Editorial

Modifying Cardiovascular Risk Factors: Newer Advances in Cardiovascular Metabolism and Diagnostic Technologies

The metabolic disorders, both as such and associated with other cardiovascular risk factors, are a group of pathological alterations in the steady expansion with regard to their rate [1]. In addition, a clear adverse interference with the heart and blood vessels has been widely described [2-5]. When other cardiovascular risk factors are associated, cardiovascular damage gets worse exponentially depending also on the type of metabolic disorder that individuals, who are affected, show.

Evidence indicates that a careful assessment of the role of metabolic changes requires always more sophisticated methodologies [6] using those diagnostic technologies that are continuously in progress.

A key impact to technical methodologies of metabolic cardiovascular risk factors is given by the findings on exposure to second-hand smoke mainly involving the endothelium [7-9] and, then, the responses of those metabolites that regulate the function [10-14], the use of the vascular ultrasound for these studies, and the variable response of some blood markers [1].

All these studies, although with some differences in the recruited subjects, identify both a metabolic effect of cardiovascular risk factors and use of technical devices to be demonstrated. In addition, during recent years, it has been well seen that vascular endothelium has a pivotal role in maintaining vascular tone [10]. The findings lead to establish that endothelial dysfunction is an early marker of impending atherosclerosis. Papers [7-9] indicate clearly that there is a strong relationship between environmental tobacco exposure classified by the American Heart Association as an independent risk factor for coronary heart disease [15] and endothelial dysfunction with impaired endothelium-dependent vasodilation in healthy people. A normal response in endothelium-dependent vasodilation is a good marker of endothelial integrity that is related to release of endothelium-derived nitric oxide. This chemical plays an important role in maintaining endothelial homeostasis. Nitric oxide release is impaired by atherosclerotic progression, smoking and, probably, other major coronary risk factors [11]. Endothelial dysfunction with impaired endothelium- dependent vasodilation due to passive smoking exposure of healthy volunteers was very recently found by Giannini *et al*. [16].

The metabolic characteristics of the major cardiovascular risk factors are stressed by the excellent and innovative review of Landini [17].

The author underlines that cardiovascular risk factors, whatever is the approach to their assessment have been always analyzed with regards to their effects on inducing cardiovascular events but poor attention has been given to metabolic responses.

The metabolic features met during the analysis of cardiovascular risk factors, either those defined as major or, conversely, minor require a more careful settlement. According to their role and characteristics, classifying cardiovascular risk factors may follow three basic categories: 1. Predisposing risk factors (Age, gender, medical history, and genetic factors); 2. Clinical and metabolic factors (Hypertension, changes in lipid metabolism, diabetes mellitus, obesity, metabolic syndrome, homocysteine, serum uric acid concentrations, L-arginine and dimethylated derivatives); 3. Modifying behavioural factors (Cigarette smoking, high caloric diet, alcohol intake and sedentary life).

It is worth noting that some of these factors are metabolic components of body metabolism, acting in this way, while others characterized by structural alterations towards cardiovascular system, really, at least initially, exert their harmful action by metabolic substrates.

Analyzing the metabolic responses that act initially as cardiovascular risk factors, there is evidence, therefore, that an early treatment of the altered parameters observed should be a useful approach to reduce the rate of heart attacks with a significant improvement in the outcome of cardiovascular disease since metabolic markers can be also easily documented in affected individuals.

The data in the review are consistent with the observations on the relationship between metabolic disease and cardiovascular system. Indeed, it is well established that an increased incidence of cardiovascular events, particularly on the subjects suffering from coronary heart disease, has been documented in the course of metabolic syndrome and diabetes mellitus [18-19]. Coronary heart disease, cardiovascular disease, and total mortality were significantly higher in US adults with than those without metabolic syndrome [18].

A new metabolic topic to be carefully assessed is the relationship between urate metabolism and cardiovascular damage. Several papers [20-23] have demonstrated an always major incidence of artery wall damage due to uric acid deposits in the coronary arteries.

