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Caotino' Sign and Gentile's Sign in beside Diagnosing
CAD Inherited Real Risk and Acute Miocardial Infarction, even initial or silent.
Pathophysiology and Therapy.

*Sergio Stagnaro**

Abstract.

In spite of the paramount progresses of the lat 50 years, mechanisms that underlie individual differences in the presentation and patho-physiological features of cardiovascular disease are poorly understood. In the paper, the Author illustrates some original methods of quantum biophysical semeiotics (www.semeioticabiofisica.it), utilizing bedside quantum-biophysical-semeiotic signs parameter values, useful and reliable in detecting coronary artery ischemic disease, even clinically silent, from its very initial stage, i.e. CAD inherited real risk, based on a mainly functional mitochondrial cythopathy, Congenital Acidosic Enzyme-Metabolic Histangiopathy (CAEMH), and characterized by microcirculatory remodelling, wherein newborn-pathological, type I, subtype b, aspecific, Endoarteriolar Blocking Devices (DEB) play a central role. To evaluate clinically these events in a reliable, easy, and quick way, CAD Inherited Real Risk patho-physiology is based on, from the technical view-point, physician has to know at least the auscultatory percussion of stomach. With regard to bedside evaluation of quantum-biophysical-semeiotic ureteral-reflexes, unavoidable in assessing coronary EBD structure and function, vasomotility and vasomotion, it is unavoidable further technical knowledge. Finally, CAD Inherited Real Risk diagnosis, by means of Caotino's Sign, and initial, *Impending Infarction*, or silent Miocardial Infarction diagnosis, performed with the aid of Gentle's Sign, their patho-fisiology, therapeutic monitoring, and therapy are illustrated in details.

Introduction.

Analogously to what happens in every serious disorder, mitochondria and mitochondrial DNA (mit-DNA) play a central role in the process that underlies the ischemia of myocardial cells. To bedside assessing the patho-physiology of these events, a clinical tool proved tool proved to be useful, and reliable; I mean the Quantum-Biophysical Semeiotics - QBS, extension of the classical semiotics with the support of quantum and complexity theories, a scientific approach first described by Stagnaro S., based on the Congenital Acidosic Enzymo-Metabolic Histangiopathy, CAEMH [1-7], a remarkable mitochondrial cytopathy, present at birth and cured by medical therapy.
We shall see how the presence of deterministic chaos is crucial for understanding the patho-physiology, diagnosis, therapy, therapeutic monitoring, and thus primary prevention of Coronary Artery Disease, CAD, and especially to bedside recognizing the Inherited Real Risk of CAD [1-7, 16-25].
According to Stagnaro works [35, 36], today the doctor could be able to evaluate, at the bedside, simply using a stethoscope, the mitochondria activity of his patients, as well as in all biological systems, at the condition of learning Quantum Biophysical Semeiotics.
In fact, it is possible, since birth, to make a diagnosis in order to detect the presence of Inherited Real Risk of CAD linked to a lot of QBS constitutions, like diabetic, hypertensive, arteriosclerotic, dyslipidemic ones [1-7], so that an efficacious, primary prevention just on rationally enrolled subjects, i.e., involved by Inherited Real Risk, can be performed, without loosing money, in the interest of both NHS and people.
On the basis of QBS constitutions - i.e. Oncological Terrain, Diabetic Constitution, and so on, [1-7], is possible to prevent the onset of more serious diseases that human being is suffering today, which

are growing epidemics, as, for example, cancer, diabetes, ischemic heart diseases, including myocardial infarction.

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 [38, 39].

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 [38]. 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 [39].

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 [40].

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 [41].

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 [42].

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 problems.

Firstly, 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.

Secondly, they do not address the underlying problem, namely investigating the causes of CAD, for example by analyzing the lifelong behaviour 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, erroneously termed "unforseeble and sudden", although they undergo regular cardiac monitoring by skilled cardiologists, utilising modern sophisticated semeiotics of image department.

For all these reasons it needs to explore new approaches, such as that introduced by Quantum Biophysical Semeiotics - QBS, [3, 16] which through bed-side evaluation, not only can diagnose the presence or absence of CAD, even silent, assessing it in a quantitative manner, but can also assess the existence of pre-metabolic syndrome [21], that can last for years or decades, preclinical stage of the disease still potential or on training (evolution to pathology, pre-morbid state or gray zone), so allowing an effective prevention, performed in rationally and early selected individuals [43].

Coronary artery disease (CAD): quantum-biophysical-semeiotic viewpoint.

As generally admitted, Coronary Artery Disease (CAD) is the end result of the accumulation of lipids (atheromatous plaques) within the walls of the coronary arteries that supply the myocardium with blood – i.e., material-energy-information - and is the leading cause of death worldwide. While its symptoms and signs are manifest 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

and unforseeable" 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. Under these occasions, there is type I, coronary, microcirculatory activation, typical of artery obstruction, even initial [3, 9, 10].

Individuals with this degree of CAD typically have suffered from one or more myocardial infarctions (heart attacks), and may have signs and symptoms of chronic coronary ischemia, including symptoms of angina at rest and flash pulmonary oedema.

Limitation of blood flow to the heart causes ischemia of the myocardial cells, which may die from lack of oxygen and this is called myocardial infarction. It leads to heart muscle damage, heart muscle death and later myocardial scarring without heart muscle re-growth. Chronic high-grade stenosis of the coronary arteries can induce transient ischemia which leads to the induction of a ventricular arrhythmia, which may end 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, analogously to Tako Tsubo Cardiomiopathy, whose I have recently described bedside diagnosis (65).

