

A plea for interdisciplinarity: Cardiodiabetology - Arterial Hypertension Branch

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It is unknown when and who used for the first time the term "interdisciplinarity," which is relatively recent. However, we must remember that the concept of medicine in all that time was a mixture between philosophy, religion, astrology, etc. Aristotle from Stagira (384-322 BC), known as a famous philosopher (his mentor had been Plato) approached also the embryology, anatomy and physiology, among others (astronomy, physics, geology and geography). I always remember the sentence: "Knowledge means to know the cause." The causal roots of the diseases appeared only in the 19th century. A little earlier, Pitagora of Samos (580 - 500 BC), a mathematician and philosopher, had also elaborated his own concepts of medicine. However, the father of medicine remains Hippocrates of Cos (460 - 377 BC). Many of his recommendations remain valid nowadays and the oath of Hippocrates (460 - 377 BC) is still taken by all the medics entering the profession.

More interesting appeared to be the ancient Chinese medicine and I was surprised to see mentioned the famous book "Nei Jing Su Wan" dated sometime between 1500 and 500 BC, recalled by Martin S. Martin in the chapter "History of cardiology" from the re-

cently published (2015) "Clinical Cardiology"[1], where he noted the first description of the blood circulation: "the blood circulation flows continuous, in circle and never arrest." So, the description of circulation in the body by William Harvey (1578 - 1657) published in 1628 has been preceded with more than 2 millennia by Chinese writings. It is worthy to note that in the year 300 AD, Wang Shu-Il wrote in 10 volumes "The classical treatise about pulse", describing at least 18 characteristics of the pulse in various conditions. It's obvious that "hard pulse" or "amply pulse" corresponds with hypertension and induration of arteries, the arteriosclerotic process. In addition, 2 of the 12 meridians (Heart, Circulation-Sex) correspond to cardiovascular function and several of their points are used in the treatment of cardiovascular disease.

A pathogenic association

Diabetes and arterial hypertension represent an old couple of two major syndromes which, by their high frequency in the adult population and by their pathogenetic interference, contribute to the actual escalation of the cardiovascular mortality, which must include also the deaths by renal failure and all vascular related complications of diabetes [2-5]. The association between metabolic pathology (obesity and diabetes, known today as "diabesity") and cardiovascu-

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Table 1. Interdisciplinary specialities.

1	Cardiometabolism	10	Gerontometabolism
2	Neurometabolism	11	Stomatometabolism
3	Nephrometabolism	12	Rheumatometabolism
4	Ophthalmometabolism	13	Pneumometabolism
5	Oncometabolism	14	Adipometabolism
6	Dermatometabolism	15	Imunometabolism
7	Urology	16	Psychometabolism
8	Hepatometabolism	17	Epidemiometabolism
9	Maternal-fetometabolism	18	Pharmacometabolism

lar disease is supported by a wealth of epidemiological studies, irrespective if this has been dealt by cardiologists [2,3] or diabetologists [4,5]. That is why, between various interdisciplinary chapters, cardiometabolism is on the first place (Table 1). In addition, the increase in the incidence of these two pathologies has been associated to the same environmental factors, related to the changes in lifestyle. This includes the decrease in the physical activity due to the technological revolution; the increase in the social stress (insecurity of the working place; insecurity in transportation; insecurity related to the future of our children, etc.); finally, the radical changes in food intake, associated with the devastating process of globalization: a perverted strategy to ensure low cost food, using a high number of chemical additives, for their increased consumption. That is why, the "chemical disruption" is claimed more and more by these additives, as potential actors in the transcription factors of human genes encoding some important molecules of various biochemical pathways, including, on one side, the metabolic regulation, and on the other side, the hemodynamic changes leading to hypertension and its consequences [6].

These environmental changes could hold the answer to the question: where do the metabolic pathways and hemodynamic regulation intermingle? The answer could be the hypothalamic neurons, especially in the arcuate nucleus, including the limbic system. These are influenced by various cortical areas, where visual, olfactory or auditory impressions are recorded, processed

and finally, through the hypothalamic region, influence our pathogenic behavior [7,8].

