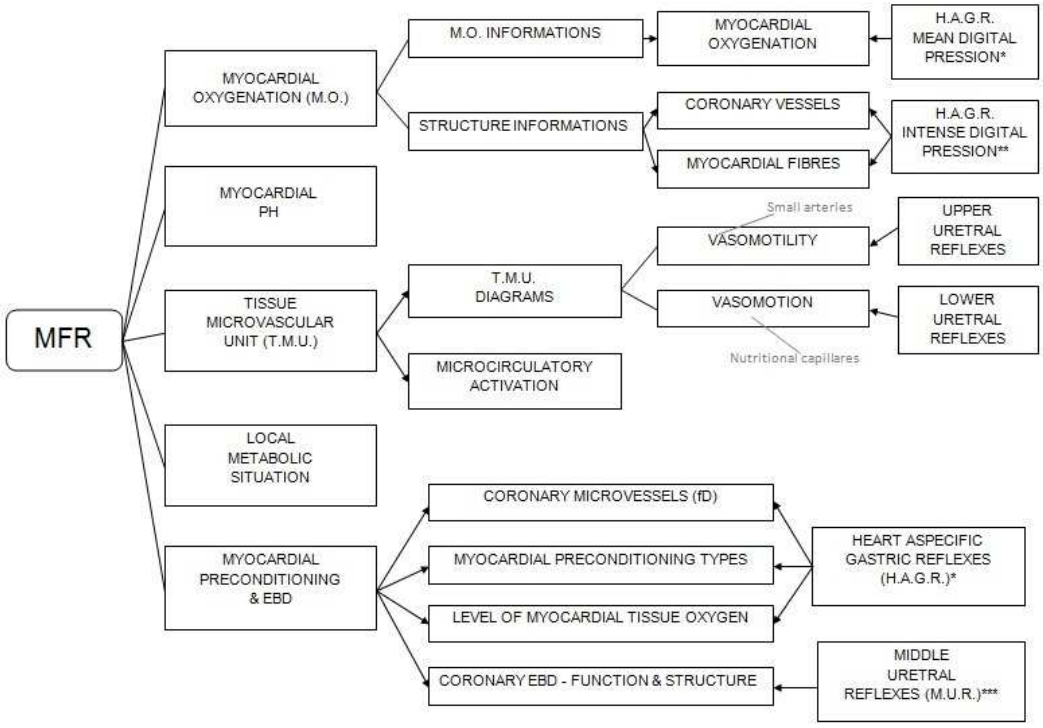
3. Quantum Biophysical Semeiotics and Microcircular Functional Reserve

Microcircular Functional Reserve

Alterations of mit-DNA and n-DNA cause CAEMH in myocardial area, a parenchymal gene mutation that induces, in case of intense CAEMH-α, a local microcirculatory remodeling (LMR), a congenital microvascular remodeling possible to evaluate and investigate getting information about heart parenchymal cells through several biophysical semeiotic signs and behavior. For instance, through the observation of EBD and their structure and functioning on coronary microvessels we can study the LMR and investigate if there is CAD or inherited real risk of CAD and entothelial dysfunctions.

A lowering microcirculatory blood flow induces a LMR due to EBD type 1 subtype b), aspecific, synonymous of reduced tissue oxygenation (scheme 4). Through biophysics semeiotics we can measure and evaluate the Microcirculatory Functional Reserve (MFR) activity of related coronary microvessels. MFR is correlated with microcirculatory bed or Tissue Microvascular Unit (T.M.U.) and is possible to evaluate it through the observation of myocardial oxygenation, myocardial pH, T.M.U. structure and function, local metabolic situation, myocardial preconditioning and EBD investigation (scheme 5).

Quantum Biophysical Semeiotics and Microcircular Functional Reserve – MFR -



*Scheme5. Legend: MFR (Microcircular Functional Reserve); EBD (Endoarteriolal Blocking Device); fD (fractal Dimension); H.A.R.G. (Heart Aspecific Gastrix Reflexes); M.U.R. (Middle Uretral Reflexes); T.M.U. (Tissue Microvascular Unit); M.O. (Myocardial Oxygenation); * (Table 1); ** (Scheme 6); *** (Table 2)*

Myocardial Oxygenation

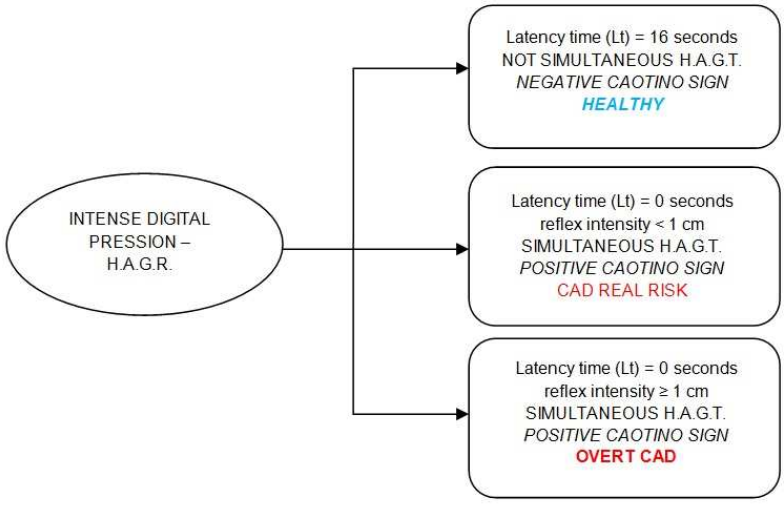
Myocardial oxygen supply can be assessed clinically in a precise way (Stagnaro, 1996). In healthy, digital pressure of "mean" intensity, applied upon cutaneous projection area of the heart (precordium), brings about heart aspecific gastric and caecal reflexes (H.A.G.R.) after a latency time (Lt) of 8 seconds (table 1), informing on myocardial oxygenation at rest, as well under stress situations, such as Valsalva's Manoeuvre - which allows doctor to assess bed-side endothelial function - lasting about 7 seconds (Stagnaro, 1994). In fact, primary reduction in myocardial blood flow rather than increase in demand seems to be responsible for many angina episodes, even clinically silent.

In addition, Lt of both caecal and aspecific gastric reflexes (i.e., caecal and gastric dilation) increases significantly (negative Caotino sign), raising to 16 seconds (scheme 6), when digital pressure becomes "intense", because it stimulates coronary vessels and myocardial fibers (scheme 5), hence inducing local metabolic regulation of tissue-microvascular-units (T.M.U.), i.e. activating microvascular functional reserve - MFR (Goldberger, 1987).

In pathological states such as overt CAD, digital pressure of "mean" intensity on precordium brings about H.A.G.R. after a Lt less than 7 seconds (table 1), while a Lt between 7 and 8 seconds informs us about a CAD inherited real risk in evolution.

Furthermore, *Caotino sign* is positive in case of intense digital pression (Lt = 0) revealing a CAD real risk if the reflex intensity is less than 1 cm, and an overt CAD if the reflex intensity is 1 cm or more (scheme 6). In this last case H.A.G.T. is simultaneous and its intensity is correlated to the numbers of EBD type 1, subtype b), aspecific, pathological neoformed in small coronary arteries, accurate assessment on the basis of the parametric values of middle uretral reflexes (table 2).

Heart Aspecific Gastric Reflex (H.A.G.R.)
intense digital pression on cardiac trigger points (precordium) – Caotino sign



Scheme 6. Legend. H.A.R.G. (Heart Aspecific Gatric Reflex); CAD (Coronary Artery Disease); Lt (Latency time)

Heart Aspecific Gastric Reflex (H. A. G. R.)
mean intensity digital pression on cardiac trigger points (precordium)

Latency time (Lt) in seconds	Latency time after preconditioning (pause of 5 sec.)	MFR in seconds	fD & equilibria	EBD	Preconditioning	Diagnosis
Lt = 8	Lt = 16	3< MFR <4 normal MFR, associated activation, outcome +	fD ≥ 3 (ideal value fD=3.81) stange attractor	Normal EBD phisiological function	Type I Physiological tissue microvascular unit	Health
Lt = 8	Lt < 16	MFR = 4 compromised MFR, dissociated activation, outcome ±	2<fD<3 limit cycle	Normal, slightly modified EBD function, small number of pathological EBD	Type II A Intermediate tissue microvascular unit	CAD Inherited Real Risk
7<Lt <8	Lt < 16	4< MFR≤ 5 growing compromised MFR, dissociated activation, outcome ±	1<fD≤2 limit cycle	Modified EBD function, increasing number of pathological EBD	Type II B Intermediate tissue microvascular unit	CAD Inherited Real Risk in evolution
Lt≤7	Lt < 14	MFR>5 absent MFR, dissociated activation, outcome – (MFR≈8 angina pectoris)	fD=1 fix point	Normal EBD function pathological, large number of pathological EBD	Type III Pathological tissue microvascular unit	Overt CAD

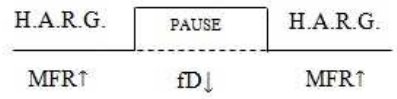
Table 1. Legend: MFR (Microcircular Functional Reserve); EBD (Endoarteriolal Blocking Device); CAD (Coronary Artery Disease; fD (fractal Dimension); Lt (Latency time)

Myocardial pH

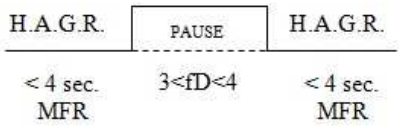
According to clinical and experimental evidences (Stagnaro, 2004a), tissue myocardial pH is related to the reduction of latency time (Lt) and to the extension of the duration of the H.A.G.R., which expresses the local MFR - microcirculatory functional reserve. MFR is inversely proportional to fractal dimension (fD), calculated as simply as the disappearing time of H.A.G.R. before the appearance of the next one (scheme 7).