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 dysfunction"*.

From Quantum Biophysical Semeiotics view-point, these pathological conditions shows the "variant" form of "parenchymal" microcirculatory remodelling, illustrated in details later on.

Interestingly, CAD occurs exclusively in individuals involved by CAD Inherited Real Risk [3, 53].

From diagnostic and differential-diagnostic view-point, the following clinical evidence appeared very interesting: characteristically, in CAD Inherited Real Risk, the intense digital pressure upon whatever point of Precordium brings about "simultaneously" aspecific gastric reflex, whose intensity is about 0,5 cm

Interestingly, from diagnostic and differential diagnostic point of view, such a reflex appears after a latency time of 2 sec., showing an intensity of 2- 3 cm., in case of AMI outcome (heart scar).

Finally, in presence of a coronary stent, heart-gastric aspecific reflex latency time raises to 3 sec. with an intensity higher than 3 cm., allowing a interesting bedside differential diagnosis.

To summarise, Caotino's Sign under these two pathological conditions is not "simultaneous", showing a significant, different latency time.

Myocardial Vasomotility and Vasomotion Quantum Deterministic Chaos

In health, in the supine position and psycho-physically relaxed, with his/her eyes opened, aiming to lower melatonin secretion, digital pressure of "low-mean" intensity, applied on the heart cutaneous projection area, brings about aspecific gastric reflex (a.g.R.), as well as upper, middle, low-ureteral, caecal-, and choledocic- reflexes, i.e. upper-, mean, low-ureter as well as stomach, caecum, and choledocus dilation, the latter three after a latency time of 8 seconds exactly.

In health, at rest, the upper (followed by the low) ureteral reflexes appears after 6 seconds, during which appears the ureter dilation, realised in two phases of 3 sec., whose intensity informs about heart interstitium size. These reflexes last 6 seconds, while the heart-gastric aspecific reflex duration is less than 4 seconds; such a parameter value proved to be of paramount importance, from a diagnostic viewpoint, identifying precisely the local microvascular structures and function, i.e. local microcirculatory functional reserve (MFR), hence indicating microvessel remodeling. Importantly, when a.g.R. duration is less than 4 seconds, the doctor is authorized to exclude whatever coronary disorder!

Interestingly, "light-mean" digital pressure, applied upon coronary trigger-points (= different parts of precordium), provokes rapid oscillations of upper ureteral and choledocic reflexes (= small arteries and arterioles, according to Hammersen) and subsequently fluctuations of lower ureter (= nutritional capillaries), which parallel fluctuations of the related microvessel structure, according to synergistic model.

In addition, "more intense" digital stimulation causes numerous, pressure-dependent, middle ureteral reflexes, informing respectively on various type EBD, type A, group I, and II, AVA, and type B, group I and group II, AVA, according to Bucciante [8,9].

In health, the intensity of these reflexes – i.e., ureteral diameter – appears to oscillate from 0.5 cm. to 1.5 cm. at rest, in an unpredictable manner, which last about 10.5 seconds (fractal number) and vary from 9 seconds to 12 seconds (6 cycles per minute): mean value 10,5 sec.

Physiologically, after two normal, different in intensity, unpredictable fluctuations, we observe the 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, as I demonstrated earlier [1, 8-15]. Finally, these signs must be evaluated also under stress tests.

I emphasize that the duration of a.g.R. disappearing, before the subsequent reflex, is physiologically > 3 seconds < 4 seconds, average value 3.81, paralleling the fractal dimension of these microvessel deterministic-chaotic dynamics, evaluated in a more difficult, refined way.

To summarize, quantum-biophysical-semeiotics allows doctor to detect the chaotic behaviour of both the intensity and period of ureteral (and choledocic) oscillations. However, doctors can gather at the bedside the same data – vasomotility (= upper ureteral reflex: small arteries, and arterioles) and vasomotion (= low ureteral reflex: nutritional capillaries) of the microcirculatory bed of all organs and tissues, including the heart – in an indirect and easier way, by means of aspecific gastric reflex duration (NN < 4 seconds).

From the quantum-biophysical-semeiotic point of view, it is useful and easy to calculate the so-called fractal dimension (D) of microvascular chaotic system: in 120 seconds we observe 4 HS that divide the space in 4 segments; each segment is subdivided in 3 tracts by two normal oscillations. It is, therefore, possible to calculate the fractal dimension, which, roughly speaking indicates how much space a figure takes up, i.e. the degree of chaos, and is a measure of the complexity of the figure itself [16]:

$$r = N-(1/D) \text{ when } r = 3 \ N = 4$$

$$\log.n\ 4/\log.n\ 3\ [14]\ \text{X "f", fractal factor}$$

From the quantum-biophysical-semeiotics viewpoint, fractal factor – f – corresponds to the ratio HS/minimal oscillation.

In health, for example, D is > 3 sec. < 4 sec. (precisely 3.81); in the case of the metabolic syndrome, both classical and variant, evolving to diabetes mellitus, D is > 2 sec. ≤ 3 sec. (i.e. 2.4); and in type I and type 2 diabetes, D is 1, a topological dimension [3,11-27].

Assessed in the phase space, the trajectories of a deterministic chaotic system of D 3, present as a strange attractor; in case of D > 1 < 3 the trajectories correspond to a closed loop attractor. Finally, when D is 1, the attractor is at fixed point.

