Coronary Artery Disease and Inherited Real Risk of CAD

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STRUCTURED ABSTRACT

Objectives
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 mitochondrial functionality, with the support of chaos theory, opens new ways to understand and face the very beginning states of Coronary Artery Disease - CAD, even silent and not yet clinically diagnosed, and of the inherited real risk of CAD.

Background
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 the Quantum Byophysical Semeiotics – QBS – is essential.

Methods
According to Stagnaro's researches, today the doctor can bedside evaluate, simply using the stethoscope, mitochondrial functionality of his patients 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.

Results
On the basis of QBS constitutions - i.e., Oncological Terrain, Diabetics Constitution etc. - it is possible to prevent the onset of serious diseases as, for example, cancer, diabetes, ischemic heart diseases, including myocardial infarction.

Conclusions
Since 1980, the doctor can bedside evaluate the way of being and functioning of mitochondria, in any biological system of his patients, so to provide an appropriate, targeted and effective primary prevention and treatment. 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 under the theoretical and practical points of view.

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 and microvessels dynamics opens new ways to understand and face the very beginning states of Coronary Artery Disease, CAD, even silent and not yet clinically diagnosed, 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 essential the knowledge of Quantum Byophysics Semeiotics - QBS, extension of the medical 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 Enzyme-Metabolic Histangiopathy, CAEMH (Stagnaro, 1985), a unique mitochondrial cytopathy, present at birth and subject to medical therapy. We shall 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's works, the doctor can bed-side evaluate, simply using the stethoscope (Stagnaro, 1978), the mitochondrial functionality of his patients in all biological systems. It is possible, since birth, to make a diagnosis in order to detect the presence of Inherited Real Risk of CAD linked to

specific QBS constitutions (Stagnaro, 2009), so that an intelligent prevention in subjects with Real Risk can be implemented. On the basis of QBS constitutions - i.e. Oncological Terrain, Diabetics Constitution (Stagnaro, 2004c), etc. – it can be prevented the onset of more serious diseases such as, i.e., cancer, diabetes, ischemic heart diseases, including myocardial infarction.

CAD and non-linear dynamics

Several researches aimed to test the non-linear behavior of heart muscle. (Ristimäe 1998, Huikuri 2001, Philippe 2004, Pavlov 2008, 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.

Firstly, these are purely statistical approaches, based on clinical test's timed series, i.e., ECG, studying the changes taking place in heart rate in healthy (physiological) and diseased patients (pathological): with downstream diagnosis of CAD.

Secondly, they do not address the underlying problem, namely the causes of CAD, for example 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 cardiological visits, 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.

Finally, the above-mentioned investigations are done usually on systolic-diastolic fluctuations, that are independent from microvessels behavior and microvascular dysfunction, proved to be of primary importance for diagnostic purpose (Camici et al., 2007).

For all these reasons new approaches are to be explored, such as those introduced by Quantum Biophysical Semeiotics – QBS – (Stagnaro, 2007b) which can diagnose the presence or absence of CAD, even silent. It can also assess the existence of pre-metabolic syndrome[1] that can last for years or decades, pre-clinical stage of the disease still potential (evolution to pathology, pre- morbid state or gray area), so allowing an effective prevention.

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 growing 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, 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 QBS constitutions[2] (Stagnaro, 2004c) which could bring about the congenital Real Risk - RR[3] of CAD (Figure 1) characterized by microcirculatory remodeling from QBS viewpoint, intense under environmental risk factors. Such 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, EBDs, localized in small arteries, according to Hammersen (1968). Interestingly, the Inherited Real Risk of CAD is associated to endothelial dysfunction[4], which doctor can bed-side assess in an easy and reliable way, at rest as well as under stress tests[5]. As a consequence of the above, briefly referred remaks, physicians can demonstrate the presence of typical pathological EBDs in coronary microvessels, which play a central role in CAD Inherited Real Risk.

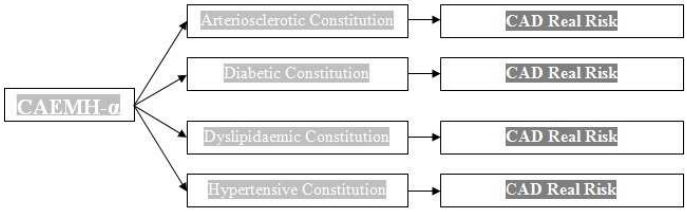

Figure 1. CAEMH-α, Quantum Biophysical Semeiotcs constitutions and Inherited Real Risk of CAD

The objective QBS examination allows to recognize and quantify, in a few minutes, the presence of CAD or of the congenital Real Risk of CAD through the evaluation of the Microcirculatory Functional Reserve (MFR) activity of related coronary microvessels.

