https://doi.org/10.46344/JBINO.2025.v14i03(a).06

NEUROCARDIOLOGY: PATHOPHYSIOLOGICAL MECHANISMS IN MYOCARDIAL INFARCTION IN YOUNG PATIENTS AND IN ACUTE CARDIOVASCULAR EVENTS WITH EMOTIONAL INFLUENCE

Furlanetto Jr MI

neuroscientist specializing in Neuroclinical Syndrome Research, vascular and endovascular neuropsychiatrist surgeon, master in Health and Aging. *Coordinator of Clinical Studies of Disorders and Syndromes* at CPAH - Heráclito Research and Analysis Center.

ABSTRACT

Introduction: Notably, a phenomenon of increased early incidence of some diseases is without control and real understanding, affecting young adults and adolescents, as in the case of obesity, colon cancer, metabolic syndrome, and acute myocardial infarction (AMI). Although the mortality rate of AMI has decreased, it is currently increasingly common to find young people diagnosed with AMI; studies have already shown this increase in incidence in this age group. ***Objective:*** The integration of intricate processes of genetic pathways related to lipid metabolism, inflammation, and coagulation helps in the understanding and identification of early AMI (IAMP), in addition to guiding primary prevention strategies. ***Methodology:*** A clinical synthesis with theoretical implications was performed, based on neurobiological and neurogenomic mechanisms, which presents the integration of maladaptive neuroscience with cardiology. ***Results:*** By reviewing the data on the risk factors of IAMP, its little-known pathophysiological processes, we identified its possible relationship with psychosocial stress, which can currently be assessed through a clinic focused on clinical neuromarkers related to stress and emotional dysfunctions that are attributed to neuromaladaptivebiobehaviors. To bring better understanding, we performed the integration of the clinical and pathophysiological components related to cardiology and psychosocial neuropsychology. ***Discussion:*** Stressful factors have been involved in CVD for a long time, and there has never been a methodology to objectively assess the neuropsychological clinic, in addition to the lack of integration of the various underlying and intricate pathophysiological mechanisms, which must be assessed for the strength of the causal effect through new population research. ***Conclusion***: We present a clinical model with an approach to stressful effects through an unprecedented clinical approach to maladaptive biobehaviors, which involves objective assessment through clinical neuromarkers and enables a new organization of research and insights, in addition to the attempt to elucidate the origins of NCDs and MI.

Keywords: Neurocardiology, early myocardial infarction, neuroscience, inflammatory biomarker.

1. Introduction

Non-communicable chronic diseases (NCDs), such as cardiovascular diseases (CVD), neoplastic diseases, metabolic diseases (obesity and diabetes), and chronic respiratory diseases, are responsible for 74% of global mortality, causing 41 million deaths annually, and are associated with high rates of premature morbidity and mortality, reduced quality of life, loss of productivity, and high economic costs for countries. [1]

Notably, a phenomenon of increasing early incidence of some diseases is without control and real understanding, affecting young adults and adolescents, as in the case of obesity, colon cancer, metabolic syndrome, and acute myocardial infarction (AMI). [1-2]

Although the mortality rate from AMI has decreased, it is currently increasingly common to find young people diagnosed with AMI; studies have already shown this increase in incidence in this age group. [1-2]

The terms "myocardial infarction in young patients" or "early acute myocardial infarction" (AAMI) are not defined by guidelines and protocols; most studies consider the cutoff point to be less than 40 to 50 years to identify this group of patients. [1-2] The few studies that address this topic have shown that 6 to 12% are under 45 years old, 3.4 to 5.6% are under 40 years old, and 1.6% are under 35 years old, and thus AMI in young adults is gaining a considerable proportion of the total incidents of CVD events. [3-7]

The young adult population has undergone changes in lifestyle over the decades, favoring the onset of atherosclerosis at earlier stages and, consequently, the onset of cardiovascular events earlier. [3-7]

However, the underlying pathophysiological features, as well as the characteristics of the atherosclerotic plaque and the risk factor profile, differ between young and older patients with MI. [2]

Classical risk factors for atherosclerosis include psychosocial factors, smoking, alcohol consumption, diet, physical inactivity, obesity, hypertension, diabetes, and dyslipidemia, and they contribute to more than 90% of the risk of CVD. 3-7 The differences already identified in the risk factor profile of PAMI are higher prevalence of smoking, family history of premature coronary heart disease (CHD), and male gender. [3-7]

In addition, PAMI may be associated with the use of illicit substances, stimulants, psychosocial stress, addiction, and, inductively, with new genetic dysfunctions caused by mutations, especially in the coagulation and lipid metabolism pathways (increased lipoprotein-a). [3-7]

PAMI patients generally have eccentric atherosclerotic plaques with inflammatory characteristics, fewer lesions, and the lack of real clinical and pathophysiological understanding may lead to the underestimation of important differences that favor the delay or absence of diagnosis. [2]

Studies using electrocardiogram data indicate that in the vast majority of cases of early AMI, absence of ST-segment elevation is expected; however, currently there is an increase in MI with ST-segment elevation. [2]

The short-term prognosis of young patients with MI is better than for older patients; however, current data raise concerns about long-term outcomes, particularly in those with reduced left ventricular systolic function, as the

tendency for progressive complication is heart failure. [3]

Still, there is a large knowledge gap regarding modifiable risk factors that may help alter the course of this end of the CAD spectrum among young patients. [3]

IMAP is a significant problem, but there is a paucity of illuminating data, and in this review we present an integrative neurocardiology approach that addresses different risk factors that are intricately linked to the pathophysiological processes in IMAP. [2-4]

2. Objective

To highlight the neuropsychological clinical aspects of common biobehaviors, which are integrated into the intricate processes of inflammatory, immunological, genetic, and epigenetic pathways that help in the destabilizing effects of an atherosclerotic plaque, which causes an acute cardiovascular event, in addition to their direct relationships that maintain the epidemic of obesity and addictive disorders, which may be associated with some early diseases that present common risk factors such as IMAP, and thus organize and guide new prevention and treatment strategies.