Three main morphological features may accompany uric acid disorders: acute arthritis, chronic tophaceous arthritis and uric acid deposits in several body organs. Evidence indicates that patients with metabolic disorders of the uric acid can have a higher incidence of obesity, hypertriglyceridemia, diabetes mellitus and hypertension, although a direct relationship with high acid uric levels have not been clearly assessed. However, acid uric deposits in the coronary artery wall could reduce lumen patency.

The review of Grassi *et al*. [24] emphasizes that several experimental and clinical studies reported that hyperuricemia may trigger hypertension, metabolic syndrome, vascular damage and renal disease. Furthermore, a substantial proportion of epidemiological studies are compatible with the hypothesis that hyperuricemia may be an independent risk factor for cardiovascular disease as well as for an increased cardiovascular mortality. Xanthine oxidase is a critical source of reactive oxygen species contributing to vascular inflammation and endothelial dysfunction. Although a causal relationship between these conditions has not been clearly clarified, the capacity of uric acid to negatively affect vascular function by pro-oxidant effects and by decreasing the nitric oxide bioavailability and consequently induce endothelial dysfunction may explain the association among hyperuricemia, hypertension, the metabolic syndrome, and cardiovascular disease, also by a common mechanistic point of view.

There is evidence that the observations of the authors are on line with the reports of the literature that allow concluding that further studies are required in an attempt to establish correctly the urate-related mechanisms of the cardiovascular damage.

With regards to the metabolic link between cardiovascular risk factors and cardiovascular pathology, high blood pressure and disorders of cardiac rhythm cannot be overlooked.

From the analysis of previous studies [25-30], there is evidence that the risk linked to elevated blood pressure may be modified with non-pharmacological and pharmacological measures. In addition, the large-scale clinical trials clearly demonstrated that lowering blood pressure may be obtained by the combined action of the above preventive interventions. Changes in lifestyle and associated pharmacological treatment reduce the cardiovascular risk similarly to what happens for the other major cardiovascular risk factors [12].

Atrial fibrillation requires specific care not because of the rhythm disorder in itself, but, primarily, for the thrombo-embolic complications that accompany these arrhythmias with high incidence [31-34]. The disorder is characterized by disorganized atrial electrical activation and

irregular atrial contraction. Intratrial thrombi occur progressively with peripheral embolism. The anticoagulation treatment using warfarin is the goal to reduce vascular complication primarily stroke [35], although it could be of limited use in hypertensive patients.

The excellent review of Ghiadoni *et al*. [36] shows again how hypertension and atrial fibrillation are the most common cardiovascular risk factor and clinically significant arrhythmia, respectively. These conditions frequently coexist and their prevalence increases rapidly with aging.

Despite several different risk factors and clinical conditions predisposing to, hypertension for its high prevalence in the population is still the main risk factor for the development of atrial fibrillation. Several pathophysiologic mechanisms (such as structural changes at the level of left ventricle and or atrium, neurohormonal activation, arterial stiffness, etc.) can contribute to the onset of atrial fibrillation. Some antihypertensive treatments have been shown to contribute to reducing the risk of new-onset atrial fibrillation.

Atrial fibrillation is a major risk factor for stroke, which is further increased in the presence of hypertension. For this reason, hypertension is included as a major risk factor in the available models for the risk stratification and the prevention of thromboembolism in patients with atrial fibrillation. The relationship between atrial fibrillation and hypertension is widely discussed in the review, looking at the possible specific indications of the antithrombotic treatment with new classes of anticoagulants in the prevention of thromboembolic events in hypertensive patients with atrial fibrillation.

There is evidence that arterial stiffness is strongly related to both elevated blood pressure and other major cardiovascular risk factors including metabolic syndrome. Arterial stiffness is a vascular parameter [37,38] whom characteristics depend on the structural elements within the arterial wall for example muscle, elastin and collagen. These bear the pressure on the wall when the wall is distended. In the circulatory system, there are several sites where there is obstruction resistance or impedance. This includes arterial branch points, places where there is stagnation of flow, and areas where the lumen diameter moves from large to small or vice versa. Therefore, impaired blood vessel dilation influences arterial stiffness and, consequently, might increase blood pressure [39,40].