Quantum Biophysical Semeiotics and Microcirculatory Functional Reserve

Microcirculatory 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 be evaluated and investigated getting information about heart parenchymal cells through several QBS signs and behaviors.

A lowering microcirculatory blood flow induces a LMR due to EBD type 1 subtype b), aspecific, synonymous of reduced tissue oxygenation. Through QBS 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 it can be evaluated through the observation of myocardial oxygenation, myocardial pH, T.M.U. structure and function, local metabolic situation, myocardial preconditioning and Endoarteriolar Blocking Device (EBD) investigation (Figure 2).

Quantum Biophysical Semeiotics and Microcirculatory Functional Reserve – MFR -

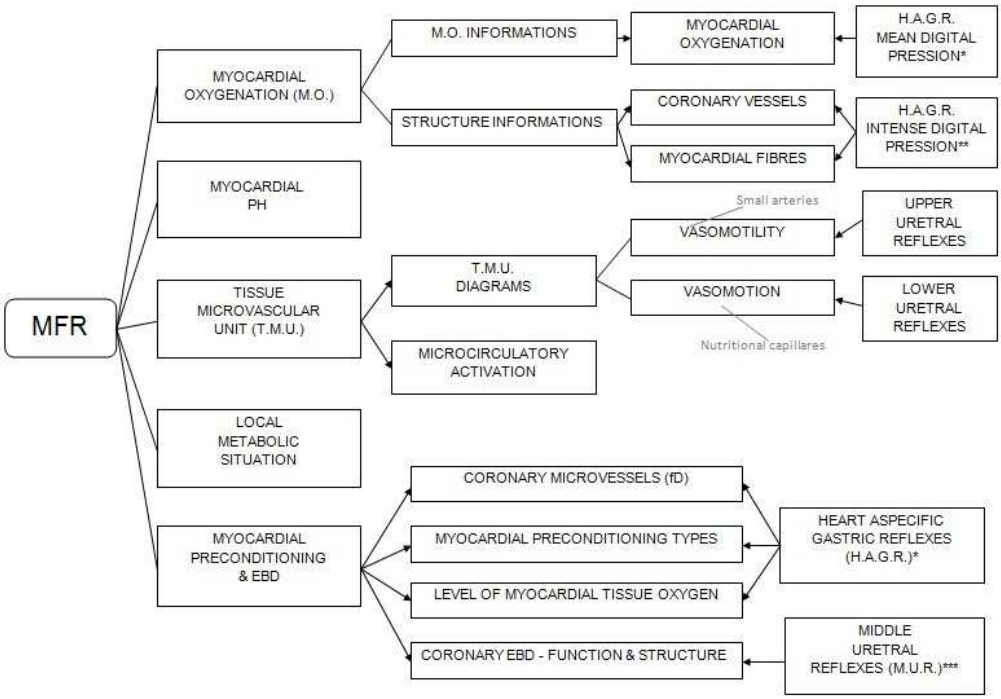

*Figure 2. Legend: MFR (Microcirculatory Functional Reserve); EBD (Endoarteriolar Blocking Device); fD (fractal Dimension); H.A.R.G. (Heart Aspecific Gastric Reflexes); M.U.R. (Middle Ureteral Reflexes); T.M.U. (Tissue Microvascular Unit); M.O. (Myocardial Oxygenation); * (Figure 3); ** (Figure 4); *** (Figure 6)*

Myocardial Oxygenation

Myocardial oxygen supply can be assessed clinically in a precise way (Stagnaro 1994, 1996). A digital pressure of "mean" intensity, applied upon the cutaneous projection area of the heart

(precordium), brings about heart aspecific gastric and caecal reflexes (H.A.G.R.), whose latency time (Lt), duration (D), intensity, MFR (pause in seconds between two reflexes), inversely correlated with fractal dimension (fD) inform on myocardial oxygenation at rest, as well under stress situations (Stagnaro, 1994). In Table 1 is resumed the study case about H.A.G.R.