Summarizing, fD is directly (d) or inversely (INV) related to:

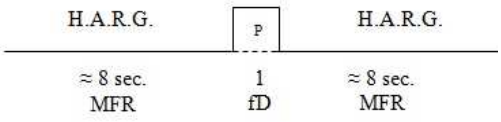
A) (d) the local MFR (vasomotility and vasomotion);
B) (d) the presence, or not, of CAD or inherited Real Risk of CAD (scheme 9);
C) (d) the Lt of H.A.G.R. and then to tissue myocardial pH (table 1);
D) (INV) H.A.G.R. length (scheme 8, scheme 10).



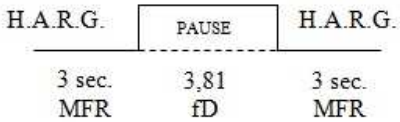
Scheme 7. MFR and fD are inversely correlated



Scheme 8. Physiological MFR – healthy state



Scheme 9. "Angina pectoris" and related fD



Scheme 10. An optimal MFR and physiological fD

Tissue Microvascular Unit

According to Tischendorf's concept of Angiobiotopie (Curri, 1986), biological tissue-microvascular system can be described as formed by single units: the tissue-microvascular units.

In its turn, the tissue-microvascular unit (T.M.U.) is made up by three fundamental components:

1) *microvessels*, diameter < 100 μ,
2) *the blood*, flowing in them,
3) *perivascular connective*, periangium, interstitium or "environment" in which microvessels are placed, formed by water, free- and bound- water, cells and connective fibers, and interstitial matrix, glucosamino-glycanes.

Microvessels can be subdivided as follows (Pratesi, 1990):

1) *Para-microcircle*: small arteries and arterioles, according to Hammersen, venules of I, II, III order, shunts or Arterio-Venous Anastomoses (AVA), functionally speaking (Bucciante, 1949);
2) *Microcircle*: nutritional capillaries, post-capillaries venules, "meta"- arterioles.

With the aid of Biophysical Semeiotics, doctor is able to evaluate, in dynamic manner, T.M.U. of every biophysical system, from both structural and functional view-point, according to a synergistic[24] pattern, i.e. the clinical evaluation of microvascular dynamics.

Notoriously the microvessels carry on a motor activity, autoctonous and deterministic chaotic, which represents one of the most remarkable manifestations of microcirculatory hemodinamics, characterized by a *flow-motion* and hematocrit rhytmically fluctuating due to the particular behaviour of both *vasomotility* and *vasomotion*[25].

A biological system, as the tissue-microvessel system, so much highly evolved and well differentiated, as regards anatomy and physiology, can not react to attacks, different in origin, which involve it, by a lot of ways.

As far as tissue-microvessel unit is concerned, cells, transformed in *smooth muscle cells* and in *ramified smooth muscle cells*, when stimulated, either contract or dilate, although there is a residual possibility of further response.

On the contrary, smooth muscle cells of the media of great arteries – elastic and muscular – which are less differentiated, react to various stimuli, even, de-differentiating and, then, evolving towards cells with secretory activity (Simonescu 1990, Gimbrone 1997).

These concepts account for the reason of the restricted number of tissue-microvascular unit reactions, doctor can observe at the bed-side by biophysical semeiotics and *Clinical Microangiology*[26].

According to biophysical semeiotics, in a supine healthy subject, psycho-physically relaxed, with his (her) open eyes, aiming to inhibit melatonin secretion, digital pressure of "low-mean" intensity, applied upon the skin projection area of heart, brings about upper, middle, low-ureteral-, gastric aspecific-, caecal-, and choledocic- reflexes, i.e., upper-, mean, low-ureter as well as stomach, caecum, and choledocus dilate, the latter three after a latency time of 8 seconds.

In health, the dilation of upper and low ureteral reflexes, appears after 6 seconds and lasts for 6 seconds, while all other reflex duration is less than 4 seconds. The latter parameter value proved to be of paramount importance, from diagnostic viewpoint, informing precisely about local microvascular structures and function, as well as microvessel remodeling. In fact, such as digital pressure brings about "low-mean" stimulation of coronary trigger-points, inducing "rapidly" oscillations of upper and choledocic reflexes (small arteries, according to Hammersen) and subsequently those of lower ureteral (arterioles, nutritional capillaries), which parallell fluctuations of the related microvessel structure, according to a synergetic model (Stagnaro, 1994).

The oscillations of "upper" reflexes define the vasomotility – the general dynamics of microcirculatory vessels, while those of "lower" one express the vasomotion – capillary-venules dynamics (Figure 1).

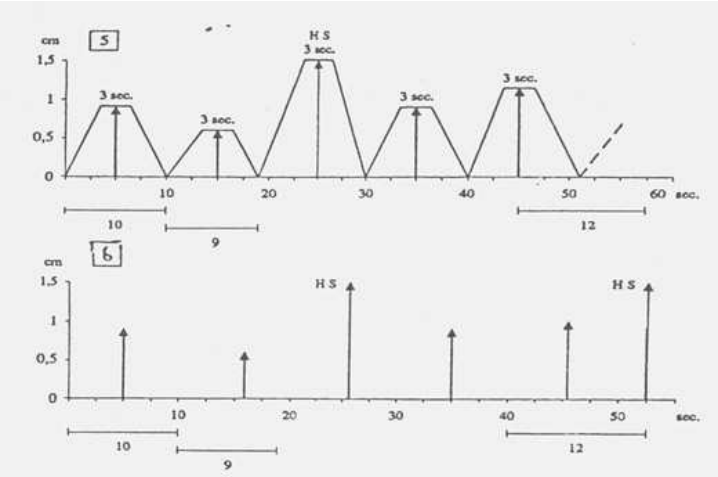


Figure 1: Physiology fluctuations of upper and lower ureteral reflexes, at rest (vasomotility and vasomotion); HS stands for Highest Spike or highest oscillation

In figure 1 we can see how are practically evaluated vasomotility and vasomotion. Drawing a Cartesian diagram, in the x-axis is represented the reflex's duration (in seconds), while in y-axis is represented the reflex's intensity (dilation of parenchyma, in cm). Interestingly, the period of oscillations is not fixed or constant: under physiological condition, it varies from 9 seconds to 12 seconds showing 6 cicles per minute. The average duration of fluctuations is 10.5, i.e., a fractal number. Furthermore, the intensity of "normal" oscillation is variable in a unpredictable manner, varying in health from 0.5 cm to 1.5 cm. Physiologically, after two normal, different in intensity, unpredictable fluctuations, we observe an highest oscillation - highest spike (HS) – that corresponds to "quantic", maximal, periodic adrenalin and nor-adrenalin discharge from autonomic nervous system endings, which occurs exactly every 25 seconds. Finally, these signs can usefully be evaluated under stress tests (Stagnaro, 1996).

Vasomotility and vasomotion of every T.M.U. physiologically show an highly complex type of variability, "constrained randomnes", reminescent of chaos (Goldberger, 1991, Murry, 1986), which may be evaluated nowadays at the bed-side with the aid of biophysical-semeiotics, as demonstrated for the the first time clinically (Stagnaro, 1994).

Biophysical-Semeiotics allows doctor to detect the chaotic behaviour of both intensity and period of ureteral (and choledocic) oscillations, i.e. vasomotility (upper ureteral reflex: small arteries) and vasomotion (low ureteral reflex: nutritional capillaries) of the microcirculatory bed of all organ and tissue, including the heart (Figure 1).

In addition, more intense stimulation provokes numerous, pressure-dependent, middle ureteral reflexes, informing respectively on different types of EBD and AVA, according to Bucciante (1949). Middle ureteral reflexes are correlated with EBD both physiological and newborn-pathological (Table 2). Furthermore, low ureteral reflex oscillations give information on nutritional capillaries. Interestingly, mean digital pressure upon Th-1 – Th-2 dermatomeres stimulates cardiac β-adreno-receptors. Physicians assess the capillary diameter as intensity of low ureteral reflex. Highest spike (HS) intensity divided for minimal oscillation gives a ratio 3/1 under physiological condition. This value is unavoidable in calculating biophysical-semeiotic fractal Dimension (fD) of microvascular deterministic chaotic systems. It is perfectly identical to the value of differential latency time of heart-aspecific gastric and –caecum-reflex, surely easier to be evaluated (table 1).

Middle ureteral reflexes

Low intense stimulation: 1 cm.; 7 sec. duration;
6 sec disappearing time. = type II EBD.

Mean-moderate intense stimulation: 1,5 cm.; 15 sec. duration;
6 sec. disappearing time = type I, A, AVA

Moderate-intense stimulation: 2 cm.; 20 sec. duration;
6 sec. disappearing time = type I normal and newborn-pathological, subtype b) EBD.

Mean intense stimulation: 1,5 cm.; 15 sec. duration;
6 sec. disappearing time = type II, AVA.