Similarly, metabolic syndrome has a role as the strongest metabolic risk factor for cardiovascular disease. It may act as an isolated factor or, conversely, associated with others.

Metabolic syndrome [41], differently named as syndrome X, metabolic syndrome X, Reaven syndrome, consists of a large number of metabolic disorders characterized by obesity, high blood pressure, changes in lipid profile with elevated LDL-Cholesterol and low HDL-Cholesterol, increased triglyceride concentrations, and, particularly, high blood insulin levels. The fundamental defect in this syndrome recognizes a different, but elevated, degree of insulin resistance to two levels: adipose tissue and muscle. Insulin resistance syndrome is usually associated with endothelial dysfunction and changes in those haemostatic metabolites having a prothrombotic effects.

The association of the metabolic syndrome with changes in the arterial wall characteristics needs a further explanation.

The review of Tziomalos *et al*. [42] sets the arterial stiffness independently associated with increased cardiovascular risk in patients with cardiovascular risk factors and in the general population. Metabolic syndrome (MetS) is frequently characterized by increased arterial stiffness since all components of MetS are implicated in the pathogenesis. The management of arterial stiffness in patients with MetS is widely discussed in the review. Several small, short-term studies showed that lifestyle changes, antidiabetic, antihypertensive and lipid-lowering agents improve arterial elasticity. However, differences appear to exist between different classes of agents, with statins and inhibitors of the renin-angiotensin-aldosterone system having the more favorable effects on arterial stiffness. A multifactorial approach appears to be the optimal management of increased arterial stiffness in patients with MetS.

Still on the diagnosis of hypertension and its consequent treatment, guidelines, which are in continuously and progressively update, are the basis of a proper proceeding.

The 2013 guidelines [43] emphasizes the subject that 2013 guidelines on diagnosis and management of high blood pressure have been recently issued by the European Society of Hypertension/European Society of Cardiology (ESH/ESC), which have prepared and published a new document. The guidelines provide a comprehensive assessment of what needs to be done by general practitioners in assessing the blood pressure values, the cardiovascular risk profile and the target organ damage as well, They also provide recommendations on when and how to start with antihypertensive drug treatment, emphasizing that the primary goal of the therapeutic intervention is the blood pressure control. Additional goals are represented by the regression of target organ damage, and the improvement in overall cardiovascular risk profile. Particular emphasis is given by new guidelines on the need to make use of a combination drug treatment to achieve such goals.

It is worth noting that several factors and disease may cause vascular damage either under the metabolic or clinical profile. Among these, the psoriasis, which shows an increased incidence, plays a significant role [44-47].

Kannel *et al*. [47] in their excellent paper spoke properly of cardiometabolic risk in psoriasis assessing that psoriasis is associated with an increased risk of cardiovascular (CV) complications. Overall, the pathogenic mechanisms involved in premature CV complications in psoriasis appear to be complex and multifactorial, with traditional and nontraditional risk factors possibly contributing to the increased risk. Based on what is known about the pathogenesis of psoriasis and extrapolating the current knowledge on CV complications in other inflammatory diseases, the authors underline as studies are needed to investigate if appropriate control of the inflammatory, immunologic and metabolic disturbances present in psoriasis can prevent the development of this potentially lethal complication. It is clear that there is a great need for heightened awareness of the increased risk of vascular damage in patients with psoriasis. It is also crucial to closely monitor patients with psoriasis for CV risk factors, including obesity, hypertension, diabetes, and hyperlipidemia. Whether treatment regimens that effectively manage systemic inflammation will lead to prevention of CV complications in psoriasis needs to be further investigated. Clearly, studies should focus on establishing the exact mechanisms that determine CV risk in psoriasis so that appropriate preventive strategies and treatment guidelines can be established.