In day-to-day practice, it is sufficient to assess the fluctuation intensity of either upper (= small arteries and arterioles) or low ureteral reflex (= nutritional capillaries), caused by the digital pressure of small-mean intensity, applied upon the skin projection area of the heart, and evaluate the ratio HS/minimal oscillation, i.e. "f," fractal factor.

However, as I noted above, the fractal dimension D is directly related to the value, calculated easily in seconds, of the differential latency time (= disappearing time) of caecum- and/or aspecific gastric-reflex [1,12].

In health, during digital pressure of "mean" intensity upon heart projection area, as above-illustrated, both caecum- and aspecific gastric-reflex appear after 8-second latency time, then persist for less than 4 seconds (the parameter value is of paramount importance from a diagnostic view-point), before disappearing.

After > 3 sec. < 4 sec. (= "differential latency time," identical to the related fractal dimension), aspecific gastric-reflex and caecum-reflex occur again; such as parameter value, positively related to coronary Microvascular Functional Reserve (MFR), proved to be the same to fractal dimension, indicating myocardial oxygenation, myocardial pH, microcirculatory bed structure/function, local metabolic situation, and then myocardial preconditioning. Under such conditions, the doctor can exclude the presence of CAD inherited real risk, as when Caotino's Sign is absent: regarding the pathological situation, See later on [10, 15-25].

Heart Quantum-Biophysical-Semeiotic Preconditioning

It is well known that a precise sympathetic nervous correlation exists between dermatomeres and related visceromeres, which I fully corroborated and described in earlier papers [1,3,11,12,14,15]. Due to this fact, ischemic coronary diseases bring about an evident alteration of the corresponding dermatomeres, Th 1 - Th 2, easily detectable by means of palpation [16,17]. On the contrary, with the condition reversed, Th 1- Th 2 dermatomere stimulation of diverse intensity brings about sympathetic-dependent coronary tone modifications.

In the day-to-day practice, myocardial ischemic preconditioning can be evaluated at the bedside in a rapid, easy, and reliable way.
In health, in the supine position and psycho-physically relaxed, with open eyes to reduce melatonin secretion, the physician provokes the digital pressure of "mean" intensity, applied upon skin projection area of the heart, precordium, and than exactly upon ventricular and/or atrial, as well as valvular projection areas. Due to its selectivity, is advisable in day-to-day activity performing the stimulation of related trigger-points by means of the thought, according to Psychokinetic Diagnostics (55-63).

The above-illustrated stimulation induces the aspecific gastric-reflex (i.e. their dilation), as well as ciecal reflex, after latency time (lt) of 8 seconds precisely; reflex lasts less than 4 seconds, giving precious information on MFR (this value is inversely correlated with disappearing time of reflex, i.e. fractal dimension (fD: NN = 3.81), indicating normal tissue pH, as clinical and experimental evidence suggests [1,3,11,12,14,15].
After exactly a 5 second interruption, the newly applied digital pressure, as mentioned above, causes both caecal-, and aspecific gastric-reflex after doubled latency time, i.e. 16 seconds: type I, physiological preconditioning.

On the contrary, in the case of CAD Congenital Real Risk, the first value at base line may be yet normal (i.e. 8 seconds), but reflex duration is 4 seconds or more. In addition, after preconditioning, latency time raising is impaired, namely less than 16 seconds, in inverse relation to the seriousness of underlying real risk: type II, intermediate, preconditioning.

Finally, in overt CAD, since its initial stage, basal latency time is already altered, resulting less than 8 seconds, and the gastric aspecific reflex is clearly pathologically prolonged, i.e. more than 4 seconds, paralleling disorder seriousness: type III, pathological preconditioning.

In conclusion, 55 year-long clinical experience allows me to state that a new era in the war against CAD has been initiated [18,33]. In fact, physicians are now able to bedside recognize from birth all individuals at inherited real risk of CAD, treat them successfully with the Mediterranean diet, conjugated melatonin, according to Di Bella-Ferrari, associated with histangioprotective drugs

(e.g., Cellfood), personalized NIR-LED, LLLT, and especially Cem-Tech application, under clinical monitoring.

CAD Inherited Real Risk.

As I have demonstrated in previous articles [1-5], nuclear and mitochondrial genome informations are transmitted simultaneously to both parenchyma and related microvessels, so that mutations in parenchimal and microvascular cell n-DNA and mit-DNA, my theory of Angiobiopathy is based on, are the *the conditio sine qua non* of the most common human disorders, like CAD, type 2 diabetes mellitus, and cancer, today's growing epidemics.

In fact, these diseases are based on a particular congenital, functional, mitochondrial cytopathy, almost always transmitted through mother, I termed Congenital Acidosic Enzyme-Metabolic Histangiopathy [1-6, 25, 34-36, 47].

In addition, parenchymal gene mutations cause local microcirculatory remodelling, so that doctor can evaluate it at the bedside in a reliable manner, gathering indirect information of relative parenchymal cell inherited modifications, since biological system functional alterations parallel gene mutation, according to Angiobiopathy theory [1-4, 49, 50].

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, which could bring about their respective heritable Real Risks, characterized by microcirculatory remodelling from quantum-biophysical-semeiotic viewpoint. Such a predisposition to disorders can become "intense" under environmental risk factors.

Interestingly, the congenital microvascular remodelling, including also *vasa vasorum* of large coronary arteries, shows since birth interesting structures, i.e., newborn-pathological, type I, subtype b) aspecific, Endoarteriolar Blocking Devices, EBD, localized in small arteries, according to Hammersen [51,52] (Fig.1).