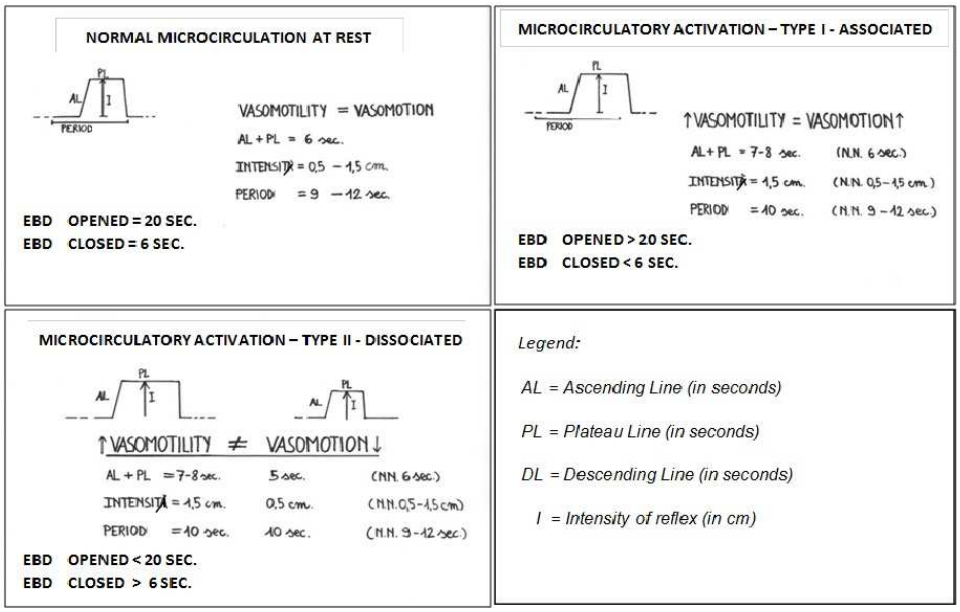
Intense stimulation: 2,5 cm.; 20 sec. duration; 6 sec.
disappearing time = type I, newborn- pathological, subtype a) EBD.

***Table 2**: parametric values of different middle ureteral reflexes as well as their significances*

Numerous conditions, physiological and pathological, bring about "rapidly" modifications of deterministic-chaotic fluctuations of the small arteries, arterioles, nutritional capillaries, post-capillaries venules, and AVA, functionally speaking, in particular EBD, ubiquitous structures, essential in causing flow-motion in the microcircle of biological systems. It is easy to understand that such microcirculatory modifications aim to adapt in a better way the biological system to new conditions. Obviously, the activation of "peripheral heart" aims to realize and maintain a sufficient flow-motion in nutritional capillaries in relation to actual functional situations of local parenchyma, whose local microcircle has to supply material-energy-information in a perfect way.

The normal microcirculation at rest can become physiologically *active* when the parenchyma starts to work. The important set of microvascular dynamic events, related to *microcirculatory activation - M.A.*, can be subdivided in three types (scheme 11):

- type I or "associated", "physiological", in which both the *vasomotility* and *vasomotion* result increased and consequently blood-flow in nutritional capillaries and post-capillary-venules is augmented, due also to right AVA reaction; (e.g. during parenchyma work);
- type II or "dissociated", "pathological", in which the *vasomotility* shows increasing of both intensity and oscillation duration, while the *vasomotion* shows a highly differentiated behaviour, in relation to the presence of microcirculatory "compensation" or "decompensation" (failure), as we will say later on. (e.g. during pathological conditions);
- type III or "intermediate", when vasomotility is activated, while vasomotion shows basal activity, and hemoderivative structures are not activated. The transition from type I to type II goes through numerous intermediate stages, which from the compensation reach the total irreversible decompensation of microcirculation, showin a large variety of different and significant forms.



Scheme 11. Vasomotility and vasomotion. Microcirculatory activation types

M.A. - type I shows the increasing of oscillation waves: the sum of AL[27] (ascending line) and PL[28] (plateau line) duration is equal to 7-8 seconds, maximal intensity (1.5 cm) as well as a period of 10 seconds. Arrows indicate the activation[29] of both vasomotility and vasomotion. Consequently, fractal dimension appears clearly reduced (scheme 11). The under curve area "shows" microvessel sagittal surface during their highest and prolonged opening phase so that, under such condition, microcirculatory blood-flow is greatest.

In healthy, who is invite, e.g., to bend and extend repeatedly homolateral foot or, more easily and refined, to "think" of perform such movements, avventitial arterial microcircle of common femoral artery moves rapidly from basal microcirculatory condition, characterized by microvessels deterministic-chaotic oscillations, revealed by upper and lower ureteral reflex fluctuations (figure 1), where fD is 3,81, to the typical type I, associated, activation, in which all fluctuations show the same, greatest, intensity (*highest spikes*) and fractal dimension lowers from 3,81 to 1,5 (figure 2).

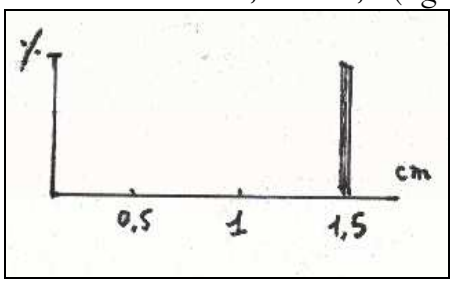


Figure 2

Figure 2 illustrates the "at far column" type of Fourier's transformation of oscillations observed in the M.A., type I, associated, in which capillary as well as arteriolar fluctuations intensity are all identical and highest, showing value of about 1,5, as conventional measure.

Among microcirculatory structures, a primary role in the microvessel blood-flow is played by Endoarterial Blocking Devices (EBD), which are largely present in human body (scheme 12).

Physiological Endoarteriolar Blocking Devices Type and Type II: location

Type I and Type II:

Skelatal Muscle, right cerebral hemisphere (individuals positive for CAEMH-alpha), etc.

Type II: really UBIQUITOUS

Brain (without CAEMH-alpha), Heart, Lung, Stomach, Duodenum, Liver, Gall-Bladder, Prostate, Womb and Ovaries, Endocrine Glands,e.g., Adrenal, Pituitary, Thyroid Glands, Diencephalic NeuroneCenters, Adipose Tissue, etc.

Scheme 12: Doctor who knows the exact location of physiological type I EBD (skeletal muscle, right emisphere of individuals CAEMH-positive, conjunctival mucosa) can recognize in easier way the type I pathological DEB, that play a pivotal role in diagnosing biophysical-semeiotic real risk of most common and serious human disorders

Both physiology and anatomy of EBD, evaluated "clinically" for the first time, play a primary and pivotal role in diagnosis and prevention of the most common and serious human diseases, including diabetes, hypertension, ATS, CVD, and cancer, permitting, for the first time "clinically", to define the link existing between *genetic* factor and *phenotype*, according to the theory of Angiobiopathy (Stagnaro, 2004).

EBD, derived from arteriolar medial layer, and located in a single point of vascular wall with two (arterioles) or more (small arteries, according to Hammersen) layers of smooth muscle cells, protruding to the lumen, show very different structure and form, under physiological and pathological conditions: small cushions with wide base, polypoid formations, generally pedunculated, sphincteric formations, intimal contractile architectures (figure 3).

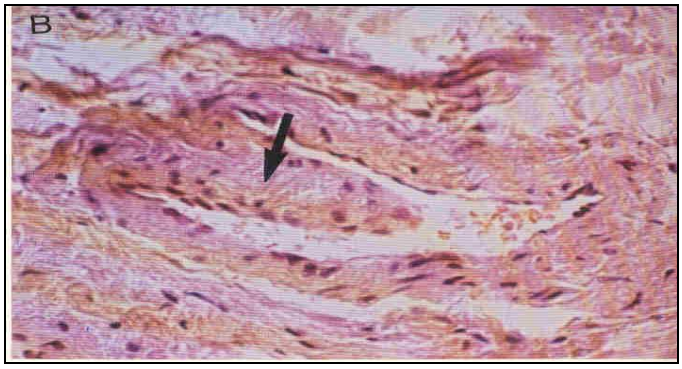


Figure 3. For kind permission of Curri S.B. (1986), the figure shows a refined imagine of EBD with a large base of the type "proboscide"

They are ubiquitous since they are located in all biological systems; more precisely speaking, only type II, normal, EBD, localized in arterioles, according to Hammersen, are ubiquitous. EBD are playing a primary role in the regulation of local microcirculatory *flow-motion*, as the following clinical evidence demonstrates: when abnormal, at least from functional biophysical-semeiotic viewpoint, EBD bring about impairment of MFR, which contribute to conditioning the "real risk" of disorders, like CAD, whose onset will possibly occur after years or decades.

EBD contraction, i.e. the contraction of its muscular cells, at the base of mean ureteral reflex (arteriolar opening), brings about blood flow increase in the capillaries, microcirculatory stasis and, then, if lasting, possible hypertensive damage of related capillary net, and subsequently dilation at first, and, thereafter, basal membrane thickening. In case of microcirculatory activation type I, associated, EBD contribute significantly to increasing matter-energy-information supply to parenchyma, according to the physiological behaviour.

During M.A, *type I, associated,* EBD are "open" mean ureteral reflex, brought about by "middle" digital pressure on the artery, lasts for > 20 seconds (NN = 20 seconds), i.e., for a time longer than that observed at baseline, and, moreover, reflex disappearing (EBD decontraction, expressed by reflex cessation from biophysical-point of view) is < 6 sec. (NN = 6 seconds). These functional "vasomotion" modifications aim to increase the blood-

flow in nutritional capillaries of arterial wall external, outward third and, consequently, to remove efficaciously H^+ as well as various catabolites.

On the contrary, M.A., type II, dissociated, in which *vasomotion* is reduced, is always associated to EBD dysfunction, indicating pathological local microcirculation: *microcirculatory bad distribution of blood flow*[30], according to S.B. Curri (1986).