A paradox of our times

Our generation assists hopeless to the following paradox: the duration of life increased significantly, in parallel with the continuous increase in the incidence of both metabolic and cardiovascular disorders, including hypertension. It is a hard question: "Why we are winning the battle but losing the war?"[9]. Indeed, the increased life expectancy of our patients is explained by the technological progress in the tertiary prevention, especially in interventional technology and procedures, such as by-pass surgery, stent procedures, pacemakers, tissue and organ transplant, oncologic therapy and, generally, a better treatment of diabetes and hypertension. However, all that with higher and higher costs.

Beginning with the 60-70's of our last century, diabetes displaced the diabetes from either internal medicine or endocrinology, therefore opening a new world in which cardiology and, inside it, arterial hypertension is an important part. As we mentioned already, between diabetes and hypertension are many overlapping territories that could be efficiently addressed only by an interdisciplinary approach, as resulting from Table 1. Otherwise, obesity and diabetes, by their complications, could be a turntable for many diseases [9]. It is obvious that the metabolic pathology interferes with all other systems of the body, especially with the cardiovascular system, which must respond to all the changes in the composition of the whole blood (mainly the increase in glucose, fatty acids, amino-acids, chemokines, cytokines and other pathogenic messengers released by exosomes from organs or tissues which are interconnected through the arterio-venous and lymphatic system[10-13]. The relationship between obesity and hypertension might be related to the up-regulation of a high number of genes encoding the proteins for extracellular matrix of muscles, [14] and probably in adipose tissue and in other structures.

The metabolic pathogenic trap

The main cause of the metabolic pathology (obesity, metabolic syndrome, type 2 and type 1 diabetes) is re-

lated to the increased biochemical pressure, in the semi-closed / semi-open energy system, in which the input of the fuels (carbohydrates, lipids and proteins) is higher than the energy expenditure [15]. It is worth knowing that the "human machine" is better adapted to a lower than normal energy intake (either imposed by religious rules, or by an accidental isolation of an individual), due to the storage compartment of energy, represented by the subcutaneous adipose tissue, and in extreme conditions by utilization of some structural proteins for producing glucose by neoglucogenesis processes. In addition, the yield of utilization of such fuels can increase by incompletely known mechanisms. Such an adaptive mechanism has been developed in the early anthropogenesis, when food availability was very limited, at times, so that our human genetic construct (so-called paleolithic genotype) has been adapted to save energy under such conditions [7]. It is obvious that, in all the time, with food, they ingested more potassium than sodium. This can explain why the modern salt intake is one of the factors leading to hypertension [6,8,10].

In contrast, the adaptation to higher energy input into the system is very limited compared to the efficient adaptation of the human body to accidentally low energy intake. The first step is to store the energy as triglycerides in the subcutaneous adipose tissue, which is the "legal" depot. Its capacity is substantial, in the order of several kilograms, especially in subjects with a body mass index (BMI) below 25 mg/m². When the capacity of the subcutaneous adipose tissue is overwhelmed by the circulatory fatty acids will be stored as triglycerides in some "semi legal" locations, represented by visceral adipose tissue and finally in "illegal" locations represented by the liver, pancreas, kidney, skeletal muscles, and perivascular. These "illegal" depots generate an immune reaction known as "low-grade inflammation".

The only escape valve should be the increase in the brown adipose tissue rich in uncoupled proteins (UCP), which can increase the energy expenditure by dissipating chemical energy as heat, via UCP. However, their role is to enter into action only in a dangerously cool milieu, in order to increase the temperature of the body and not to spend energy in vain. The actual attempts to oblige some white adipose tissue cells to adopt a thermogenic phenotype, successful in some small animals, [16] might not be efficient in humans.