3. Methodology

A bibliographic search was conducted in the PubMed and Web of Science databases. The inclusion criteria were research that demonstrated clinical evidence associated with neurobiological mechanisms associated with cardiovascular diseases, acute myocardial infarction, and myocardial infarction in young adults and genetic alterations associated with IAMP.

Studies were also chosen for convenience, which presented data on adverse childhood emotions. A clinical synthesis with theoretical implications was performed, based on neurobiological and neurogenomic mechanisms, which presents the integration of maladaptive neuroscience with cardiology.

4. Results

By reviewing the data on the risk factors for MI and its little-known pathophysiological processes, we identified its possible relationship with psychosocial stress, which can currently be assessed through clinical studies focused on clinical neuromarkers related to stress and emotional dysfunctions that are attributed to neuromaladaptivebiobehaviors.

To provide a better understanding, we performed the integration of the clinical and pathophysiological components related to cardiology and psychosocial neuropsychology.

We present the syntheses in cardiological and neurological components, with subsequent exploration of the pathophysiological mechanisms and findings of genetic alterations related to MI.

4.1 Cardiological Component

4.1.1 Pathophysiology of Atherosclerosis

Habitual atherosclerotic disease is characterized by chronic and local traumatic immunoinflammatory mechanisms, which can evolve with the accentuation of these same mechanisms in an acute form, causing a new event, because with the instability and rupture of the plaque, there is exposure of molecules and coagulation factors to the lumen of the arteries, which generates the formation of a thrombus immediately and causes occlusion of blood flow and thus produces the ischemic event, such as AMI. [6-8] This cardiovascular event is more expected in older individuals (>55 years), because atherosclerosis has a slow and insidious onset. [6-8]

The pathophysiology of atherosclerosis begins after the ingestion of lipids and already moves towards the intimal accumulation

of oxidized lipoproteins, resulting in lipid-rich macrophages or foam cells. [6-8]

Smooth muscle cells migrate to the intima after forming the fibrosis cap, which can calcify. This fact demonstrates that, initially, the atherosclerotic lesion grows towards the lumen of the vessel, characterizing arterial remodeling. [6-8]

It is noted that in bifurcations and winding arterial paths, there is a higher prevalence of atherosclerotic lesions, as they form the division of blood flow, which tends to increase blood turbulence, associated with the increase in the shear stress mechanism. [6-8]

This mechanism, which is the increase in blood flow stress on the endothelium, activates local inflammatory mechanisms, such as the expression of the vasodilator nitric oxide and inflammatory cell adhesion molecules, modulating endothelial function and vessel caliber. [6-8]

Thus, changes in arterial anatomy and geometry can increase the risk of injury, such as the widening diameter, which is the manifestation of remodeling caused by the atherogenic process. [6-8]

4.1.2 Classical risk factors

The prevalence of CVD in the United States is expected to increase to 45% by 2035. This projected increase will be accompanied by a twofold increase in direct and indirect medical costs related to CVD. [13]

The burden of NCDs is increasing in adolescents and young adults in both developed and developing countries. Data from the Global Burden of Disease Study (2019) of the European Union member states revealed that NCDs were responsible for 38.8% of all deaths in individuals aged 10 to 24 years. [13]

Despite the multicausal nature involved in the etiology of NCDs, the main determinants of these diseases are behavioral risk factors, represented by smoking, alcohol use, unhealthy diet, physical inactivity, overweight, and obesity, which can lead to increased blood pressure, elevated serum cholesterol levels, and blood glucose. [13]

Currently, these factors are highly prevalent in adolescents and young adults and, when combined, increase the likelihood of developing NCDs, CVD, and metabolic syndrome. [13]

A recent study that evaluated the factors associated with risk factors for chronic noncommunicable diseases in adolescents and young adults in Brazil evaluated 10,460 individuals and identified that young adults, males, with less education, of Black race/skin color, with lower family income, and living in urban areas had a higher prevalence of most risk factors. [13]

The prevalence of smoking among young people was 8.9%, alcohol consumption once a month or more was 28.7%, and alcohol abuse was 18.5%. The most socioeconomically developed regions had a higher prevalence of most risk factors. [13] According to Estivaleti JM et al., the prevalence of overweight is higher in middle-aged adults compared to adolescents and adults and demonstrated a sustained increase in the obesity epidemic in all sociodemographic subgroups in Brazil. [6]

Furthermore, the prevalence of obesity increased from 11.8% in 2006 to 20.3% in 2019. The projected prevalences until 2030 are estimated at 68.1% for overweight, 29.6% for obesity, and 9.3% for obesity classes II and III.[6-11]

In the current Brazilian study, the prevalence of overweight was 32.5%. In the general population, stress has been found to increase the risk of CVD through direct and indirect behavioral pathways mediated by

biological processes, such as hormonal, immunological, and inflammatory dysfunctions. [7-11]

4.1.3 Smoking

Subclinical cardiovascular injury was assessed using markers of inflammation [high-sensitivity C-reactive protein (hsCRP), interleukin 2 and 6 (IL-2 and IL-6), tumor necrosis factor alpha (TNF-a)], and thrombosis (fibrinogen, D-dimer, homocysteine). [6-8] Acute exposure to smoking may be associated with inflammation, thrombosis, endothelial dysfunction, arterial stiffness, and coronary microvascular dysfunction. [6-8] Smoking activates the nuclear transcription factor kappa B pathway, which induces the transcription of genes involved in the systemic inflammatory process, increasing the number of neutrophils and macrophages, which release pro-inflammatory mediators, such as Tumor Necrosis Factor-γ and Interleukin-6. [6-8] Smoking promotes prothrombotic changes through platelet activation, since exposure to tobacco increases the levels of platelet activating factor and inhibits the formation of nitric oxide (due to oxidative stress), and thus influences the balance of vascular tone. [6-8]