In M.A., type II, dissociated, pathological, in which occurs the microcirculatory phenomenon of the so-called "blood-flow centralization", due to the greater opening of AVA, and subsequent removal of capillary blood, we observe an insufficient blood-flow to parenchyma, that flows mostly in AVA, shunting therefore it away from parenchymal cells.

For instance, in case of chronic arteriopathy, arteriosclerotic as well as of other origin, it is present the *dissociated type of activation*, which brings about tissue acidosis, recognized at the bed-side by caecal, gastric aspecific and upper ureteral reflexes.

At this points we must remember M.A., type III, intermediate, incomplete (zero Stage or Pre-Metabolic Stage), in which it is present the initial abnormality of AVA dynamics (AVA, functionally speaking), while is carryed out the activation of both *vasomotility* and *vasomotion,* the later, however, subsequently shows a reduced fuction: AL + PL from 7 seconds lowers to 6 seconds and ultimately to 5 seconds exclusively in the *vasomotion*. Such interesting avventitial microcirculatory situation indicates the "initial" asymptomatic stage of arteriopathy, e.g., arteriosclerotic in origin.

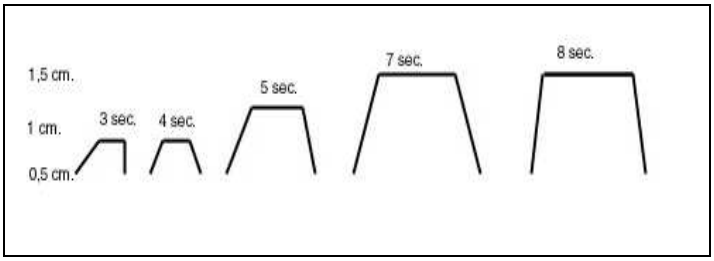


Figure 4

Figure 4 shows, from left to right, initial "morphological" modifications of microvessels fluctuation wave during physiological microcirculatory activation, which aim to increase both intensity and duration of waves themselves. Microvessel fluctuations, in the known manner, are assessed as oscillations of upper (vasomotility) and lower (vasomotion) ureteral reflex. Starting from the initial phase: firstly increases exclusively the PL duration, while oscillation height lasts unchanged; successively, we observe the increased intensity of the wave and PL shows the greatest duration. Wave carrying out occurs rapidly, indicating a higher speed of microvessel opening. In assessing tissue-microvascular unit activation, basal *vasomotility* as well as *vasomotion* show the typical physiological deterministic-chaotic behaviour.

At the end of the third stimulation, we observe microcirculatory activation, type I, associated: AL + PL of the fluctuations of III upper (*vasomotility*) and of third lower (*vasomotion*) ureter persist for 7-8 seconds (NN = 6 seconds). It is necessary to estimate together, as an identical parameter, AL + PL, wich indicate the velocity, intensity and

duration of arterioles and, respectively capillaries and post-capillaries venules opening, according to a synergistic model.

In fact, the transition from the rest state to the activation occurs by degrees: firstly PL increases (3 sec.→ 5 → 6 sec. → 7 sec. → 8 sec.), whereas intensity and height of oscillation wave remain the same. Subsequently, all fluctuations become highest spikes (HS), aiming to supply gradually a greater flow-motion (figure 4).

In this "synergetic" and "fractal" model of *microcirculatory activation*, microvessels open more quickly, more intensively and for a longer time, bringing about a greater blood-flow, while in initial stage the increase of necessary blood supply is carried out by the prolonged PL at the detriment of AL (AL + PL, 6 seconds), in presence of a higher velocity of "systo-diastolic" microvascular performance with unchanged oscillation intensity. In a second moment, when *flow-motion*, already increased by the above referred way, appears to be insufficient, facing parenchymal demands, in case of impairement of macrovascular blood supply, microvascular opening degree increases, i.e., microvessel diameter, and ultimately AL + PL duration (≥ 8 seconds) reaches maximum values to maintain a sufficient supply of material-energy-information to the related parenchyma.

Therefore, we observe a refined vasomotor fulfilment, perfectly programmed and skilfully carried out, that needs physiological free energy level within the local smooth muscle cells, terminal component of a complex chain reaction.

Resuming, the "peripheral heart" answers to an increased request of the related parenchyma and/or reacts to the lowering blood supply, cause by cardiac, vascular, blood disorders, initially by a rapid dilation of its "pump-structures", i.e., small arteries and arterioles, as well as by a prolonged opening duration, but without any modification of vessel diameters. If all these microvascular reactions are not able to meet the reduce macrovascular blood-supply, it is increased also the intensity of microvessels "dilation" in the region of sphygmicity and the duration of oscillation becomes greatest. Under such conditions of "physiological" tissue hyperactivity, in the initial phases is increased also the duration of maximal dilation or *smooth muscle cells relaxation* (about 9 seconds), that preceds the strongest contraction. Normal non-linear behaviour of microvessel fluctuations proves to be an event that aims to a possible adaptation in face at modified tissue demands.

From the above-referred remarks *M.A.*, type I, associated, physiological, event secondary to the increased demand of blood supply from the related tissue in a stage of activity greater than normal, indicates an emergency or stress situation, as regards the biological system in a precise moment.

Symptomless obstruction of a large arterial vessel (50%), for example, represents an *emergency* situation as far as biological system downstream is concerned, even at rest, which worsens obviously during physical activity, also slight.

In practice, such as condition influences favourably both the diagnosis and the prevention. For instance, in a patient "at rest", involved by "silent coronary artery disease", who does not present any clinical phenomenology, the "light" digital pressure, applied on cutaneous projection area of right or left ventricle, allows doctor to recognize the

microcirculatory activation, type I, associated, by ureteral reflexes evaluation (table 2), indicating the symptomless coronary pathological condition.

By contrast, in healthy subjects at rest, coronary "vasomotion" shows the typical deterministic-chaotic behaviour, geometrically represented by the type "at saddle" of biophysical semeiotic Fourier's transformation (figure 4, at left).

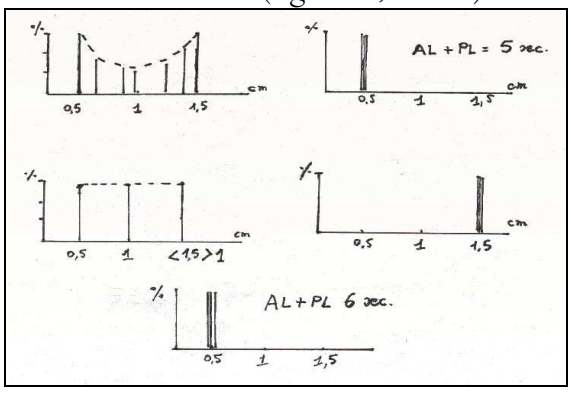


Figure 5

The vasomotion's fluctuations, grouped in relation to their intensity in Cartesian axes system, on the ordinate the percentage and on the abscissa microvessel fluctuations intensity, are geometrically represented as "saddle type", i.e.,all fluctuation types are present. At rest, all fluctuations show the typical deterministic-chaotic behaviour, geometrically expressed as "saddle type" in Fourier's biophysical-semeiotic transformation (figure 5).

Among numerous and different clinical-microangiological tools, a primary role is played by biophisical-semeiotic diagrams, "microvascular" as well as "macrovascular", which can be subdivided in five groups:

1) tissue-microvascular unit (T.M.U.) diagram;
2) lymphatic diagram;
3) venous diagram;
4) arterial diagram;
5) various biological systems diagram: cardiogram, renogram, pancreogramm, hepatogram, surrenogram, a.s.o.

Interpreting correctly and utilizing properly *the ureteral reflexes*, it is possible to transform in a "geometrical" way the deterministic-chaotic activity of microcircle of all biological systems, under both physiological and pathological situations, giving, thus, an innovative way to "clinical" investigation of T.M.U. structure and function, and consequently of related parenchyma. Beside this biophysical-semeiotic method, there are a large variety of bed-side assessments of blood circulation in peripheral arterial vessels, more difficult to perform, but really refined.

For instance, the evaluation of the microcirculation in the pulps of toes is done as follows: in healthy, in supine position and psycho-physically relaxed (with open eyes), digital pressur of "light-moderate" intensity, applied upon the pulp of a toe, brings about gastric aspecific reflex lasting for 6 seconds, after a Lt of 6 seconds, intensity about 1 cm, and three subsequent re-enhancements, followed by tonic Gastric Contraction (CGt).

Soon after the rapid interruption of the stimulation, after only 2 seconds the stomach reaches the basal volume and subsequently appears a small gastric aspecific reflex, Z wave, indicating elasticity of microvessels wall, as shown in *T.M.U. diagram* (figure 6).

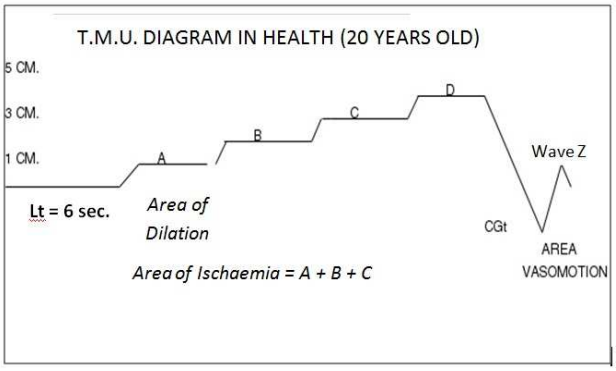


Figure 6

One more examples of byophisical semeiotic diagrams is given by figure 7, which shows the *arterial diagram* in healthy (continuous line) and in case of AOPA (Arteriosclerotic Obliterating Peripheral Arterial disease), where there is lower Lt as well as diagram "verticalization" with shifting to the left of critical point - CP (CP must be always equal to 5 cm on the y-axis), rapid CGt and the absence of Z wave. Interestingly, phase E is clearly compromised: soon after rapid interruption of arterial occlusion, stomach return physiologically to its basal value, and then appears a small gastric aspecific reflex (E), which indicates normal elaticity of arterial wall.