Recently, we divided the adipose sites in three categories: 1. "quiet" (silent) adipocytes, at a BMI < 25

kg/m²; 2. "restless" adipocytes, when the BMI progressively increases from 25 to 30 kg/m²; 3. "the aggressive" adipocytes, when the BMI > 30 kg/m² [17-18]. The evolution of BMI from normal value to higher and higher numbers is also associated with the accumulation of fat in the visceral adipose tissue, a compartment which can be well-documented using certain resistometric methods. Apart from the low-grade inflammation, the progression of the BMI towards higher values is associated with lower production of adiponectin, in association with a higher production of proinsulin, which indicate the β -cell dysfunction related to the increased number of insulin receptors from the excessive adipose tissue [19]. In our experience, the increased proinsulin / adiponectin ratio is a better predictor for the evolution of obese people towards type 2 diabetes [17].

Blood pressure vs. plasma glucose

Interesting to mention is the succession of the two disturbances: more often, arterial hypertension precedes the onset of diabetes (in about 50-60% of cases); in other instances, in lower percentages (~ 30-40% of cases) diabetes precedes the onset of arterial hypertension. These successions require a comment! First, in relation to the reproducibility of the parameters used for the diagnosis of each of the two conditions, arterial hypertension might increase artificially if the cut-off values for systolic/diastolic blood pressure (SBP/DBP), for instance 130/80 mmHg vs. 140/85 mmHg [3]. For the diagnosis of diabetes, the decision to take create a "grey zone" interposed between normal values [fasting blood glucose (FBG) <100 mg/dl, instead the previous <110 mg/dl and <140 mg/dl at 2 h after an oral glucose tolerance test (OGTT) using 75 g of glucose] and diabetes (a FBG \geq 126 mg/dl and/or 200 mg/dl, any time during the OGTT) imposed the two new "glycemic categories" (so-called "dysglycemia"): impaired fasting glucose (IFG) - defined by fasting blood glucose between 100 mg/dl and 126 mg/dl, with the value at 2 h during OGTT <140 mg/dl; and impaired glucose tolerance (IGT) - when the fasting blood glucose <100 mg/dl, but >140 mg/dl at 2 h during OGTT. These two categories have been sustained by their association with late late chronic microvascular complications. In the DCCT study, some retinal microvascular changes have been noted in patients with a FBG >100 mg/dl. An analogy

could be made between FBG and 2 h blood glucose and the SBP/DBP [11].

The association between diabetes and hypertension is well-documented: SEPHAR I and II [2]. However, the relationship between blood glucose level and blood pressure was not yet exhaustively studied. The new available technologies for the continuous recording of these two parameters open a new perspective in understanding the relationship between them, in both the healthy subjects, in patients with hypertension only and type 2 diabetes, only, and, finally, in patients with both conditions (type 2 diabetes and hypertension). Because both conditions (hypertension and diabetes) are close related with obesity, the value of BMI must be included in the analyses. The inclusion in the study groups must be done in subjects from very old age and, separately, in males and females. The results might really show if the interdependence between the three parameters: blood pressure, plasma glucose, BMI. Such a study will really be an interdisciplinary one.

Risk factors for hypertension and diabetes

If we analyse the risk factors for these two entities we will observe that the majority of them are common: the weight excess/obesity/dyslipidemia (HDL-cholesterol, LDL-cholesterol, total cholesterol), sedentarism,

smoking, food intake, age and sex of the patients. The only important specific factor for hypertension seems to be the sodium intake, over the recommended amount: <2.4g Na (which correspond to <6g salt/day). Unfortunately, in our country, the salt intake is >10g/day. In one of our studies, carried out in the 1970' on diabetic patients, the salt intake (assessed by 24 hours urinary elimination) was about 12.1 g/day. At that time, such a high intake of salt was explained by the compensation of the restriction of sweet foods with salty ones [3,20].