4.2 Subclinical Cardiovascular Disease

CVDs related to atherosclerosis can be clinically considered as secondary diseases to primary diseases such as obesity, DM, dyslipidemia, smoking, and hypertension, together with risk factors, since they are initially asymptomatic or subclinical and can evolve with chronic and acute conditions. [9-14]

Studies have shown that subclinical CVD is identified through mechanisms of microvascular endothelial dysfunction that generate markers such as coronary artery calcium, thickening of the intima-media complex of the carotid arteries, and increased inflammatory markers, which are associated with the instability burden of the atherosclerotic plaque and future CVD events. [9-14]

Hamada S et al. demonstrated through T1-weighted Magnetic Resonance Imaging that carotid plaques with high signal intensity predict the risk of CAD, and the characteristics of an unstable plaque show a correlation with the increase in many pro-inflammatory molecules, such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-γ (TNFγ). [18]

Kim S, Lee S et al. evaluated inflammation in carotid plaques of 74 patients who presented with AMI through fluorodeoxyglucose positron emission tomography/computed tomography ((18)F-FDG PET/CT) within 1 week after the diagnosis of AMI and demonstrated in vivo that carotid arterial inflammation occurs concomitantly after coronary arterial inflammation. In this group of patients who suffered AMI, 3 patients suffered stroke (CVA) of carotid origin. [14] Furthermore, the systemic inflammatory biomarker high-sensitivity C-reactive protein (CRP) correlated significantly with FDG uptake in the carotid artery, and the presence of cardiovascular risk factors was also related to inflammatory activity. 15 Thus, the evidence that acute inflammation that occurs in the thrombotic and intraplaque event in the cardiac sector can induce inflammation and destabilization of the plaque in another sector, for a certain period, such as in the carotid sector, which complicates with an acute local event, and produces CVA. [15] In the area of vascular and endovascular surgery, the large studies that evaluate the treatments of carotid atherosclerosis, either by endovascular route, which during angioplasty causes rupture of the atherosclerotic plaque, or by surgical endarterectomy, in which aggression and rupture of the plaque also occur during surgery, the surveillance of The occurrence of AMI after 30 days of these treatments is objectively evaluated due

to possible inflammation and plaque destabilization in the coronary sector. [8]

Furthermore, the same clinical effect is observed in treatments of atherosclerotic plaques in the lower limbs, whether by endovascular route or bypass surgery, with AMI being the main clinical complication after these treatments. Thus, there is unequivocally a mechanistic link between the role of systemic immune and inflammatory activation contributing to multivessel instability in symptomatic atherosclerosis, especially in AMI. [6-8]

According to Peter Libby et al., an unstable plaque may be the phenotype of the representation of the existence of systemic inflammation that frequently involves the presence of CAD and thus subclinical CVD. [19]

However, there is a long latency period between tobacco exposure and the development of overt symptomatic CVD, thus requiring the identification of validated biomarkers that can provide data in a shorter, or even prolonged, period of time. [20]

However, there are "proximal" biomarkers that are dysfunctional and act long before distal markers that reflect cumulative damage, which can be identified mechanistically, through neurocardiology, by the clinical and pathophysiological integration of common neuromaladaptive emotional mechanisms of a psychosocial nature, and are intricately intertwined in all stress medicine and significantly influence subclinical CVD and the triggering of an acute cardiovascular event. [17]

4.3 Neuropsychological Component

Currently, some mental disorders (MD), such as anxiety, depression, burnout, and various addictions (such as the internet, for example), also present a progressive and uncontrolled worsening evolution. After the Covid-19 pandemic, scientists identified a 'silent epidemic,' which is related to MD decompensations, loneliness, stress, and interpersonal conflicts as intricate factors. Studies have shown that 70% of potentially preventable deaths from NCDs in adults are the result of health-related behaviors initiated in childhood and adolescence.

4.3.1 Stress and Inflammation

Inflammatory and immunological processes play a key role in the initiation and progression of a wide range of diseases, and several clinical models now demonstrate broad implications for understanding the role of stress in health. [20] Chronic psychological stress is associated with an increased risk of depression, CVD, diabetes, autoimmune diseases, upper respiratory infections, and poor wound healing. Although these associations are often attributed to stress-induced dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, few studies comprehensively assess stressful events and their altered HPA axis responses, which are associated with immuno-inflammatory and genetic mechanisms. [21-22]

This lack of comprehensive approaches is attributable to the lack of a complete and delimited understanding of the neurobiological effects of prolonged stress in humans, as well as their practical and systematic identification, in addition to considering which stress-induced changes play a subsequent role in disease risk. [21-22]

Studies have now shown that the way target tissues respond to cortisol may be more significant than simply increasing hormone levels. [21-22]

Cohen S et al. demonstrated a significant effect on the pathophysiology of chronic stress, such as glucocorticoid receptor (GCR) resistance, which causes a regulatory deficit in the inflammatory response, as there is a decrease in the sensitivity of immune cells to glucocorticoid hormones, which are responsible for terminating the

inflammatory response. [21-22]

Furthermore, Cohen et al. demonstrated that stress (a recent stressful life experience or major stressful life event associated with a long-term threat) can result in GCR, and, consequently, this insufficient control of the inflammatory response generates a greater expression of symptoms and signs, which are generated by the pro-inflammatory response of the disease. They concluded that stress and GCR, associated with increased levels of local pro-inflammatory cytokines, present a greater risk of clinical disease. [21-22]

Studies have shown that stress was associated with GCR, with stressed individuals showing less sensitivity of lymphocyte and neutrophil counts to distributive changes associated with higher circulating cortisol levels. [23-24]

Stress may be associated with the expression of several diseases through its effect on the sensitivity of other immune defense cells to glucocorticoids, as glucocorticoid receptors (GR) are expressed by cells involved in antigen presentation, such as dendrocytes and macrophages, not only in the circulation but also at specific sites of infection and in draining lymph nodes. [23-24]

According to Miller GE et al., chronic stress does not affect the expression of GRa, the active isoform of the receptor, and there is evidence linking stress and cytokines to higher levels of the dominant negative receptor GRβ for cortisol and a lower GRa/GRβ ratio, which may suppress GRa activity and thus contribute to GCR. [23-24] Evidence of GCR in response to chronic stress has been found in parents of children with cancer, spouses of brain cancer patients, and in individuals reporting high levels of loneliness.