In this way, the very excellent review of Katsiki *et al*. [48] supports the concept that psoriasis is a chronic systemic inflammatory disease characterized by topical skin lesions as well as an increased risk for cardiovascular disease (CVD). Similar to other reports [46,47], in this review, there is also increasing evidence that patients with psoriasis are more prone to several CVD risk factors (hypertension, obesity, dyslipidemia and smoking), non-cardiac vascular diseases (carotid, peripheral artery and chronic kidney disease) and metabolic co-morbidities (type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease and obstructive sleep apnea) compared with the general population. The associations are even greater in patients with severe psoriasis and those with psoriatic arthritis. Insulin resistance, endothelial dysfunction

and obesity induced by several adipokines and inflammatory cytokines are proposed as the common mechanisms linking psoriasis with CVD, vascular risk factors and metabolic diseases.

Drugs that reduce CVD risk and improve metabolic parameters may also beneficially affect psoriasis severity and prognosis. Furthermore, anti-psoriatic drugs can exert different effects on CVD risk and metabolic co-morbidities. Therefore, physicians should be aware of these associations in order to adequately monitor and treat psoriatic patients.

The metabolic effects of cardiovascular risk factors are the topic of the review of Hannukainen *et al*. [49]. Obesity and diabetes are growing threats for cardiovascular diseases (CVD) and heart failure. In order to identify early and effective treatment or prevention targets, it is fundamental to dissect the role of each organ and the sequence of events leading from health to obesity, diabetes and cardiovascular diseases. The advancements in imaging modalities to evaluate organ-specific metabolism in humans in vivo is substantially contributing to the stratification of risk, identification of organ-specific culprits and development of targeted treatment strategies. This review analyzes the contribution provided by imaging of the heart, skeletal muscle, adipose tissue, liver, pancreas, gut and brain for the understanding of the pathogenesis and cardio-metabolic complications of obesity and diabetes, and to the monitoring of treatment responses in humans. Emerging fields of investigation, including the role of cardiac fat in the pathogenesis of cardiovascular disease, the conversion of white into brown adipose tissue in the treatment of obesity, the control weight and energy balances by the brain, the integration between omics and imaging technologies to help establish biomarkers, and the characterization of gut metabolism in relation with the gut microbiome, opening a very promising preventive/therapeutic perspective should be kept in mind in this field of research.

In my opinion, this review requires some comments. Firstly, the paper ranges several body organ involvement treating different metabolic steps. This fact is a clear evidence of the interference of a cardiovascular risk factor not only at a cardiovascular level, but also in other districts apparently not considered. Secondly, it seems to may well ask what effect on the cardiovascular system may exert multiple metabolic interventions. The result is an enhancement of the effects, or, on the contrary, can occur between their responses in conflict? Third, as already mentioned, intuitive consideration is that must be covered a long way to deeply understand the intrinsic mechanisms that regulate very complex factors.

It is worth noting that chronically altered glucose metabolism interferes with (18) F-FDG uptake in malignant tissue and healthy organs and may therefore lower tumor detection in (18) F-FDG PET/CT. In the presence of diabetes mellitus and obesity [50] there is evidence that changes in diabetes, insulin, and obesity affect the FDG biodistribution in muscular tissue and the brain. Although tumoral uptake is not significantly impaired, these findings may influence the tumor detection rate and are, therefore, essential for diagnosis and follow-up of malignant diseases.

Some topics related to the use and impact of the newer imaging technologies for assessing the diagnostic characteristics of the cardiovascular system need to be investigated thoroughly.