If we look carefully for each risk factor, we have good therapeutic solutions. In addition, we need good practitioners to find the best medical therapy for each specific case. Indeed, Cefalu et al. (2016) conclude that "intensive glycemic control, early in the natural history of diabetes, at the time when CVD is not established, can reduce later CVD," invoicing here the so-called "metabolic memory," which yet needs further confirmation [21].

However, due to the multiplication of antidiabetic drugs, Smith et al. (2016) conclude that "to consider a more targeted approach to what is, in effect, global CVD safety trial requirements for all new type 2 diabetes trial medications in development." Indeed, the treatment of diabetes and the other CVD risk factors need a careful scrutiny and responsibility for our patients [22].

Table 2. The main risk factors for cardiovascular mortality.

Risk factors for cardiovascular disease	Biomarkers	Organ/cells involved	Main pathologic target	Main deadly cause
Diabetes	HbA1c / Proinsulin/insulin ratio	Pancreatic β -cells	Heart muscle (cardiomyopathy)	Myocardial infarction* / Stroke
Dyslipidemia	LDL-cholesterol / TG/HDL-cholesterol	Liver	Heart muscle (cardiomyopathy)	Myocardial infarction* / Stroke
Blood pressure (BP)	Systolic / diastolic BP	Hypothalamic centers	Endothelial cells**	Heart failure Renal failure
Obesity	BMI Proinsulin/adiponectin ratio Leptin	Visceral and subcutaneous adipose tissue	B-cell overstimulation Proinflammatory reaction	Cardiovascular complications

*circulating cardiac bio-markers: troponin T <14 μ g/L; NT-ProBNP >125 pg/mL

** many cytokines and chemokines (see [11])

Any prevention requires a good prediction

In all studies for the prediction of a chronic disease, the first step is to conceive several risk scores: clinical (including anthropometric data), biochemical, neuro-hormonal and genetic one. For the last one (the genetic risk score), there were big expectations when the first genetic studies were designed. Except monogenic diseases and some cancers, in the systemic diseases (diabetes and cardiovascular disease included), then genes found to be associated with one or other disease, help us to understand better some phenotypic characteristics, but not to predict better the occurrence of a such disorder. The genetic studies on the essential are scarce and poor in the prediction of its clinical onset.

A good prediction needs better knowledge of the pathogenesis

The pathogenetic mechanisms operating in arterial hypertension are harder to elucidate. The involvement of higher insulin secretion, oxidative stress, or other hormones and enzymes (such as renin-angiotensin-aldosterone pathway), or of some dysregulations of neuro-hormonal networks in hypothalamic region, cannot fully explain their involvement in the cardiac, cerebrovascular or peripheral disease. Who read carefully our book, related to renal hypertension [23], could observe that the majority of the mechanisms associated with hypertension had already been described before (1971). The major news comes from the careful study of endothelial function, which, in our textbook on diabetes [11], already in 2004, a chapter of 18 pages had been devoted to this extremely interesting cell, whose adaptive plasticity is well known. The pro-inflammatory phenotype is adopted when other components of the circulatory system (increased sympathetic tonus or of the heart output), especially in overweight or obese subjects [24-26].

A look in the future

The next step in understanding the pathogenesis of hypertension and cardiovascular disease is that of the careful analyses of endothelial cells and their underlin-

ing morfo-functional support: smooth muscle fibers, subjacent adventitia, pericytes, autonomic sympathetic and parasympathetic nerves and the intercellular matrix. The remodellation of this matrix is under the control of the multiple functions of the endothelial cells: vasodilation, vasoconstriction, fibrinolysis antiplatelet and anticoagulant. To do that, a high number of molecules, starting with nitric oxide, various prostaglandins, endothelins and other tens such factors [11,21,27-30]. Intuitively, the endothelial cells for various organs and tissues must have specific genetic expressions and chemokines production for interconnection with various remote organs. Their continuous turnover requires complex biochemical pathways and a capacity of adaptation to all regimens of blood pressure. Therefore, a novel molecular world is welcoming clever researchers from now on, for many years.

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