The phenomenon of *microvascular diagram verticalization with shift*

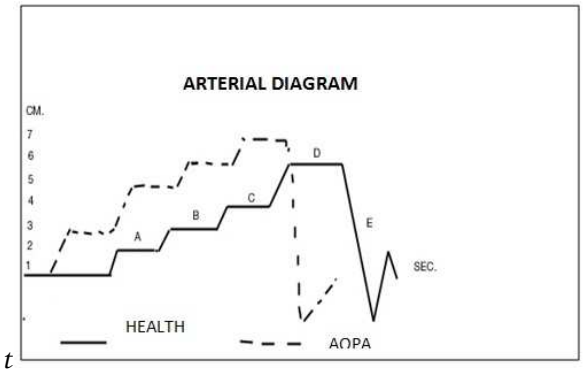


Figure 7

o left, indicating always a pathological event, shows a "general", "aspecific" tissue disorder.

In practice, the reflex disappearing velocity as well as the velocity of CGt appearing, are really useful, giving a lot information, because they are related to the highest tissue acidosis: in healthy, gastric aspecific reflex disappearing velocity and CGt appearing are slower. Furthermore, a Lt shorter than normal denotes a pathological state, while the possible last gastric aspecific reflex (as well as cholecyst-choledocus and ureteral reflexes), ***Z** wave***,** shows physiological microvessel elasticity.

E Phase – correlates with post-ischaemic reactive hyperaemia – corresponds to the *Area of Vasomotion (AV)*, so called because the presence of ***Z** wave* is expression of normal microvascular elasticity or, better, venular-capillary physiological elasticity, as well as of normal blood-flow in T.M.U., as shown by local *vasomotility and vasomotion,* Lt of caecal reflex, a. s. o., while the rapid CGt disappearance (NN = **2 sec**.) indicates normal, efficacious post-ischaemic reactive hyperaemia, physiological pH recovery[31].

In conclusion, this analysis, brief but certainly ehaustive, of haemodynamic-haemorrheological and biochemical-metabolic significances of the various parameters of tissue-microvascular unit (1, 2, 3), shows the importance and diagnostic value of diagram.

Diagram *verticalization with shifting to left* (of CP) and the *absence* of **Z wave**, always correlated, indicate without any doubt histangium damage, i.e. lacking endocellular free energy of local histangium, as regard molecular-biological situation (ATP reduction).

Myocardial preconditioning and EBD

In healthy individuals – in supine position – digital pressure of mean intensity, applied on cutaneous heart projection area, brings about heart gastric aspecific reflex[32] (H.G.A.R.) after a latency time (Lt) of 8 seconds. H.G.A.R. lasts less than 4 sec., soon thereafter disappears for 3-4 seconds. Disappearing time corresponds to *fractal dimension – fD* (scheme 7). Afterwards, a second reflex occurs. The duration of H.G.A.R. unfolds the microcirculatory functional reserve (MFR) activity of related coronary microvessel, thus correlated with the function and anathomy of the microcirculatory bed, or microvascular tissular-unit - M.T.U.

At this point of investigation, the physician quickly interrupts the digital pressure for a length of exactly 5 seconds. Than, Lt and H.G.A.R. are evaluated again: Lt raises to 16 seconds, H.G.A.R. lasts less than 4 seconds, disappearing after roughly 4 seconds: these values evidence a *physiological preconditioning*.

In summary, physiological Lt of H.G.A.R. is 8 seconds at the first evaluation (*basal-line value*), but increases clearly in the second (is double) as well as in the third one, due to the physiological activation of MFR.

In individuals at risk of CAD, Lt at *base-line* is physiological during the first evaluation (8 seconds). However, H.G.A.R. lasts 4 sec. or more and disappears for less than 3 seconds: lowering of fractal dimension[33]. Moreover, preconditioning results "pathological", as Lt is less then 16 seconds: these values evidence a *pathological preconditioning*.

Interestingly, in patients with coronary heart disorder, even clinically silent, the *basal value* of latency time of gastric aspecific reflex appears to be less than 7 seconds at first evaluation and becomes lower in the second one, in relation to the seriousness of underlaying disorder.

Another note-worthy preconditioning permits to discover subjects at "real" risk of artheriosclerosis, as well as artheriosclerotic patients, even clinically silent: digital pressure of mean intensity, applied upon femoral (or other) artery of healthy individuals provokes

gastric aspecific reflex, after a latency time of 8 sec. or more, that increases in successive evaluations as far as 12 sec.: *physiological preconditioning*. On the contrary, in subjects, even apparently healthy, but at risk of, or already involved by ATS, *preconditioning* results *pathological*, in relation to the degree of disorder or of its risk.

The above-described biophysiological semeiotic method is proper for clinical preconditioning of almost every organs, it is proved to be useful and suitable for mass preventing or detecting ischaemic heart disease, kidney disorders (including future stones), artheriosclerosis, even clinically silent, arterial hypertension, diabetes mellitus, and so on.

In healthy the *preconditioning* brings about, as natural consequence, an optimal tissue supply of material-information-energy, by increasing local *flow-motion as well as flux-motion* - preconditioning, type I. On the contrary, if real risk is present, *preconditioning* data are almost the same as the basal ones, but Lt is a little shorter than physiological one - preconditioning, type II. Finally, in overt disease, *preconditioning* shows an altered and shorter Lt of reflex in relation to seriousness of underlying disorders - preconditioning, type III (table 1).

At this point, we come back to the former example: in the initial phase of coronary heart disease, which evolves very slowly toward successive phases, "basal" biophysical-semeiotic data can "apparently" result normal. However, under careful observation, the duration of H.G.A.R. is equal or more than 4 seconds (NN < 4 seconds), indicating a local microcirculatory disorder.

Really, in these conditions, EBD function is clearly compromised, but for some time the increased *vasomotility* counterbalances efficaciously the impaired supply of normal blood amount to parenchyma: also the *vasomotion*, at rest, shows parameter values oscillating in physiological ranges, due to the augmented arteriolar sphygmicity; such a condition can be "technically" defined *peripheral heart compensation*.

Noteworthy, from the diagnostic point of view, are also the cardio-caecal and - gastric aspecific reflexes, when accurately assessed: after a Lt still normal (8 seconds), doctor observes a reflexes duration, before the successive one initiates, of 4 seconds (NN < 4 seconds), and a differential Lt (fD or duration of reflex disappearing before the beginning of the following) of just 3 seconds (3 < NN < 4).

Clinical recognizing of these "slight" abnormalities, really useful in diagnosing initial and/or symptomless disorders, altough not difficult to perform, requests a good knowledge, a steady experience and a precise performance of the new semeiotics.

In these cases, *preconditioning* allows in simple and reliable manner to recognize the pathological modifications, mentioned above, which indicate the altered physiological adaptability, even initial or slight, of the biologial system to changed conditons as well as to increased tissue demands. The various parameters of caecal, gastric aspecific and choledocic reflex, type of activation and, then, EBD function, related to a defined biological system, parallel and are consistent with the data of *preconditioning*.

CAD and silent ischaemia: prevention and therapy

It is well known for many years that patients with coronary heart disease may have no symptoms, and that the electocardiographic feature of ischaemia may be induced by exercise without accompanying angina. Neverthless, such "silent ischaemia" has only recently been recognized to be an important feature of ischaemic heart disease. The silent ischaemia prevalence is unknown, although over a quarter of myocardial infarctions are unrecognized and half of them cause no symptoms at all. According to Cohn, there are three categories of people with silent ischaemia, who may be at such risk. People of type 1° have no symptoms and no history of myocardial infarction or angina; those of type 2° are symptomless survivors of myocardial infarction; finally, patients of type 3° have angina together with episodes of silent ischaemia, whose mechanisms in most cases are obscure.

Clinical and experimental data suggested by biophysical-semeiotic methods and applications, are reliable, helpful, and then advisable in bed-side detecting individuals, even asymptomatic, who have to undergo, promptly and rationally, whatever stress testing, such as electrocardiographic exercise test, atrial pacing, thallium stress redistribution scintigraphy, exercise radionuclide ventriculography, spiral CT, a.s.o., during which silent ischaemia usually may be elicited, corroborating bedside diagnosis. Furthermore, the clinical, biophysical-semeiotic selection of symptomless patients is interesting, because it can be applied on very large scale, helping doctors in actively searching for ischaemic heart disease, particularly serious when silent, from the clinical viewpoint. As a matter of facts, a lot of data suggest that episodic silent ischaemia carries a poor prognosis in stable CAD.