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.)	Duration (D) in seconds ; MFR	fD & equilibria	EBD	Preconditioning	Diagnosis
Lt = 8	Lt = 16	3sec.<D < 4 sec. 3< MFR <4 normal MFR, associated activation, outcome +	fD ≥ 3 (ideal value fD=3.81)	Normal EBD phisiological function	Type I Physiological tissue microvascular unit	Health
Lt = 8	Lt < 16	D≥ 4 sec. MFR = 4 compromised MFR, dissociated activation, outcome ±	2<fD<3	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	D>4 sec. 4< MFR≤ 5 growing compromised MFR, dissociated activation, outcome ±	1<fD≤2	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	D>4 sec. MFR>5 absent MFR, dissociated activation, outcome – (MFR≈8 angina pectoris)	fD=1	Normal EBD function pathological, large number of pathological EBD	Type III Pathological tissue microvascular unit	Overt CAD

Figure 3. Legend: MFR (Microcirculatory Functional Reserve); EBD (Endoarteriolar Blocking Device); CAD (Coronary Artery Disease); fD (fractal Dimension); Lt (Latency time)

In addition, Lt of both caecal and aspecific gastric reflexes (i.e., caecal and gastric dilation) increases significantly (negative Caotino's sign), raising to 16 seconds, when digital pressure becomes "intense", because it stimulates coronary vessels and myocardial fibers (Figure 4), hence inducing local metabolic regulation of tissue-microvascular-units (T.M.U.), i.e. activating microvascular functional reserve - MFR (Goldberger, 1987).

On the contrary, *Caotino's sign* is positive in case of intense digital pression (Lt = 0) revealing an inherited Real Risk of CAD, if the reflex intensity is less than 1 cm, and an overt CAD if the reflex intensity is 1 cm or more. In this last case H.A.G.T. is "simultaneous" and its intensity is correlated to the numbers of aspecific, pathological EBD type 1, subtype b), neoformed in small coronary arteries, accurate assessment on the basis of the parametric values of middle ureteral reflexes (Figure 6).

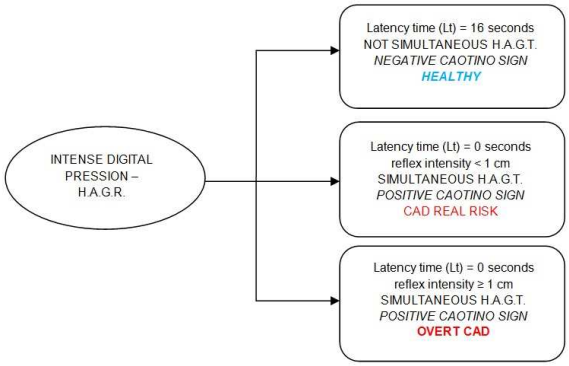

Figure 4. Legend. H.A.R.G. (Heart Aspecific Gastric Reflex); CAD (Coronary Artery Disease); Lt (Latency time)

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, 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 (Caramel, 2010).

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: microvessels, blood and perivascular connective periangium interstitium. 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 QBS, doctor is able to evaluate, in dynamic manner, T.M.U. of every biophysical system, under both structural and functional view-point, according to a synergistic[6] pattern, i.e., the clinical evaluation of microvascular dynamics. Notoriously the microvessels carry on a motor activity, autoctonous and chaotic deterministic, which represents one of the most remarkable manifestations of microcirculatory hemodinamics, characterized by a *flow-motion* and rhytmically fluctuating hematocrit due to the particular behaviour of both *vasomotility* and *vasomotion*[7]. 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 restricted number of T.M.U. reactions, doctor can observe at the bed-side through QBS and *Clinical Microangiology*[8].

According to QBS, in a supine healthy subject, psycho-physically relaxed, with open eyes, so 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 provs to be of paramount importance, from the diagnostic viewpoint, informing precisely about local microvascular structures and function, as well as microvessel remodeling. In fact, this digital pressure brings about "low-mean" stimulation of coronary trigger-points, inducing "rapidly" oscillations both of upper and choledocic reflexes (small arteries, according to Hammersen) and subsequently those of lower ureteral (arterioles, nutritional capillaries) ones, which parallell fluctuations of the related microvessel's 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 5).