The review of Thijssen and de Korte [51] is specifically intended for the interested outsider of the field of echocardiography and it presents a short introduction into the numerous ultrasound (US) methods and techniques for anatomical and functional diagnosis of the heart. The basic techniques are generally used for some time already, as there is the one dimensional (1D) Motion) mode, the real time 2D B (rightness) mode technique and the various Doppler measurement techniques and imaging modes. The M-mode technique shows the movements of the tissue in a 1D B-mode display vs. time. The 2D B-mode images are showing the heart contractions and dilations in real time, thus making this technique the basic tool for detecting anatomical disturbances and myocardial (localized) abnormal functioning. Improved image quality is achieved by Second Harmonic Imaging and myocardial perfusion can be quantified using Contrast Agent Imaging. Doppler techniques were introduced in the fifties of last century and used for blood flow velocity measurement. Continuous wave (CW) Doppler has the advantage of allowing measurement of high velocities, as may occur in vascular or valvular stenosis and insufficiency. The exact location of the major Doppler signal received cannot be estimated made this technique ambiguous in some clinical problems. Single gated Pulse Wave (PW) Doppler velocity measurement delivers exact location of the measurement position by using an interactively positioned time (=depth) gate in which the velocity is being measured. The disadvantage of this technique is the relatively low maximum velocity that can be measured. Multigate PW Doppler techniques can be used for the assessment of a velocity profile over the vessel cross section. A more sophisticated use of this technique is the combination with 2D B-mode imaging in the color Doppler mode, called “color flow mapping”, in which the multigate Doppler signal is color coded and shown in 2D format overlayed in the conventional 2D B mode image. In the past two decades, technique to quantify myocardial function were developed: Tissue Doppler Imaging (TDI), Strain Rate and Strain Imaging. The temporal resolution of ultrasound imaging can be further improved by Plane Wave Imaging, and Synthetic Aperture Imaging. The recent introduction of 2D matrix transducers extended the real time imaging potential by allowing 3D imaging and sophisticated segmentation techniques for the estimation of quantitative functional parameters, as for instance cardiac output.

Still, Lauritzen *et al*. [52] in their review treating the hiperpolarized metabolic MR in the study of cardiac function and disease, analyze mainly the metabolism of the heart and cardiac disease as well as the principal aspects of other disease under this profile.

Hyperpolarized magnetic resonance (MR) is a novel technique that can visualize and quantify myocardial metabolism. Hyperpolarization can enhance the signal from biological molecules of interest by more than 10,000 times. After injection of the biological molecule, the cellular uptake and conversion can be measured and specific enzymatic pathways can be examined in real time. We review the role ofhyperpolarized MR in identifying changes in cardiac energy metabolism in vivo, and present the extensive literature on hyperpolarized pyruvate that has been used to characterize cardiac disease in various models, such as myocardial ischemia, hypertension, diabetes, hyperthyroidism and heart failure. The technical aspects of the technique as well as the challenges of translating the technique into clinical practice suggest very promising results. Hyperpolarized MR has the prospect of transforming diagnostic radiology by offering new insights into cardiac disease.

Advances in nuclear cardiology methods are the most obvious expression of the continuous progress of this branch of medicine [53,54]. Over 5 million examinations per year are practiced in the United States that are about one-third of all diagnostic nuclear medicine exams. It is now well accepted that the basis of nuclear medicine is the use the properties of several radionuclides to have a particular tropism for different cardiac structures.

Santarelli *et al*. [55] underline that cardiac health is dependent on the heart’s ability to utilize different substrates to support overall oxidative metabolism. To characterize a variety of cardiac diseases, there is an ever growing demand for accurate noninvasive approach of myocardial substrate metabolism evaluation. Data obtained from quantitative metabolic imaging modalities add functional material to the anatomic imaging modalities and can aid patient management. Therefore, the role of noninvasive imaging techniques (such as PET, SPECT, MR spectros-

copy and chemical-shift imaging) to detect the metabolic footprints of heart disease has to be carefully examined. The progress on models and methods to estimate kinetic parameters of dynamic processes using data acquired from cardiac imaging modalities is worth to be known.

Finally, it seems appropriate to ask what is the role and metabolic responses of the heart in different stages of development, particularly in old age. Regardless of the mechanism, a common feature of aging-related disease, including the heart, is the involvement of metabolic systems in general, and the mitochondria in particular [56,57]. Cardiac muscle meets a progressive decline in its function due to a mechanism of remodeling, which depends on the advanced age as well as changes in gene characteristics [58].

In conclusion, this issue allows useful updates in the field of cardiovascular metabolism and diagnostic technologies, whose studies are continuously in progress.

Therefore, significant perspectives on the future development of cardiovascular disease may be obtained.

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Aurelio Leone, MD
FASH, FRSPH
Via Provinciale 27
Castelnuovo Magra, Italy
19030
Tel/Fax: +390187676346
E-mail: reliol@libero.it