Given the accumulating evidence that ischaemia, whether silent or not, carries a poor prognosis in patients with known CAD, it is justified to follow an active policy even in patients who are totally free of symptoms. Essentially, the rationale for the use of histangioprotective drugs (like L-Carnitine, Co Q10, Coniugated-Melatonine, a.s.o.) in patients with ischaemic heart disease clinically silent, relates three primises: the favourable effects of these products on lipid and glucose metabolism, the positive influence of these drugs on angina pectoris as well as on myocardial ischaemic preconditioning, because they improve blood flow in cardiac tissue microcirculatory units, and the improvement of coronary microcirculatory remodelling, e.g., lowering the number of newborn-pathological type I, subtype b) EBD, when histangioprotective drugs are utilized in early stage, in fact the intensity of specific middle ureteral reflex significantly decreases under such treatment.

Practically, in order to ascertain clinically silent ischaemia it is advisable to assess shape and intensity of low ureteral reflex oscillations, i.e. vasomotion, as illustrated above (figure 1), which permits doctor to calculate the fractal dimension of myocardial microvessels deterministic chaos ($3 < NN < 4$; ratio HS/Minimal oscillation, $fD = 3$), corresponding perfectly to the differential Lt of H.G.A.R., as well as the duration of this reflex ($NN < 4$ seconds) easily assessable (table 1).

As far as myocardial ischaemic preconditioning is concerned, it is sufficient and hence advisable in day-to-day practice to assess the Lt of the second H.G.A.R., i.e., in the

second evaluation, performed exactly after a pause of 5 seconds from the end of the basal evaluation: in health, latency time raises in a significant manner from 8 seconds (basal value) to 16 seconds, i. e., to doubly value.

Another refined, elegant method proved to be reliable, is the assessment of shortening of left ventricle enlargement duration during the above described test (5 < NN < 7) and/or conversely the prolonged Lt from 3 seconds to 5 seconds or more, preceding another ventricle dilation. This latter evaluation, however, may be a little more difficult to ascertain by doctors not experienced and skilled in the field of the original semeiotics.

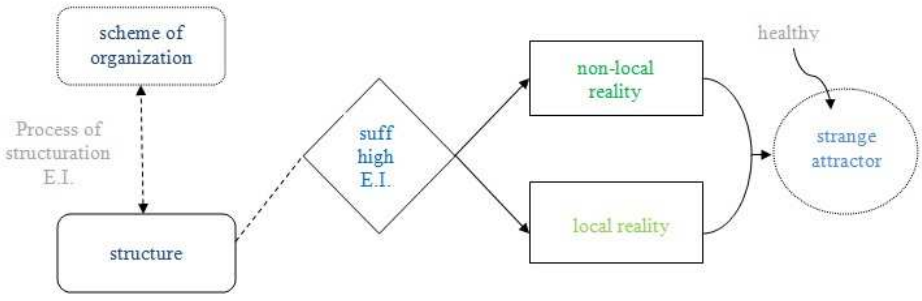
From the practical viewpoint, both duration (NN < 4 seconds) and differential Lt, i.e., disappearing time (3< NN < 4), of cardiac-caecum and/or -aspecific gastric reflex, i.e. fD, gives exhaustive information about coronary vessels morphological and structural situation, according to Angiobiopathy theory (Stagnaro, 2004).

Actually, important data are easily obtained also by means of the Lt of heart-caecum and/or -aspecific gastric reflex, which informes about myocardial oxygen supply: in health, during digital "mean" pressure upon cutaneous projection area of the heart, basal Lt value is 8 seconds. However, doctor must remember that in case of CAD "real risk" and CAD initial stage, such as parameter value is still normal (8 seconds), but reflex lasts 4 seconds or more (NN < 4 sec.), indicating coronary pathological condition.

Furthermore, in health, during "intense" digital pressure upon cutaneous projection area of the heart, as above described, and immediately after about 7 seconds apnea test or Valsalva's manoeuvre, the basal Lt of H.G.A.R., (basal value is equal to 8 seconds) raises significantly to 16 seconds, giving a *negative Caotino sign* (scheme 6), as well as after preconditioning, i.e., doubly value (table 1), showing a physiological coronary artery dilation and consequently normal endothelial function, physiological MFR, type I, physiological Preconditioning, and absence of newborn-pathological, type I subtype b) EBD (table 1).

In conclusion, in a long, well-established, clinical experience, the above-described biophysical-semeiotic methods proved to be reliable, easy to performe on very large scale, useful, and suitable for detecting ischaemic coronary disease, even clinically silent or really initial, i.e. since inherited real risk of CAD.

In absence of inherited real risk of CAD (scheme 13), all CAD risks factors will be mere spectators, because that person will never be affected by ischemic heart disease or myocardial infarction: pathologies and chronicity of this kind will never happen.



Scheme 13. Autopoiesis and Energy Information in absence of Inherited Real Risk of CAD

Scheme 13 shows that in human bodies there is physiologically the healthy co-existence of two different realities: local reality and non-local reality. The nonlocality disappears if the mitochondrial respiratory activity - and consequently EI – significatively decrease. For example Lory's experiment (Stagnaro 2008) fails, if is applied a stimulation in a subject following the apnea test, with the result of an impaired mitochondrial activity. The compensation takes place because of nuisances involving dissipative structural changes, but always subject to the power system's inherent conservative autopoietic organization.

The congenital biophysical-semeiotics Real Risk (RR) arises at an intermediate stage between the scheme of organization and the structure, a first structuration from the scheme (not observable) on which we can identify it (in case there was) using simple clinical tests at bedside, in a vision in which if there were RR, it would be able to tend to a pathology (potential disease), a pathology which, if occurred, would amount to a fully structuration of the scheme of organization (e.g., genetic alteration of mit-DNA) to disease. RR, if pathologically evolving, is the slow eventing of disease events. Also considered in itself, whether static, is a manifestation of the structuring process of the organization. The process is reversible in the sense that through histangioprotective drugs like L-Carnitine, Co Q10 and melatonin-conjugated[34], application of energy (e.g., NIR-LED), proper diet understood in the etymological sense, etc. the RR can become "residual", so that will not disappear nor will evolve towards the structure.

The principle of the process is the Energy-Information - EI - catalytical nature, according to Manzelli. The level of Vibrational-Energy - EV, energy related to energy-information - EI - from the perspective of semiotics biophysics is measured on the level of tissue oxygenation: namely the Lt of reflex. Indeed, stimulating the trigger - points to a biological system, such as the liver, "simultaneously" there is built up a simpatic hypertonicity after a latency dependent on the intensity of the stimulus - related to the intensity of liberation in the biological system of adrenaline and nor-adrenaline - we observe the nonspecific gastric reflection - stomach swells - "simultaneously" to reach the critical level of low energy or low oxygen.

Under these conditions, in fact the biological system has become thermodynamically isolated. We are in this case, in the non-local reality: there is simultaneity and synchronicity. On a completely healthy human being (without RR) EI is in fact high enough, and then there is simultaneity of information. Local and non-local reality co-exist, exist simultaneously but in parallel, they do not overlap. When EI decreases, EM –Energy Matter – as a consequence increases, and whether EI falls below a certain threshold, non-local reality "disappears" and we can observe just local reality. In summary, if there is enough high EI, there is not RR, while if there is low EI, non-transitory and not occasional - low EI in transient form, for instance, is with the apnea test in individuals completely healthy without RR – since permanent, then there is inherited RR of CAD (associated, e.g., with arteriosclerotic constitution).

The production of EI may be endogenous - it is created endogenously in humans through a transformation of breath in subtle and vital energy, and through mitochondrial activity - or

exogenous - through the release of substances like melatonin, the adoption of a appropriate diet, NIR-LED (near infrared light) – that stimulate the mitochondrial respiratory function[35], ie oxidative phosphorylation.

The endogenous EI born and is formed in the mitochondria, the power plant of human body. The autopoietic system self-produces EI, by transforming EM - Energy Matter - including food, water and O_2 - which is converted into EV-EI. Endogenously we produce ourselves the EV-EI indirectly with the breath, in the sense that vital energy is a subtle energy that occurs through breathing (it is not air, it is not breath, but it travels and is created together with it).

Exogenously the EI is created by chemical transformations and biological properties of certain food we eat or through the release of specific substances (eg melatonin conjugated) or certain stimuli (eg NIR-LEDs) to improve the mitochondrial respiration.

In biological systems the Energy-Information can be transmitted chemically - through metabolic processes - and / or electrically - with the neurotransmitters - peptides. The peptides can be imagined as "antenna", which carry information (waves) non-locally, simultaneously and synchronously by resonance (in case of non-local reality with high EI), or locally in space-time.

In biological systems the EI is transmitted through the classic routes in the local reality, using substrates that reach the target tissue via blood, lymphatic, venous (hormones, cytokines, etc.) or through the nerve pathways (neurotransmitters) characterized by polarization - depolarisation: there is time and energy consumption (if I move a substance from A to B, there is energy and time). On the contrary, in non-local reality pure and catalytic EI acts according to what is known in the microscopic world, expression of entanglement, observable with the semiotics biophysics, of both worlds. DNA, like an antenna, simultaneously to "intense" stimulation on certain trigger - points, begins to "vibrate" catalyzing the reactions without energy expenditure, between the compound A and B, with production of C! For example: abdominal lateral pinch of fat "simultaneously" active function of liver PPAR (the mill that burns fat and glucose) revealed by the "simultaneous" local microcirculatory activation[36].

There is a continuous structural coupling bodies-environment in all directions. If there is a tendency to disease (RR), the complex dynamics in biological system decreases: there is no chaos or lesser according to the fractal dimension (fD-fractal dimension), detectable through the reflex-diagnostic-percussio-auscultatory, with the simple use of the stethoscope, measuring the latency and duration of reflex. The absence of the strange attractor or of deterministic chaos, is signal of low EI, the entropy is tending to zero, then in this case there is a local reality of information transmission – there is not the non-local reality. We must therefore enter EI (or create the conditions to increase it) in order to restore a sufficiently high level of EI.