Without sufficient glucocorticoid regulation, the duration and/or intensity of the inflammatory response increases, increasing the risk of acute exacerbations, such as those that occur in asthma and autoimmune diseases, as well as the onset and progression of chronic inflammatory diseases, such as CVD and type II diabetes (T2DM). [23-24]

There is now evidence consistent with the effects of stress resulting in an increased risk of CVD due to increased gene expression with the production of interleukins and local inflammatory cytokines. [23-24]

4.3.2 Neurobiology of Stress

Stress is an important part of modern life. Humans, like other species, have developed adaptive mechanisms to limit the physiological or psychological impact of stress. However, exposure to traumatic or cumulative stressors can contribute considerably to the development of several comorbidities. [25]

In fact, the stress response is fundamentally an adaptive phenomenon directed at the reallocation of physiological resources in response to an external or internal stimulus that has threatened homeostasis. [25]

This process of active adaptation through the mobilization of neuroendocrine and immunological mechanisms has been called allostasis. Allostatic load refers to the cost of this rebalancing process for the organism. In situations of acute or sporadic exposure to stress, the cost is low and transient. [25]

However, in situations where the stressor is persistent or the organism is weakened, prolonged engagement or overstimulation of allostatic systems causes a physiological burden that can lead to disease. [25]

This chronic engagement of the stress response system has been associated with a

number of health disorders, including cardiovascular, immunological, and reproductive dysfunction and an increased incidence of stress-related psychiatric disorders. [25-27]

Thus, the current view is that stress-related pathologies develop from unnecessary, excessive, or long-lasting activation of the stress response system that affects physical and mental physiology. [25-27]

Investigation of the mechanisms of adaptive and maladaptive stress response, as well as interpersonal interactions, is critical and includes effects on cognitive and translational function. [25-27]

Acute stress can be defined as a temporary real or perceived challenge to the organism's ability to maintain homeostasis and can be physiological or psychological in nature. [25-27]

The body responds to acute stress by rapidly mobilizing the autonomic and neuroendocrine systems, producing physiological changes that facilitate the response to the threat and the return to homeostasis. [25-27]

Activation of the autonomic system releases epinephrine (E, secreted by the adrenal medulla) and norepinephrine (NE, from the adrenal medulla and sympathetic nerves) that act on peripheral adrenergic receptors. Catecholamines are released into the brain, where they activate receptors in the central nervous system (CNS). The acute effects of catecholamines are short-lived, disappearing within 1 hour, and include cardiovascular actions, allocation of metabolic resources, and sustained alertness. [25-27] The neuroendocrine response is under the control of the hypothalamic-pituitary-adrenal axis (HPA axis), which is the system of glucocorticoids (cortisol) released by the adrenal cortex in response to circulating adrenocorticotropic hormone (ACTH) released by the anterior pituitary. [25-27]

In contrast to catecholamine-induced responses, the effects of glucocorticoids can be rapid (within minutes of stimulation) and long-lasting. [25-27] Long-term effects develop over several hours and include transcriptional effects from activated glucocorticoid receptors (GRs) and epigenetic effects, such as methylation changes in target genes. [25-27]

With prolonged and/or intense exposure to stress (chronic stress), the physiological burden of reestablishing allostasis can produce detrimental consequences for the organism. Chronic glucocorticoid secretion decreases GR expression in the brain, resulting in reduced negative feedback and dysregulation of the HPA axis. [25-27] Due to reduced GR levels, CRH levels increase, and the balance between MR and GR expression is altered; these changes affect the function of other brain areas, particularly the prefrontal cortex (PFC) and hippocampus, and may underlie the emotional and cognitive impairments produced by chronic stress. [25-27] Disruptions in glutamatergic transmission have been linked to depression in clinical studies and in animals analyzed with molecular markers of glutamatergic transmission. It has been suggested that similar adaptations may also underlie HPA axis dysfunction. [25-27]

4.3.4 Development of the Common Maladaptive Biobehavior Cluster

The clinical neuroscience of family interactions and childhood adversities develops a three-level maladaptive connectome through common biobehaviors, which represents a delimited structure of personality traits with the exclusive function of emotional

homeostasis. [36]

The first level represents individual characteristics, where adverse (toxin exposure, physical abuse) and protective exposures are assessed from the prenatal period, along with individual moderators such as subjective experience and protective metacognitive processes, perceived predictability, and emotional intelligence. [36] The second level represents family and peer characteristics, where beneficial and risk-associated influences are captured (type and frequency of social contacts, family environment, bullying events). [36]

The third level represents characteristics of extra-home environments and violent crimes, such as socioeconomic status, social organization, and criminality. [36]

The model begins with the formation of the first group of the system, which is essentially composed of clinical alterations of the objective neuropsychological factors, which are attributed to common neuromaladaptive elements that develop through social interactions between family members early in life and initiate the dysfunction of the first neurological mechanism of family synchrony. [26-35]

4.3.4.1 Family Synchrony System as an Initial Dysfunction

Family synchrony is a neurological signaling mechanism between two individuals that occurs without our knowledge, as it is an automatic mechanism between two brains (two individuals) that initially occurs between family members and modulates the cognitive and behavioral state, with positive or negative changes in the individual emotional state and in the relationships of synchronized people. [28-36]

Family synchrony is characterized by being a common biobehavior, that is, it has its origin and predominance in the neurological and hormonal factor and is common to all human brains, regardless of race, culture, education, and socioeconomic status. Therefore, it depends on the neurobiological component for its execution and effectiveness. [28-36]