At this point, it's unavoidably necessary to emphasise an interesting aspect of EBD, especially significant from CAD pathophysiological view-point. In fact, the subdivision of pathological EBD in two variants proved to be extremely important:

A) coronary artery wall pathological EBD, whose microcirculatory remodelling is located in *vasa vasorum* of epicardial coronary arteries, which are the only really dangerous in the predisposition to CAD;

B) myocardial parenchymal pathological EBD, located in small arteries of myocardial tissue, that are either associated to the former EBD, worsening the predisposition to CAD and its complications, or isolated, as in *X coronary Syndrome* as well as in Taho Tsubo Cardiopiopathy (65).

Interestingly, CAD Inherited Real Risk is associated to localised endothelial dysfunction (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-referred remarks, physicians are able nowadays to bedside demonstrate the presence of typical pathological EBD in coronary microvessels, which play a central role in CAD Inherited Real Risk [18, 31].
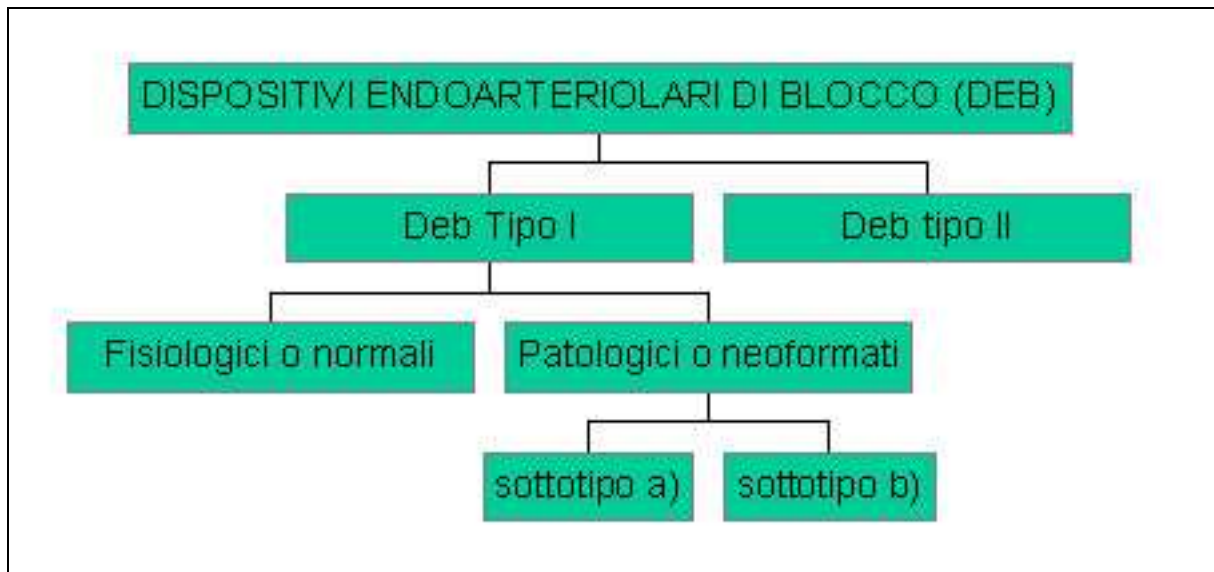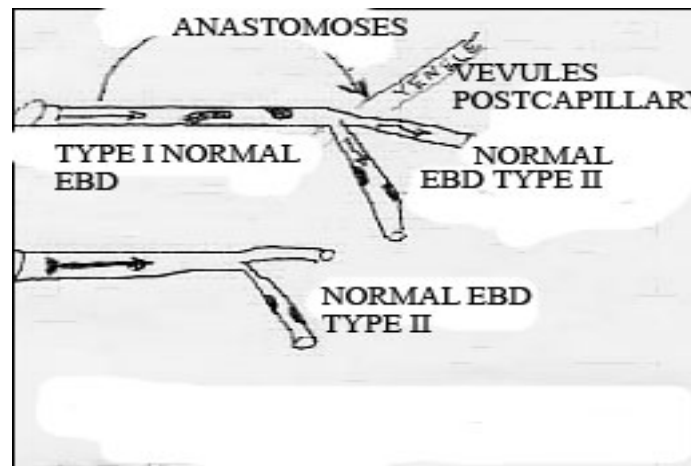
Tab. 1

Fig. 1

Through the quantum biophysical semeiotic examination, in a few minutes it is possible to recognize and quantify if a patient has got any Inherited Real Risk (IRR) to have a disease by mean the observation of EBD, type I, subtype a) oncological and b) nonspecific (Tab. 1).

The EBD is a kind of dam which opening or closing itself regulates blood flow in microvessels directed to the parenchyma (tissue), 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 primary prevention on a huge hall in individuals clinically 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 IRR 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, i.e., cells of various tissues. If these EBD are tough, rigid, inelastic, rich of smooth muscle cells, there is IRR.

There are EBD Type I - located in small arteries, according to Hammersen – and Type II – located in the arterioles, according to Hammersen, between small arteries and capillaries: only type

II is ubiquitous, in the sense that it is observed everywhere, in all arterioles (Tab 1). Even these physiological types get sick or old.

However, the other types, pathological-newborn, are expressions of the IRR, 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 [5].

At this point, I emphasise the fact that the evaluation of Caotino's Sign and hearth-aspecific gastric Reflex results more clear when the physician has no great knowledge and experience, during a lot of stress tests: insulin secretion acute pick test, adiponectine, Valsalva's Manoeuvre, boxer's test, a.s.o. (I, 9-12).