In accordance to angiobiopathy, improving mitochondrial activity in the parenchyma and in microvessel cells is involved favorably intracellular free energy and are improved various biological activities: the microcirculation will be normalized. Semeiotics Biophysics allows accurate and direct study of being and functioning of microvessels and only indirectly of the related parenchyma[37]. If it improves the way of being and

functioning of the microcirculation does mean that it also improved the way of being and functioning of its parenchyma. This is done by stimulating the activity of mitochondria by acting on the vehicles that transmit EI: metabolism (chemical process), peptides' net (electric-electronic process), but also improving, normalizing tissue oxygenation, expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy is the "sine qua non" of more frequent and severe human disease and not.

Exogenous prevention and therapy (with environmental action) is done directly on EI – and related EV – at chemical level: proper diet, conjugated melatonin, NIR-LED, or at electric level: such as acupuncture, which also acts on neurotransmitters or peptides. Endogenous prevention and therapy (autopoetic) can be implemented for example through: improving the quality of breath, improvement of lifestyles and rhythm styles and slow pace of the same (eg eating serene, calmly, as appropriate as possible) choice of appropriate physical activities (exercise, sports), yoga, meditation, prayer.

We are a continium of biological systems that interpenetrate and interact each other, and that in health conditions show a chaotic behavior (measured by the fractal dimension).

Fractal Dimension fD	**Equilibria**	**State of health**
$fD = 1$	fix point	chronicity – chronic and acute pathology
$1 < fD < 1.9$	limit cycle tending to fix point	pathology – tendency to chronicty State of variable severity of disease evolution
$1.9 \leq fD < 3$	limit cycle	initial implementation of the tendency to disease /potential pathology- i.e. inherited Real Risk of CAD associated with arteriosclerotic consitution – initial evolution to disease
$3 \leq fD < 3.81$	limit cycle tending to strange attractor	tendency to physiologic condition (only potential phase)
$fD \geq 3.81$	strange or chaotic attractor	Physiologic condition – healthy state

Table 3. fD and equilibria in biological systems

Table 3 shows as fD is a suitable marker to reveal the health of biological system. Followed this approach, deterministic chaos appears to be a source of health life. If chaos is not (or is missing) we should create the conditions for it emerges again. Chaos in biology is linked to life: whether is missing and at the same time we can not restore it, is the end. For example, through the use of melatonin conjugated, the energy level raises and then

EV-EI increase fostering and perpetuating the non-local reality parallel to local reality. If there were only local reality (which denotes a tendency to disease or pathology or potential disease) it would then need to return to a more complex order (chaotic attractor), but only if there is deterministic chaos arising from well-functioning mitochondria.

4. Conclusions

This article highlights the central role of mit-DNA in the process that underlies the ischemia of myocardial cells. Mitochondrial function in coronary artery diseases explains why CAD is a growing epidemic. Without enough energy, EI - Energy Information - associated with EV - Vibratonal Energy - originated by EM - Energy Matter (i.e., glucose, aminoacids, fats, etc.), the cell can not perform its normal functions. Under these conditions, therefore, the diseases arise under the action of the many negative environmental and acquired risk factors, which are not, however, to define the causes of diseases such as diabetes and cancer, since merely facilitators only for those at risk! In fact, in absence of inherited Real Risk of CAD, based on CAEMH mitochondrial cytopathy, all factors achieved are innocent bystanders (Stagnaro, 2009b).

In conclusion, the doctor is now in a position to evaluate with a simple stethoscope the way of being and functioning of mitochondria, in any biological system of his patients, so that can provide appropriate, targeted and effective prevention and treatments.

For this purpose, the new discipline of chaos theory with its invariant statistic measures, such as entropy and fractal dimension, plays a key role, both from theoretical and practical point of view. Today, the deterministic chaos emerges everywhere: in quantum physics, chemistry, biology, genetics, neuroscience, cognitive psychology, economics, art, cryptography, meteorology, even in the stock exchange.

This article celebrates the importance of complexity theory in medicine, following a multidisciplinary approach where biology and quantum physics, chemistry and modern genetics, mathematics and genomics, are walking softly in harmony, penetrating each other, on its wake and assistancy.

"In the human body and animal there is deterministic chaos that is not disorder, but a higher order type in physiology. Only in the pathology there is a lower order: the measure of the first order is an equilibria called strange attractor, while the measure of the second one is called fixed point.

In case of fixed point equilibria the biological systems are linear, but when sufficient energy is introduced in them and they are properly stimulated, they show the characteristic behavior of non-linear dynamical systems far from equilibrium (dissipative). Chaos requires enough energy to activate dissipative mechanisms, and life is the trajectory of an attractor: from strange attractor to fixed point, passing through the limit cycle.

The main task of the doctor is to recognize promptly the various moments of the trajectory of the patient's life (in all and each of its biological systems), to intervene rapidly with appropriate therapy, useful and effective to reverse the dangerous direction of the trajectory toward irreversibility."
Sergio Stagnaro

An example of this with incontrovertible evidence of the presence of deterministic chaos in the human body is given by clinical microangiology[38], where the universal constant of Feigenbaum (mark of chaos, comparable in importance to the greek pi, the golden section and the number e of Euler) always emerges as a relationship between Lt and fD - fractal dimension[39] (i.e., gastric aspecific reflex) in healthy subjects, while in the disease this measure disappears.

This article is a hymn to life and celebrates the extraordinary work of Stagnaro, who like Poincaré and Lorenz, can not even begin to imagine today what will happen in the wake of the immeasurable quality of this initial condition: the chaos as the life is inherently unpredictable, full of beauty, harmony and charm. The deterministic chaos is linked to life! If all this were to fail, as when the sublime energy of love tends to fade, we would inevitably encounter different equlibria of lower order – pathologies, diseases, chronic or heat death, in biology.

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Endnote

[1] NHS stands for National Health Service

[2] Myocardial infarction means that the tissue has undergone irreversible death due to lack of sufficient oxygen-rich blood. An individual may develop a rupture of an atheromatous plaque at *any* stage of the spectrum of coronary artery disease. The acute rupture of a plaque may lead to an acute myocardial infarction (heart attack).

[3] Myocardial ischemia means that the amount of blood supplied to the tissue is inadequate to supply the needs of the tissue. When the myocardium becomes ischemic, it does not function optimally. When large areas of the myocardium becomes ischemic, there can be impairment in the relaxation and contraction of the myocardium. If the blood flow to the tissue is improved, myocardial ischemia can be reversed.

[4] Cell starvation secondary to a lack of oxygen

[5] The term "microvascular" refers to very small blood vessels and, in this case, very small arteries (arterioles, capillaries) of the heart.

[6] Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes. It is also known as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome. The pre-metabolic syndrome, as defined by Stagnaro, is the syndrome that precedes the metabolic one, and is linked with congenital real risks and their associated biophysical semiotics constitutions.

[7] Mendel (1822-1884), studying the behavior of chromosomes in the nucleus, showed that the hereditary characters are transmitted as a unit. Chromosomes are located in individual hereditary characteristics of these units, then called genes. The transmission of characteristics from parents to offspring is called heredity: the majority of such characters of an organism passes from parents to children when organisms reproduce. But he had no knowledge of the existence of mitochondria described by Altmann in 1894 and rediscovered by Benda in 1897, who baptized them with their current name.

[8] The human mitochondrial DNA is inherited by matrilineal (not Mendelian inheritance) as during the process of fertilization of sperm mitochondria are marked with ubiquitin, a protein that binds to other proteins to be degraded. As a result, the mitochondrial genome of the offspring will be almost equal to the mother (subject to possible mutations) and also if the mother is suffering from a mitochondrial disease transmission, then all children inherit. In literature there are very few reported cases in which the mitochondrial DNA seems to derive from the father or both parents.

[9] The Royal Society, London, 1986

[10] Lyapunov Characteristic Exponents – LCE – is a statistic measure to test the presence of 'sensitive dependence on initial conditions' – SDIC – in a system. SDIC is at the root of the 'disorderly' behavior of deterministic dynamical systems and is responsible for their random appearance and unpredictability.

[11] Fractal dimension is a measure of the way orbits fill the phase space under the action of a flow or a map, suitable for fractal objects, characterized by a non-integer dimension.

[12] Entropy is a measure of the uncertainty in deterministic dynamical systems, or equivalently is the amount of information we get on the average by making an observation. In particular, the presence of positive entropy indicates that the observation of the system continues to generate information for an arbitrary long interval of time. Consequently, unless the position of the system can be observed with

absolute precision, there will forever remain uncertainty about its future course, even when the dynamical rule governing the system is known with precision. Zero entropy is interpreted as absence of chaotic or complex behavior, typical of linear or periodic systems with fixed point or limit cycle equilibrium, so that they are fully and exactly predictable: none new quality information emerges for an arbitrary long interval of time.

[13] The particle paths fluctuate chaotically, so that causal interpretation is not strictly deterministic as in Newton physics: unpredictability and uncertainty are intrinsic property of the deterministic dynamical systems observed, as in chaos theory, and not random or casual like in classical interpretation of N. Bohr.

[14] This electron turns out not to be a simple structureless particle but a highly complex entity that is effected by the quantum potential – QP - in a extremely subtle way. Indeed QP is responsible for some novel and highly striking features which imply qualitative new properties of matter that are not contained within the conventional quantum theory.