The neurobiological component is a system of specific neuronal mechanisms (peripheral oxytocin and dopamine neurons), activations of specific brain regions delimited in a parental care network (PCN), and hormones such as oxytocin (love and trust), vasopressin (aggression), melatonin (depression and insomnia), and cortisol (stress). [28-36]

The parental care network is integrated by subcortical neurons (supporting motherhood), neurons in cortical areas (related to simulation, mentalization, and emotional regulation), and neurons in primary sensory/somatosensory areas, amygdala, insular regions, anterior cingulate cortex (Nac), bilateral temporal cortex, parahippocampal gyrus, superior temporal sulcus, and prefrontal cortex. [28-36] This synchrony system is developed during the first three years of life through the baby's affective and emotional interactions with its biological parents and can be better developed when parents stimulate the babies through the physical senses, which should be observed through the babies' reactions. [28-36]

However, if the parents do not have this synchrony system well developed, their children will clearly not be stimulated and consequently will not develop synchrony correctly and will present deficits or absence of synchrony. [28-36] In addition to being a behavior that begins mechanically and depends on the presence of these neurobiological components, it is considered in the literature as a biobehavior. [28-36]

Family synchrony is characterized by the presence of a deep and effective bond in the interpersonal relationship within the family environment, trust, mutual engagement (partnership), and effective and deep attention, which is reflected in the ability to effectively identify the emotional state of the family member (a process called mentalism). [28-36]

Clinically and rationally, the cerebral mechanism of synchrony between brains begins on the first day of life, and the absence or deficit of family synchrony generates some degree of discomfort between the baby and the parents, which objectively represents the child's first negative experience, and thus the newborn's brain reacts with secondary neurological processes that can become more maladaptive during the experience lived during the first five years of life. [28-36]

However, the first deficient mechanism of family synchrony triggers secondary processes, which all occur simultaneously, which are maladaptive (negative) rather than adaptive (positive) neurological mechanisms, and are all also involved through the quality and effectiveness of the infant's relationships with the biological parents, and are all dependent on neurobiological components:

(1) neuronal deficit of family synchrony;

(2) development of schematic behaviors; (3) neuromirroring in psychosocial contexts through mirror neurons and important concordance in cross-brain synchrony, with activation of parental care networks (PCNs) in the regions of the striatum, parahippocampal gyrus, superior temporal sulcus, anterior cingulate cortex (ACC), and prefrontal cortex (PFC).

(4) dysfunctional family neuropsychodynamics, with automatic behaviors that reproduce the attachment relationship received in childhood. (5) dopamine and reward system dysfunctions,

(6) neuroenzymatic deficits in emotional self-regulation,

(7) neuroenzymatic deficits in inhibitory control systems (impulsivity, compulsion, and addictions),

(8) neuroenzymatic deficits responsible for extrafamilial social skills (shyness) and family skills (introspection).

The child's first 'mental discomfort' is involved in neurological development that responds to fear, insecurity, frustration, and validation. The second neurological process that reacts to this "discomfort of asynchrony" is the formation of amygdala behaviors (emotional defense), which are relieving or maladaptive behaviors and are currently well defined by the clinical cognitive psychology of family schemas. [28-36] Family schemas always have a sudden, automatic (involuntary) presentation and occur between two or more family members; that is, they are simultaneous activations of schemas, which can occur with the simple presence, memory, or hearing of a voice, and which are always harmful and chronic, some with a punitive, aversive, denialist, and escape character, and persist throughout life. [28-36]

Childhood stimuli provoke a broad neural (cognitive) and behavioral response in human adults, and this massive allocation of resources attests to the evolutionary significance of primary attachment. [28-36] (for a better understanding, see references 28-36).

Furthermore, they are influenced by genetic components (epigenetics, gene expression, polymorphisms) and

hormonal dysfunctions (cortisol, oxytocin, vasopressin, and melatonin dysfunctions) and immuno-inflammatory disorders. [28-36]

Hierarchical Nosology of the Neuromaladaptive Set

1) Deficit/absence of peripheral oxytocin and dopamine neurons that are responsible for synchrony, depth attention, and family social skills.
2) Positive feedback dysfunction of the primitive emotional system of the dopaminergic SEEKING system. It develops in the presence of childhood adversity and expresses chronic and oscillatory hypodopaminergic states.
3) Reward system dysfunction (RDS)
4) Navigation mode in the family environment, with predominance of activity in the hippocampus and amygdala system, due to the formation of engrams of increased interneuronal connectivity strength of these systems of the amygdala and limbic systems with predominance of their activity in the hippocampus, forming an exclusive navigation mode in the family environment. Chronic aberrant and sudden amygdala inputs occur, generating maladaptive states expressed as family schemas (Young) that produce neurodysfunctional interpersonal relationships (NIRs) such as misconduct, neglect, and psychological abuse among family members. The navigation mode with predominance of amygdala systems and automatic behaviors generates neurocognitive states with Alexithymia: the inability to effectively self-observe (self-identify) emotional and affective awareness at the same time, and Secondary Anosognosia: the inability to effectively identify the emotional and affective state of another person. 5) Commissuroctomy: Interhemispheric disconnection of the ungual and arcuate fascicles, secondary to toxic parental behaviors, mainly verbalizing, which causes secondary simultanagnosia (inability to identify more than 2 objects at the same time), causes cognitive inflexibility, decreased processing speed, and limits the extent of consciousness with dense intelligence.

6) Neuromirroring dysfunction of mirror neuron networks due to inversion, increase, or decrease of the functional roles of the family system. The inversion of a mode has an important cumulative effect on the SEEKING system and the RDS. Replication of the experienced effect occurs in an increased, decreased, or inverted form of these functional modes of neuropsychodynamics and involves the entire circuitry of attachment with neuromirroring.

7) Neurological and enzymatic deficit of emotional regulation: chronic and acute stress, behavioral deviation.