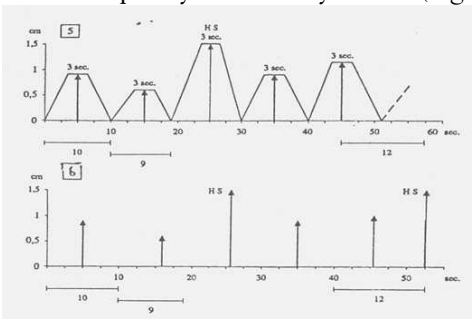

Figure 5: Physiology fluctuations of upper and lower ureteral reflexes, at rest (vasomotility and vasomotion); HS stands for Highest Spike or highest oscillation; x-axis (reflex's duration in seconds); y-axis (reflex's intensity – dilation of parenchyma in cm)

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 nervous autonomic 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 randomness", "reminiscent of chaos" (Goldberger 1991, Murry 1986, Stagnaro 1994). QBS allows to detect the chaotic behaviour of both intensity and period of ureteral (and choledocic) oscillations, i.e. vasomotility and vasomotion of the microcirculatory bed of all organs and tissues, including the heart (Figure 5), by means of the statistical invariant of deterministic chaos called fractal dimension (Caramel, 2011).

While vasomotility and vasomotion oscillations provide functional information about microcircle, its structural diagnosis is done by means of the observation of EBD, type I, subtype a) cancerogenous b) nonspecific. The EBD is a kind of dam which by opening and closing regulates blood flow in microvessels directed to the parenchyma (tissue, substance of a body). If these DEB are tough, rigid, inelastic, there is a Real Risk of disease. 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 (Figure 8). Even these physiological types get sick or old. However, the other types, pathological-neoformed, are expressions of the RR, of potential disease, they are more occlusive, but through therapy they can be transformed from subtype a) tumoral, to subtype b) aspecific, and then to "physiological" type, decreasing gradually their amount[9].

Middle ureteral reflexes are correlated with both physiological and newborn-pathological EBD (Figure 6). 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.

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.

Figure 6: parametric values of different middle ureteral reflexes as well as their meaning

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 (Bucciante, 1949), functionally speaking, in particular EBD, ubiquitous structures, essential in causing flow-motion in the microcircle of biological systems. Such microcirculatory modifications aim to adapt in a better way the biological system to new conditions, given that the activation of "peripheral heart" aims to realize and maintain a sufficient flow-motion in nutritional capillaries in relation to 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 (Figure 7):

- 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, i.e., 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, i.e., 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 to the total irreversible decompensation of microcirculation, show a large variety of different and significant forms. In Scheme 11 the study case of vasomotility and vasomotion investigation is shown.

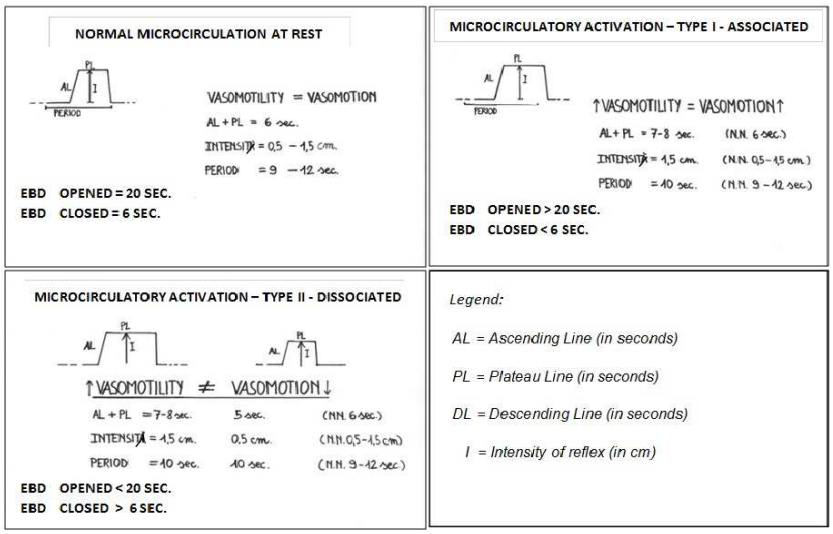

Figure 7. Vasomotility and vasomotion. Microcirculatory activation types

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 (Figure 8).