[15] Unlike the particles of Newtonian physics, the electron is never separated from a certain quantum field which fundamentally affects it, and exhibits certain novel features. This quantum field satisfies Schrödinger's equation, it is therefore causally determined.

[16] The form of QP can dominate behavior: information contained within QP will determine the outcome of a quantum process. There is an active information, a form having very little energy enters into and directs a much greater energy. There is an energy form acting to inform.

[17] Information, from the latinum verb 'in-formare', which means 'to give a form' is a truly more primitive fundamental activity than energy and matter, is something that precedes every physical form (Aristotele). Information's action is therefore related to the potential codification plan of producing an objective form and in turn we can perceive an object as form's of information transmission.

[18] Biophysical semeiotic constitutions, detectable since birth, are the inherited congenital ground or terrain of well defined potential diseases clinically hidden, which can last several years before appearing, in the slow transformation process from potential (pre-metabolic syndrome, pre-clinical stages) to effective pathology (metabolic syndrome)

[19] Real Risk – RR - means any mutation, limited at level of cells belonging to a well-defined biological system - for example, beta cells of islets of Langerhans, for diabetes - which occurs in one or more cells when energy information EI (and ATP) decreases strongly for any reason.

[20] In the lining of the arteries (endothelial cells) and the smooth muscle cells in the walls of the arteries. The endothelial dysfunction is likely to be multifactorial in these patients and it is conceivable that risk factors such as hypertension, hypercholesterolemia, diabetes mellitus and smoking can contribute to its development.

[21] See http://www.semeioticabiofisica.it/microangiologia/common_eng.htm

[22] The parenchyma is a characteristic substance of the bodies such as the liver and the lung parenchyma.

[23] See Microangiology in http://www.semeioticabiofisica.it

[24] The *synergetics* enables us to study the relation between microscopic level and the macroscopic one, with the principle of "self-organization". This is possible exclusively if, at microscopic level, complex system can modify in qualitative manner; let's think about the fluids in Bènard's cells and the laser. Technically speaking, we define "order parameters" macroscopic observables, which describe the macroscopic behaviour of a system, and "enslavement principle" the behaviour of microscopic elements, according to which it becomes defined when originate "macroscopic observables".
The laser gives us the best example, that illustrates the general rule: the casual emission of waves, under a defined current supply, becomes coherent; when it is excedeed, however, the emission moves toward a deterministic chaotic behaviour. The synergetycs, therefore, studies the characteristics of "complex" systems, without considering the nature of their elements, outlining strict analogies between the macroscopic behaviour of the complex systems in spite of the fact that they are really different.

[25] In all tissues, a part from their local different architecture, microvessel diameter oscillates rhytmically during time. The term *vasomotility* refers to small arteries and arterioles sphygnicity, according to

Hammersen, and *vasomotion* is the subsequent oscillation of capillaries and post-capillaries venules diameter.

[26] Book in progress. See http://www.semeioticabiofisica.it/microangiologia/common_eng.htm

[27] It is called ascending line because the reflex'intensity is growing for few seconds.

[28] It is called plateau line because reflex'intensity is steady for few seconds.

[29] Microvessels with diameter of 100 μ show a motor activity of 2-3 circles/min. and diameter oscillation intensity of 10-20%. As far as vascular diameter lowers, motor activity progressively becomes more intense and rapid; in terminal arterioles, the frequency is 10-20 circles/min. and the width can reach 100% of mean diameter, causing periodically opening and closure of the microvessel.

This rhythmic activity is mainly spontaneous and direct consequence of periodic contraction of smooth muscle cells of arterioles with 20-90 μ of diameter. Diameter oscillations of small vessels is due to the properties of smooth muscle sells, which have a labile membrane potential and, then, depolarize periodically.

Smooth muscle cells activation by well-known polarization-depolarization processes, which bring about periodic vasoconstrictions, is caused by nervous, hormonal, local biochemical stimuli and also by myogenic stimuli, characteristic of myocells. These stimuli provoke in smooth muscle cells of small arteries and arterioles, according to Hammersen, the onset of depolarization and consequent jonic fluxes and, then, intracellular storage of Ca^{++}, partially due to release from cytoplasmic and membraneous storages, which bring about the phosphorylation of myosine, that in turn interact with actine, to start contraction mechanism in presence of phosphorylated nucleotides with high caloric content, produced in mitochondria.

The "vasomotion" varies in relation to temperature fluctuation, O_2 concentration, pH variations, jonic concentration of vascular wall. In fact, it has been demonstrated that Ca^{++} and K^+ fluxes, due to channels voltage-dependent and, respectively, voltage and calcium dependent, at the base of the periodicity of these transports, brings about the rhythm of arteriolar contractions, ruled also by transmural pressure (Gonzalez-Fernandez J.M., Ermentrout B. On the origin and dynamics of the vasomotion of small arteries. Mathematical Biosciences. 119, 127-167,1994).

[30] Likely, typical *vasomotion* behaviour of dyssociated activation, type II, pathological, represents a *defence* mechanism against increased endocapillary pressure. In other words, one may suggest the hypothesis that the lowered *vasomotion*, secondary to blood increased supply (*increased vasomotility*) to capillary net or *microcirculatory maldistribution*, could be caused by a less elastic, more tonic state, with subsequent functional damage of endothelial as well as myocellular mitochondria of EBD and of local microvascular wall, including local periangium, under these circumstances edematous. As a matter of fact, the described micorcirculatory situation ends into interstitial obstruction, first, and susequently into basal membrane thickening of capillaries themselves. From the above remarks, it does exist a strict relation between "vasomotion" and EBD behaviour, under physiological and pathological conditions, and the abnormalities of EBD is counterbalanced, for months or years, by the increase only of vasomotility, which aims to preserve a physiologic *vasomotion* (dyssociation); this fact explains the importance of such structures as regards the regulation of microcirculatory blood-flow, corroborated *clinically* for the first time.

[31] H^+ removing and activation of "aerobic" glycolysis, soon thereafter interruption of digital pressure upon histangium.

[32] In the stomach, body and fundus dilate; on the contrary, antral-duodenal region contracts.

[33] H.A.G.R., when pathologically lasting 4 seconds or more (NN < 4 seconds), indicates local microcirculatory remodeling, and thus MFR impairment due to newborn-pathological, type I, subtype b), aspecific, EBD, which reduce tissue oxygenation, through lowering microcirculatory blood-flow.

[34] Melatonin is a natural substance that our body produces itself. It is produced by synthesis in the laboratory and placed in the body is to act on mitochondria, especially increases mitochondrial phosphorylation, it produces more EV and therefore greater EI and this must be for the benefit of the entire body, improves breathing (especially at night; we produce melatonin mainly from the early hours

of the night until around dawn), and therefore this is a hormone that is universal and is good for the treatment of multiple diseases, or tendences to pathology, and then to make the RR residual. It is also a good neurotransmitter.

[35] In therapy, based on what has been observed in patients with Oncological Terrain places on the nodes of Curry or Hartmann (worsening of psycho-neuro-endocrine-immune system), these energies released will improve and normalize respectively, by their influence on the alignment device, the orbital motion of subatomic particles, including the mitochondrial respiratory chain, which first reacts.

[36] Lory's experiment is based on the fact that "all" subatomic components and then atomic and molecular structured to form a cell and the whole cell or parenchyma, are correlated between themselves and with "all" the other branch of the same embryological in a four-dimensional space, like they are just "plot" (entanglement) two electrons observed by Aspect in his famous experiment. The effect of' entanglement means that the information takes on a "non-local" dimension. Lory's experiment is as follows: if it is done a digital pressure applied over a parotid gland, or a salivary gland sublingual, of a "single ovular" twin sister, simultaneously it is observed microcirculatory activation type I associated in the pancreas of the other twin sister, regardless of the distance that separates them: meters or kilometers (see in the references Manzelli and Stagnaro).

[37] The micro-circulatory remodeling is directed by the way of living and working on the parenchyma: if the subject is healthy, is healthy the related parenchyma on the microcirculation (see angiobiopathy theory, dealing with diseases of blood and lymph vessels in accordance with the semiotics biophysics). Certainly a loss, rheumatism, immune, infectious, can act both directly and indirectly.

See [http://www.semeioticabiofisica.it/microangiologia/common.htm]. It may be that in the long run re-organization becomes difficult or impossible because the flow decreases more, and then are built up of feedback mechanisms for which are to activate dormant cancer cells. Aging with free radicals that accumulate contributes to further damage both micro vascular and parenchymal: even endothelium (cell layers lining the inner surface of blood vessels and heart chambers) and smooth muscle cells possess mitochondria. Remodeling micro circulatory type cancer is an expression of mutations of genes within cells in that forum: any change in gene expression - cell finds its expression in the parallel alteration of its microcirculation (microvascular tissue units): the tissue here is around the vessels, interstitium, not the parenchyma! If these processes are blocked, stops the entire organization. Very important is that if there are congenital abnormalities, genetically transmitted through the mother (see CAEMH, mitochondrial cytopathy or mitochondrial functional pathology in the site www.semeioticabiofisica.it) amending the unfolding vital physiological processes occur the most serious human diseases, and not, now real epidemics. Autopoetics networks must therefore regenerate themselves continuously in normal and physiological way, to maintain its organization.

[38] See http://www.semeioticabiofisica.it/microangiologia/common.htm

[39] fractal dimension (fD) calculated in the most simple way, practical, but reliable, is the measure in seconds of the duration of the disappearance of nonspecific gastric reflection before the onset of the next. This value corresponds to the effectiveness of local microcirculatory functional reserve (MFR).