Not only due to space reasons, it is impossible to illustrate microcirculatory events, observed during stress tests, at the level of vasomotility, vasomotion, and arterio-venular anastomoses, including new-born, pathological EBD, which are to be considered like anastomoses, from the functional view-point.

To be able to perform such a assessment, the physician has to be skilled in QBS and Clinical Microangiology.

Caotino's Sign

Really, CAD environmental risk factors (about 300!) can facilitate and worsen CAD onset, rather than cause CAD, which can occur exclusively in individuals involved by CAD Inherited Real Risk, bedside recognized with a simple stethoscope in quantitative way, as I have described in a lot of former articles [1-7, 11, 12, 16-27, 53].

Unfortunately, almost all physicians and cardiologists around the world ignore (sometimes overlook) quantum-biophysical-semeiotic constitutions and related inherited real risks. This fact accounts for the reason that CAD is a today's growing epidemics, as generally admitted.

Notoriously, CAD Inherited Real Risk, as well as sub-clinical, very dangerous, silent, initial stages of coronary artery disorder precede for decades its clinical phenomenology.

CAD Inherited Real Risk is characterized by the presence of newborn-pathological, type I, subtype b), aspecific, Endoarteriolar Blocking Devices (EBD) in coronary small arteries, according to Hammersen, often associated with hypertension, ATS or diabetes mellitus constitutions.

In following, I suggest - once again - an useful, reliable and easy clinical manoeuvre, that allows doctor to bedside recognize both CAD Inherited Real Risk and silent CAD [11, 12, 16-27]. This manoeuvre proved to be really useful in my 55-year-long, well-established clinical experience, also in order to bed-side diagnosing heart ischemic disease, a long time before cardiac pathology occurs. Moreover, it is well known that patients with coronary artery disease, i.e., CAD, may have no symptoms at all for many years or decades, and that the electrocardiographic features of ischemia may be induced by exercise without accompanying angina.

As a consequence, we need a clinical tool reliable in rapid detecting CAD, even clinically silent, initiating from CAD Inherited Real Risk, doctor can utilize easily and quickly in day-to-day practice in every patient, a part from the type of his (her) clinical symptomatology [11, 12, 16-27].

I think that one among these methods is "Myocardial Ischemic Quantum-Biophysical-Semeiotic Preconditioning", described above [1-5, 16-25]. From the technical viewpoint, doctor has to know, at least, the auscultatory percussion of the stomach, described even in old academic books of two last centuries (for instance, Rasario IX Edition) (Fig. 1).
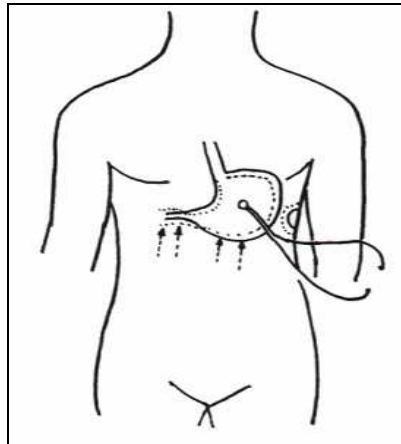
Fig. 1

In health, digital pressure of light-mean intensity, applied upon heart cutaneous projection area, brings about the gastric aspecific reflex (= in the stomach, fundus and body are dilated; on the contrary, antral-pyloric region contracts) after a latency time of precise 8 sec., that lasts less than 4 sec. (= parameter value of paramount significance since it parallels the efficacy of coronary Microcirculatory Functional Reserve).

A second, successive evaluation after an interval of 5 sec. exactly, provokes the identical reflex after 16 sec. latency time: physiological myocardial preconditioning, type I.

On the contrary, in patients involved by CAD Inherited Real Risk, and in case of CAD, even initial or silent, i.e. subclinical, latency time persists identical in both evaluations, in relation with disease seriousness: type II miocordial preconditioning.

Finally, in overt CAD, the second latency time appears more or less lowered.

Of course, quantum-biophysical semeiotic preconditioning evaluation, really more complex than it appears in the above brief description, can be applied to all others biological systems, with favourable influences on primary prevention, diagnosis, and therapeutic monitoring [1-5].

Interestingly, since November 2007, thanks to Quantum Biophysical Semeiotics, based on no local realm in biological systems, I demonstrated for the first time, besides the local realm, in biological systems [44-46], "simultaneously" to "intense" stimulation beginning, physicians can recognize clinically healthy heart, excluding CAD Congenital Real Risk, even in individuals kilometres away, according to Psychokinetic Diagostics: Caotino's Sign [15-18,47].

In health, "intense" digital pressure, applied upon a single point of Precordium (skin projection area of the heart) does not bring about "simultaneously" stomach size increasing, i.e., heart-gastric aspecific reflex (Fig. 2).

On the contrary, in individuals involved by CAD Inherited Real Risk, and overt CAD, of course, under identical experimental condition, cited above, "simultaneously" doctor observes a small (about 0,5 cm. of intensity) heart-gastric aspecific reflex (Fig.3).

Finally, CAD Inherited Real Risk can be transformed in its "residual" variant, that's not dangerous, with DIET, etimologically speaking, Coniugated Melatonin.

Fortunately, with both thermal sulphridic water (e.g., Porretta Terme, Bologna, Italy), and personalized application of Cem-Tech, LLLT, including NIR-LED, acting also stimulating hearth stem cells, among others well-known action mechanisms, CAD Inherited Real Risk disappears completely [47, 48].