8) Neuroenzymatic deficit of inhibitory control: impulsivity, behavioral deviation.9) Neurological deficit of social skills (extradomiciliary): social isolation, preferences for habits without social contact, introversion, shyness.

10) Neuronal deficit of family skills: absence of mentalism and parental incapacity. 11) Underdevelopment of the PFC: The PFC is 'hijacked' by the subcortical structures of the midbrain. It occurs due to a deficit in myelination secondary to stress. Myelination, which is involved in regulating processing speed, especially in pre-development periods.[28-36]

These mechanisms together have a primary function of emotional survival, and clinical neuroscience proves dysfunctional parenting and toxic marital relationships. [36] Dysfunctions of the family synchrony system can generate a constellation of typical signs and symptoms that are subclinical, such as emotional and affective neglect, deficient interpersonal communication, stress, anxiety, depression, and addictions

that begin, worsen, or persist after family triggers and errors in perception processes due to dysfunction of the neurological mechanism of initial perception. Pre-cueing, which generates limitations in perception and attention.[49-52]

Perception errors with precueing misalignment with emotional value limit cognitive intelligence and are responsible for many cases of irrational family conflicts, with prejudice, ableism, emotional abuse, and even domestic violence. [49-52]

4.3.4.2 Biobehavior of Family Synchrony

Family synchrony is a subtle biobehavior that is fundamental to the initiation and effectiveness of parent-infant interactions, which depend on the proper functioning of oxytocin mechanisms and peripheral oxytocin and dopaminergic neurons, which develop during the first three years of life, and depend on the synchrony and effectiveness of the interactions of biological parents, with the involvement of the physical senses and reactions of the babies. [37-38]

Parent-child synchrony is defined as an observable pattern of dyadic interaction that is characterized by social reciprocity, contingent responsiveness, and dyadic correspondence of behavior, presence of a deep and effective bond in the interpersonal relationship, capacity for mentalism (identifying the emotional state of the dyad), and involvement of biological rhythms. [37-38]

The interpersonal relationships between the infant and biological parents are directly involved in the formative experience for the maturation of the social brain; thus, the quality of synchrony impacts the development of self-regulation, use of symbols, and empathy throughout childhood and adolescence. [37-38]

The ability to engage in temporally corresponding interactions is based on physiological mechanisms, in particular oscillatory systems, such as the biological clock and cardiac pacemaker, and hormones related to attachment, such as oxytocin. [37-38] Family synchrony bio-behavior develops through the stimulation of maternal touch and through the other physical senses, between biological parents and the newborn (NB), which is involved in interpersonal emotional and affective behaviors.[37-38] These dyadic processes observed in early childhood contribute to the development of self-regulation and general socio-emotional outcomes in children. [37-38] Family Synchrony Biobehavioral is an important proximal component because, when deficient, it contributes to the development of many maladaptive responses early in life, such as the formation of soothing (amygdala) behaviors or Family Schemas (FSs). [37-38]

Peripheral oxytocin and dopamine neurons (NODP) are responsible for the mechanisms of effective, or depth, attention that are essential for identifying a family member's emotional and affective state, which is currently referred to as mentalism. [37-38]

Throughout infancy and early childhood, parent-child synchrony facilitates child autonomy, self-regulatory behaviors, and social skills and supports attachment and bond formation between parents and children. Examining the neurobiological underpinnings of observable parent-child synchrony and how it may be disrupted by stress will provide critical insight into how stress, broadly construed, influences parent-child outcomes. [37-38]

4.3.4.3 Stress and Family Synchrony

Childhood adversity or chronic stress includes ongoing environmental exposures such as abuse, maltreatment, emotional neglect, family socioeconomic status, and family conflict and is known to impair child development. [37-38]

Higher levels of

parenting-related stress have been associated with decreased behavioral synchrony between parents and children aged 3 to 14 years, and higher levels of chronic maternal physiological stress have been associated with decreased behavioral synchrony between parents and children. [37-38]

Studies have shown that disruption of the neural circuitry that underlies behavioral synchrony (the mentalizing network) may be one mechanism by which stress has an effect on parent-child synchrony. [37-38]

Thementalizing network is composed of multiple regions across the frontal, parietal, and temporal cortex that coactivate during social cognition. [37-38]

Specific to the reciprocity of behavioral synchrony, there is evidence that the dorsal/posterior portion of the dorsolateral prefrontal cortex (DLPFC) encodes the goal-directed behaviors of others, and in the presence of adversity, synchrony is disrupted through a deficit in DLPFC activation. [37-38]

Nguyen et al. (2020) found that higher levels of parent-reported stressors, such as stress about family, relationships, and finances, and parenting difficulties, were associated with decreased neural synchrony between parents and children in the bilateral prefrontal cortex during a problem-solving task and in the left anterior cluster of the prefrontal cortex during a joint passive attention task. [37-38]

Gubhaju et al. (2013) identified the adversity domains of sociodemographic risk and family risk, which are two higher-order adversity factors, material disadvantage (which included family composition, use of social services, financial hardship, etc.), and psychosocial disadvantage (which included relationships between parents, parental well-being). [37-38]

Other studies have identified dimensional structures of adversity, including the identification of higher-order threat factors (experiences of abuse or trauma) and deprivation, as well as child maltreatment and family dysfunction. [37-38] Adversity, across all domains, was significantly associated with lower parent-child behavioral synchrony across all task conditions. Several studies have shown that stress/adversity has a disruptive effect on parent-child behavioral synchrony. [37-38]

Hoyniak CP et al. demonstrated that parent-child neural synchrony in the context of adversity and induced stress, with the effect of frustration, the dyads exhibited lower levels of neural synchrony, which was associated with lower levels of shared attention, engagement, mutual responsiveness, and poorer problem-solving abilities. [37-38]

This study evaluated the regions that encompass the emotional regulation and executive control networks, and their disruptions in one or both networks contribute to the deficient effects of their functioning. [37-38]

Furthermore, dyads that experienced higher levels of sociodemographic risk were employing adaptive regulation strategies that allowed them to overcome disruptions in synchrony, which is related to research data that demonstrate increased activation of limbic and subcortical regions during socioemotional cognition in individuals who experienced high levels of adversity, and which in clinical practice is expressed through alleviating behaviors or family schemas (Young). [27]

According to Johnson et al. (2016) and Palacios-Barrios and Hanson (2018), there are several differences in executive control networks in children and adults who experienced poverty or stress early in life. [37-38] (For a

better understanding of the neurobiological mechanisms of neural and behavioral synchrony between parents and children, see Quiñones-Camacho et al. (2019), Pechtel&Pizzagalli, 2011; Sheridan & McLaughlin, 2014; and studies by the group of Feldman R. et al.)