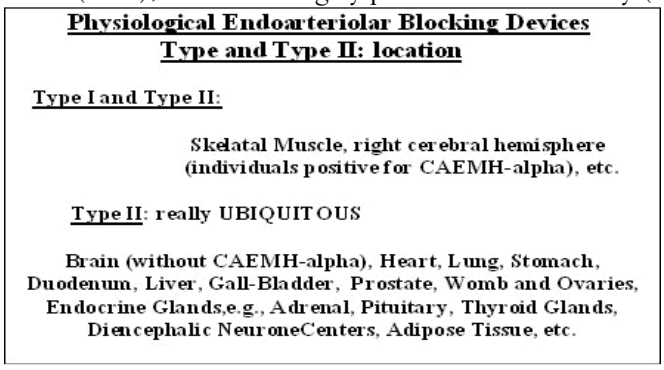

Figure 8: Doctor who knows the exact location of physiological type I EBDs (skeletal muscle, right emisphere of CAEMH-positive individuals, conjunctival mucosa) can recognize in an easier way the type I pathological DEBs, that play a pivotal role in diagnosing QBS real risk of most common and serious human disorders.

Both physiology and anatomy of EBD 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).

EBDs, 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 9).

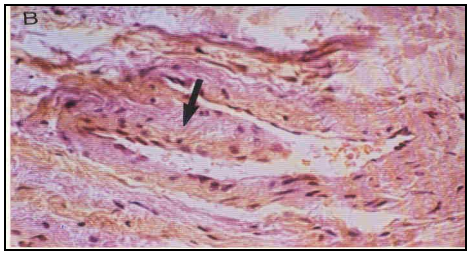

Figure 9. With kind permission from Curri S.B. (1986), the figure shows a refined imagine of EBD

EBDs 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 QBS viewpoint, EBDs bring about impairment of MFR, which contribute to conditioning the "real risk" of disorders, like CAD, whose onset shall 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, EBDs contribute significantly to increasing matter-energy-information supply to parenchyma, according to the physiological behaviour.

During M.A, *type I, associated,* EBD are "open" for more than 20 seconds: 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. Moreover, reflex disappearing (EBD decontraction, expressed by reflex cessation from the 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 part 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 with EBD dysfunction, indicating local pathological microcirculation: *microcirculatory bad distribution of blood flow*[10], according to S.B. Curri (1986).

In M.A., type II, dissociated, pathological, in which the microcirculatory phenomenon occurs 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.

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[11] (H.G.A.R.) after a latency time (Lt) of 8 seconds. H.G.A.R. lasts less than 4 sec., soon thereafter disappearing for 3-4 seconds. 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 anatomy of the microcirculatory bed, or microvascular tissular-unit - M.T.U. At this point of investigation, the physician quickly interrupts the digital pressure for exactly 5 seconds. Then, 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* (Figure 3).

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

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

In healthy subjects 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 the seriousness of underlying disorders - preconditioning, type III (Figure 7).

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, QBS "basal" data can "apparently" seem 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 are also, from the diagnostic point of view, the cardio-caecal and -gastric aspecific reflexes, when accurately assessed: after a Lt still normal (8 seconds), the duration of the reflex is 4 seconds (NN < 4 seconds), and the differential Lt (fD or duration of reflex's disappearing before the beginning of the following) is just 3 seconds (3 < NN < 4).

In these cases, *preconditioning* allows in a 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 reflexes, 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 has been well known for many years that patients with coronary heart disease may have no symptoms, and that the electocardiographic features 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 a 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 QBS methods and applications, are reliable, helpful, and 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, radionuclide ventriculography, spiral CT, a.s.o., during which silent ischaemia usually may be elicited, corroborating bedside diagnosis. Furthermore, the clinical, QBS 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 fact, 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, Conjugated-Melatonine, a.s.o.) in patients with ischaemic heart disease clinically silent, relies on three premises: 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, i.e., 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.

Finally, recent experimental evidences show the effectiveness of quantum treatments with customized frequencies and of thermal sulphydric water for CAD preventive therapeutical purposes (Stagnaro et al., 2011).

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. Under these conditions, therefore, the diseases arise under the action of the many negative environmental and acquired risk factors, which are not, however, to be pointed out as the causes of diseases such as diabetes and cancer, since they are merely facilitators only for those at risk!

In fact, in absence of inherited Real Risk of CAD, based on CAEMH mitochondrial cytopathy, all incoming environmental risk factors are innocent bystanders (Stagnaro, 2009b).

The objective QBS examination allows to recognize and quantify, in a few minutes, the presence of CAD or of the congenital Real Risk of CAD through the evaluation of the Microcirculatory Functional Reserve (MFR) activity of related coronary microvessels.

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 to supply 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 under the theoretical and practical points of view.

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Endnote

[1] 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.

[2] 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)

[3] 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.

[4]There are mitochondria also in endothels, although in small amount. 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.

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

[6] 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.

[7] 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.

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

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

[10] 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.

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