Really, a single application of Cem Tech causes the disappearing of quantum-biophysical-semeiotic signs of CAD inherited Real Risk, exactly 5 minutes after disappearance of those of Congenital Acidosic Enzyme-Metabolic Histangiopathy.
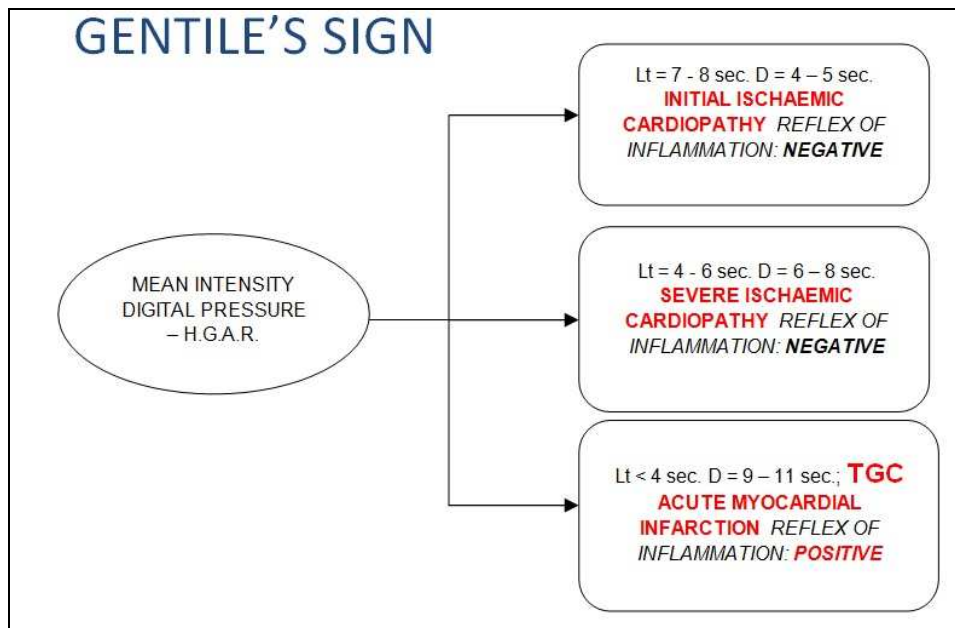

Table 2
Intense digital pressure, applied on hearth skin projection area, brings about "simultaneously" aspecific gastric Reflex in presence of CAD Inherited Real Risk; the intensity of reflex parallels the seriousness of underlying disorder. Really, such a sign is present also in other heart disorders, as septal, and valvular heritable alterations.

Fig. 3

Figure shows the characteristic pattern of Hearth-a.g. Reflex in case of Positive Caotino's Sign
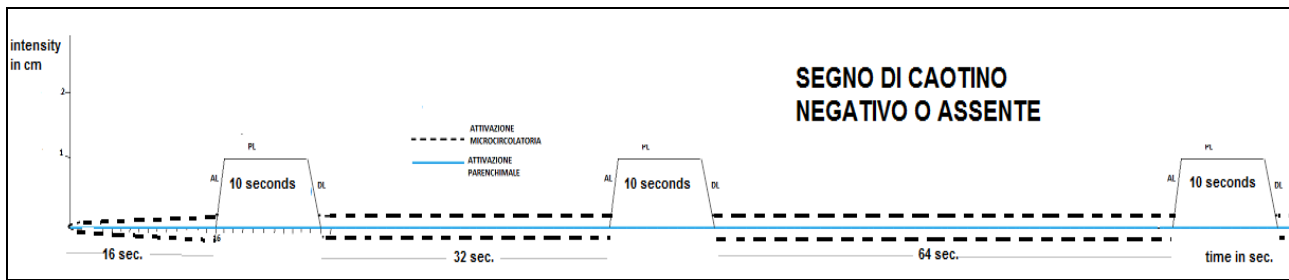
Fig.4

In health, i.e., in subject negative for Caotino's Sign, intense digital pressure activates "simultaneously" parenchimal and microvascular tissues, avoiding local acidosis, which causes aspecific gastric reflex.

Caotino's Sign Pathophysiology: the central Role of Microcirculation.

In health, intense digital pressure, applied upon a small part of skin projection area of the heart, i.e., precordium, brings about "simultaneously" highest, maximal activation of both parenchyma and related microcirculation, showing a flow-motion greatest as possible.

As a consequence, such as intense stimulation does not cause under physiological condition, local acidosis, gastric aspecific reflex is based on. As a matter of fact, hydrions, H^+, are quickly removed, because very intense blood flow drives away protons, and contemporaneously provides sufficient material-energy-information to parenchymal mitochondria, as well as to local microvasculature, thus normally functioning in environment physiological pH.

The *physiological,* type I, associated, microcirculatory activation, bedside evaluated notoriously with the aid of upper (vasomotility) and lower (vasomotion) ureteral reflexes, lasts exactly 16 sec., equal to the latency time of first gastric aspecific reflex (Fig 4), and than stops quickly.

At this precise time appears the gastric aspecific reflex, since local acidosis rises abruptly to a critical level since blood flow lowers significantly through local microvessels: the reflex persists 10 sec., paralleling microcirculatory interruption period, unavoidable to smooth muscle cells for membrane polarization.

Interestingly, after an interruption of precise 10 sec., doctor observes for the second time very intense microcirculatory activation (= upper and than lower ureteral tracts dilate maximally) lasting now 32 sec., according to quantum biophysical semeiotic preconditioning [1, 24].