4.3.4.4 Reward System Dysfunction Syndrome (RDS)

The dopaminergic and opioidergic reward pathways of the brain are critical for survival, as they provide the pleasure drives to eat, love, and reproduce; they are called "natural rewards" and involve the release of dopamine in the nucleus accumbens and frontal lobes. [28-36]

Thedeficiencies in reward neurotransmission (dopamine) interfere with the pleasure derived from powerful human physiological drives that serve the function of satisfying, or relieving, pleasure. [28-36]

The mesolimbic pathway, the "reward pathway," is a dopaminergic pathway in the brain. This pathway connects the ventral tegmental area (VTA) in the midbrain to the ventral striatum (nucleus accumbens (NAc) and olfactory tubercle) of the basal ganglia in the forebrain. [28-36]

In 1996, Blum et al. described Reward Deficiency Syndrome (RDS), which involves a wide range of addictive, compulsive, and impulsive behaviors, such as obesity. [28–36]

RDS refers to the breakdown of reward neurotransmission and destructive behaviors initiated by a combination of environmental (epigenetic) influences and DNA-based neurotransmission deficits that interfere with the usual fulfillment of human physiological drives (food, water, sex). [28–36]

RDS is a polygenic trait with implications that suggest impaired crosstalk between different neurological systems, including the known reward pathway, neuroendocrine systems, and motivational systems. [28–36]

Objectively, it is associated with substance use disorder (SUD), major depressive disorder, early-life stress, immune dysregulation, attention deficit hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), compulsive gambling, and compulsive eating disorders, which are subtypes of overlapping and interrelated neurochemical dysfunctions. [28-36]

The chronic hypodopaminergic state, in the vast majority of situations, is associated with RDS, with behaviors and habits that produce dopamine to alleviate displeasure, irritability, boredom, and duality, and indecision due to dopamine deficit.[28-36] Evidence from human studies and fMRI supports the hypothesis that multiple brain circuits are disrupted in obesity and addiction, implicating the involvement of dopamine-modulated reward circuits. [28-36]

A key feature of RDS is the lack of integration between cognition, perception, and emotions that occurs due to substantial dopaminergic increases in reward, motivation, and learning centers that lead to neuroplasticity in the striato-thalamic-frontal cortical loop, with subsequent top-down dissociation of subcortical activity. [28-36] Associated with hypofunctionality of excitatory glutamatergic afferents from the amygdala-hippocampal complex, there is a failure to produce bottom-up restraint of the ***striato-thalamic-frontal cortical loop.*** [28-36]

4.3.4.5 Family Schemas

In the human brain, a basic pattern built from past experiences occurs through learning or adaptation conditioning, which are called schemas. [28-36] In primary

interpersonal relationships with biological parents, there is a deficit of affective attention, affective and emotional neglect, and situations of adverse emotions in childhood (AEC), which can be cumulative to traumatic situations, such as post-traumatic stress disorder (PTSD). The child's brain develops maladaptive neurocognitive and behavioral states, which in clinical practice are identified through family schemas, described by Jeffrey Young. [28-36]

Family schemas (FSs) develop due to maladaptation; therefore, they are dysfunctional, and currently eighteen types of FSs are described. An individual can present activation of more than one schema at the same time and can be activated twenty-four hours a day.[28-36]

EFs are automatic, sudden, and function as non-self-identified or non-perceptible (unconscious) mechanisms that affect behaviors, cognitive states (perception, distorted and biased beliefs), and physiological states such as hormonal dysfunctions and neurodysfunctions of emotions, which begin in children and persist into adulthood. [27] EFs occur between peers unconsciously in the family environment (bidirectional), through activation of the amygdala neurological systems and also through the process of neuromirroring (unconscious neuroactivation) of'mirror neurons. [27] Typical behaviors of EFs include avoidance, denial, aversion, escape, punishment, ableism, prejudice, devaluation, and distortion of beliefs, which result in toxic relationships, chronic family fights, and cases of dysfunctional parenting.[28-36] 1) Disconnection/Rejection: inability to form secure bonds, with experiences of negative social experiences. In general, people tend to present characteristics of instability, abuse, coldness, rejection, or isolation from the outside world. Five schemes are linked to this domain: abandonment, distrust, emotional deprivation, defectiveness/shame, and social isolation.

2) Impaired Autonomy and Performance: Presents dysfunctional expectations about themselves and the world, which interfere with their ability to differentiate themselves from paternal or maternal figures and function independently. The family of origin is overprotective and cannot encourage them to perform competently. The schemas in this domain are Dependence/Incompetence, Vulnerability to Harm or Illness, Enmeshment, and Failure.

3) Impaired Boundaries: There is no development of internal boundaries and responsibility toward others. People may be selfish and spoiled, and most often they grew up in permissive families. The schemas associated with this domain are grandiosity/arrogance and insufficient self-control/self-discipline.

4) Other-Orientation: There is an excessive emphasis on meeting the needs of others rather than one's own. The emotional needs and desires of the parents are valued more than the needs and feelings of the child. The EFs developed are subjugation, self-sacrifice, and seeking approval/seeking recognition.