At this point, namely at the end of the second latency time, gastric aspecific reflex appears again, brought about by tissue acidosis, and lasts 10 sec.; at the end, vasomotility stops again.

According to quantum-biophysical semeiotic preconditioning, the third latency time, indicating type I, associated, microcirculatory activation, shows highest value, doubling the former: 64 sec. Finally, small arteries and arterioles fluctuations return to basal pattern.

On the contrary, in case of coronary remodelling, i.e., in individual involved by CAD Inherited Real Risk, intense digital pressure, applied upon a small part of skin projection area of the heart, brings about "simultaneously" maximal activation of parenchyma, but not of microcirculatory bed, which is slower and occurs some seconds later, in direct relation with the seriousness of microcirculatory remodelling.

In fact, assessing the behaviour of upper ureteral reflex (vasomotility) under the above-mentioned experimental condition, doctor observes intense dilation after 2-4 sec., paralleling the severity of underlying microcirculatory remodelling.

As a consequence, due to local, transitory acidosis, simultaneously with the intense stimulation appears the gastric aspecific reflex, lasting 10 sec. (Fig. 2).

Interestingly, a second reflex appears after a brief interval, indicating always compromised MFR, under this pathological circumstance: ≥ 4 sec. (NN > 3 sec. < 4 sec.).

Subsequently, initiating with the third aspecific gastric reflex, both microcirculatory activation and aspecific gastric reflexes show the same behaviour as in healthy individual, underlining intern and extern coherence of quantum biophysical semeiotic theory.

As illustrated clearly in Tab.3, there is a perfect correlation between latency time of the first aspecific gastric reflex, MFR, fD of microvascular oscillations (= fluctuations of upper and lower ureteral reflexes), presence of newborn-pathological EBD, preconditioning and the coronary condition.

Importantly, as referred above, Caotino's Sign may be present, but not "simultaneous", also in the predisposition to cardiac arrhythmia, valvular and atrial and ventricular septum malformations, patients with a coronary stent. It is easy to make differential diagnosis with a lot of QBS specific signs. For instance, these signs show a small and different latency and their intensity is higher than in "simultaneous" Caotino's Sign, typical of CAD Inherited Real Risk.

Fingertip - Gastric Aspecific Reflex (Pr. G. A. R.) mean intensity digital pressure on any fingertip– (endothelia trigger points)

Latency time (Lt) in seconds	Latency time after 3 deep breaths - Pulmonary Blood Oxygenation Dynamic Test	MFR in seconds	fD & equilibria	EBD	Valvava Manouvre (deep inhalation followed by exhalation with the mouth closed)	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	Lt = 12 sec.	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	Lt = 8 sec.	Type II A Intermediate tissue microvascular unit	Likely ATS/ Dysplipidemia /T2DM/ cardiopathy/ hypertension
7<Lt <8	14<Lt < 16	4< MFR≤ 5 growing compromised MFR, dissociated activation, outcome ±	1<fD≤2 limit cycle	Modified EBD function, increasing number of pathological EBD	Lt < 8 sec.	Type II B Intermediate tissue microvascular unit	Likely ATS/ Dysplipidemia /T2DM/ cardiopathy/ hypertension in evolution
Lt≤7	Lt < 14	MFR>5 absent MFR, dissociated activation, outcome –	fD=1 fix point	Normal EBD function pathological, large number of pathological EBD	Lt < 7 sec.	Type III Pathological tissue microvascular unit	Overt ATS/ Dysplipidemia /T2DM/ cardiopathy/ hypertension

Tab. 3

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

Gentile's Sign*: Bedside Diagnosing Acute Myocardial Infarction.

Bedside diagnosing Acute Myocardial Infarction (AMI) is sometimes very difficult. On the other hand, the efficaciousness of therapeutic results, especially regarding mortality rate, depend of early AMI diagnosis [1-10].
In following, a simple Quantum Biophysical Semeiotic method, easily and quickly to apply, that allows doctor to bedside recognise Gentile's Sign, is fully illustrated.

Considering that glucose and lipid metabolism impairment, as well as other environmental risk factors worsen, BUT not brings about coronary artery disease (CAD), as I have demonstrated earlier [3-8], physician has to know CAD Inherited Real Risk, rapidly detected with the Caotino's Sign [8], representing the *conditio sine qua non* of CAD, especially frequent in individuals involved by hypertension, diabetes mellitus, dyslipidemia, or elevated C-reactive protein.

In my long, well-established clinical experience, Gentile's Sign proved to be really useful also in order to bed-side recognizing AMI, even silent, *impending infarction*, and/or initial.

Really, Gentile's Sign allows, for the first time clinically, doctor to monitor CAD evolution starting from the initial stage of coronary artery disease as far as to acute myocardial infarction; characterized by qbs. signs of inflammation and Gastric tonic Contraction, indicating the inyense myocardial acidosis (Fig. 2)

Importantly, it is known that patients with CAD may have no symptoms at all for many years or decades and that the electrocardiographic features of ischemia may be induced by exercise without accompanying angina [2, 7, 8]. As a consequence, physicians need a clinical tool reliable in rapid detecting CAD, even clinically silent, initiating from CAD "inherited real risk. From the practical viewpoint, in order to apply Gentile's Sign doctor has to know, at least, the auscultatory percussion of the stomach [1] (Fig. 1).

In health, digital pressure of "mean" intensity (= stimulation of both upper and lower ureteral reflex: vasomotility and respectively vasomotion, according to Hammersen), applied upon ventricle heart skin projection area = precordium), brings about the so-called gastric aspecific reflex (= in the stomach, fundus and body are dilated, while antral-pyloric region contracts) after a latency time of 8 sec. exactly; reflex duration is less than 4 sec. (= parameter value of paramount significance since it parallels the efficacy of local coronary microvessel Microcirculatory Functional Reserve). Finally, the reflex disappearing is > 3 sec. < 4 sec. (= parameter value paralleling fractal Dimension of local microcirculatory oscillations) [1-4] (Fig. 1, 2).
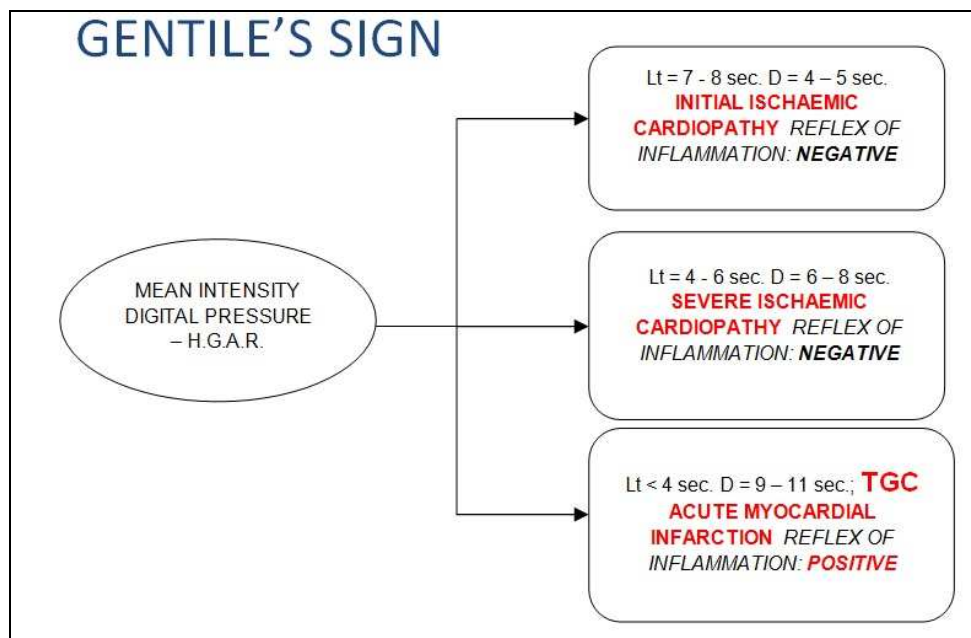

Fig. 2

On the contrary, in *impending infarction* and obviously in overt AMI, even silent or initial, latency time appears significantly lowered to < 4 sec, or more, in inverse relation with the seriousness of underlying disorder (NN = 8 sec.). Reflex lasts longer than normal, 4 sec. or more (NN ≥ 3 sec. < 4 sec.), directly correlated with the AMI severity, and is followed by tonic Gastric contraction (Fig.

2). In addition, reflex disappearing time, i.e., fractal Dimension, results lowered than normal (NN > 3 sec. < 4 sec.), once again in inverse relation to the seriousness of underlying disorder.

Finally, nail-digital pressure of mean intensity, applied on identical heart trigger-points, illustrated above, in AMI patients brings about aspecific gastric refelex after a latency time statistically lower than the normal one: 3-5 sec. (NN = 8 sec. or more).

When physicians will be able to apply Caotino's Sign and Gentile's Sign, both morbidity and mortality, caused by AMI, will lowered significantly, and CAD will end to be the well-known epidemics.

Conclusion.

Recently, in a paper published on NEJM, the Authors state that, despite the paramount progress of the last 50 years, in better defining risk factors and therapy of CAD, the mechanisms that underlie individual differences in the presentation and patho-physiological features of cardiovascular disease are poorly understood (54). These Authors, NEJM Editors and Reviewers do not clearly know Quantum Biophysical Semeiotics, thus they cannot comprehend the explanation, illustrated above, of patho-physiology and therapy of CAD, according to Quantum Biophysical Semeiotics and Quantum Therapy.

I conclude referring my comment to a recent article, published on NEJM, whose title is A Tale of Coronary Artery Disease and Myocardial Infarction. Elizabeth G. Nabel, and Eugene Braunwald, N Engl J Med 2012; 366:54-63, January 5, 2012, (64)

http://www.nejm.org/doi/full/10.1056/NEJMra1112570?query=featured_home
SERGIO STAGNARO, MD. RIVA TRIGOSO Italy. January 05, 2012.
CAD Inherited Real Risk.
Based on 55-year-long clinical experience, I state sincerely that such a "historic", refined, perfect from the formal view-point, paper does not help in hindering efficaciously today's growing epidemic of CAD. In fact, despite thousands of paramount articles, published in peer-reviews, CAD continues to be a growing epidemic. I visited an awful number of hypertensive, diabetic, dyslipidemic patients, who never suffered from AMI.

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* **Sergio Stagnaro MD**
Via Erasmo Piaggio 23/8,
16039 Riva Trigoso (Genoa) Italy
Founder of Quantum Biophysical Semeiotics,
Honorary President of International Society of
Quantum Biophysical Semeiotics (SISBQ)
Who's Who in the World (and America)
since 1996
Ph 0039-0185-42315
Cell. 3338631439
www.semeioticabiofisica.it
www.sisbq.org
dottsergio@semeioticabiofisica.it