5) Overvigilance and Inhibition: excessive emphasis on suppressing feelings, impulses, and spontaneous personal choices, reinforcing compliance with rigid internalized rules regarding one's own performance (perfectionism and self-demand). The family is severe, demanding, and punitive

4.3.4.5 Dysfunctional Neuropsychodynamics

The assessment of attachment relationships has now progressed well beyond infancy so that changes in the

quality of attachment can be traced from infancy to early adulthood. [28-36]

The infant brain expects the father to be dominant, with real control of limits, and the mother to provide nurturing. [28-36]

Newborn boys' brains block out pain (repression), disaffection, absences, and traumas from the mother, and girls' brains do the same in relation to the father. In particular, the father's exclusive role is to provide order within the group, teach limits, validate tasks, introduce new environments and novelties, explore, and provide a functional survival role. [28-36]

When there is intense or repetitive trauma or pain, due to the unconscious brain mechanism of fear, an unconscious inversion in the functional role occurs due to the neurobiology of attachment formation. [28-36]

The presence of attachment figures can block the activation of stress physiology, even when the infant is expressing strong behavioral distress, and this mechanism is known as parental social buffering. [28-36]

4.4 Neurocardiology and stress

Research in neurocardiology, psychiatry, and epidemiology has defined bidirectional relationships between psychiatric disorders and heart disease, affirming the role of the impaired autonomic nervous system (dysautonomia) in the prognosis and development of these disorders.

By considering the underlying maladaptive neuropsychological mechanisms that produce and sustain stress states, which have significant impacts on the pathophysiology of atherosclerotic plaque inflammation,

4.5 Early Acute Myocardial Infarction (PAMI)

Through clinical empiricism and inductive thinking guided by specific risk factors associated with immunological, inflammatory, and genetic mechanisms and the neurocardiology of psychosocial stress, an assertive and plausible hypothesis is generated for the understanding and development of PAMI. [39]

Sagrís M et al. demonstrated through angiographic studies the presence of different vascular lesions between young and elderly individuals with MI. In young individuals, they found a greater propensity to have no disease or disease of a single vessel, lower pulse wave velocity, and a central augmentation index in relation to the elderly, who often presented disease with multiple lesions of three or more vessels. [39]

The 'Wellington Acute Coronary Syndrome Registry' study evaluated a cohort of 1,199 patients with AMI and identified a prevalence of 12.8% of AMI in young patients. The risk factors found in the group of young patients were male gender, obesity, and family history of early CAD. Within the young MI group, 36% had none or only one traditional risk factor for MI and would have been classified as low risk prior to the index event. [40]

Zeitouni M et al. evaluated 6,639 patients with MI; 41% were <55 years of age ("younger"). Relative to the older adult groups (>55 years), younger adults had higher prevalences of smoking (52%), obesity (42%), metabolic syndrome (21%), and dyslipidemia with increased low-density lipoprotein cholesterol. [41]

To evaluate, in an unprecedented and comprehensive manner, the various mechanisms of stress through family psychosocial neuroscience by measuring inflammatory, immunological, and neurogenomic markers in patients who have suffered an MI, with systematic and objective clinical identification of

maladaptive neuromarkers. [42]

Neurocardiology, which uses the recent clinical practice of common maladaptive biobehaviors, now encompasses new pathophysiological mechanisms to be evaluated, which is of fundamental importance for both MI and AMI in elderly patients. [43]

4.6 Genetic Alterations Associated with Myocardial Infarction

In recent years, there has been a constant movement toward discovering the genetic underpinnings of CAD, resulting in the identification of approximately 60 distinct genetic loci. [42-44]

Currently, the study of genomics associated with AMI is very comprehensive and heterogeneous. Large gene banks and large studies are currently investigating serum urate levels, which are elevated by several genes and have been associated with increased risks of MI. [42-44]

Serum urate can cause platelet activation, adhesion, and aggregation and participate in the production of inflammatory interleukins. However, the sum of the effects of the various risk factors for MI has not yet allowed a pathway of intricate effects related to genetic mechanisms.

Yang F et al. examined the proteomic pathways linking obesity and lifestyle factors to CAD risk and demonstrated that circulating proteins mediated the associations of AGER and MST1 genes, along with PCSK9 and C1S, exhibiting the highest frequency among the causal mediator networks involved in the pathogenesis of CAD.[42–44]

Circulating proteins play a key role in mediating the connection between modifiable factors and CAD susceptibility. The detrimental effect of obesity on CAD appears to be mediated primarily by MAP1LC3A, ANGPTL4, RPS6KA1, PCSK9, ITPKA, and AGER. [42-44]

4.6.1 Somatic mutations of clonal hematopoiesis of undetermined potential (CHIP)

Leukocyte progenitor cells derived from clonal hematopoiesis of undetermined potential (CHIP) are associated with an increased risk of cardiovascular events. [45] It is defined as a hematopoietic cell with somatic mutations, most commonly in the DNMT3A, TET2, or ASXL1 genes, which lead to the expansion of clones in the bone marrow, resulting in an increased number of cells with epigenetic alterations in the peripheral blood, which can develop CVD in the presence of these three mutations. [45] Due to differential growth dynamics, the composition of affected driver genes among CHIP carriers also differs by age category. [45]

Whole-exome sequencing has shown that CHIP is virtually absent in individuals under 30 years of age, while it is present in 20% to 30% of individuals aged between 50 and 60 years. [45]

These functional alterations of CHIP are involved in the increase in inflammatory interleukin gene expression, which in turn can stimulate the progression of atherosclerosis. [45]

Currently, the results are still heterogeneous, but the patterns depend on the underlying mutations, as those carrying TET2 mutations presented increased inflammatory signaling, while ASXL1 mutations presented selective effects on metabolic pathways. [45]

Most studies have shown that the presence of CHIP involving the JAK2 locus presents a significant increase in the risk of coronary artery disease. [45] A study of 7245 participants was evaluated

for the association between CHIP and early-onset myocardial infarction and showed a four-fold increased risk of atherothrombosis among CHIP carriers compared to the control group. MI has been strongly associated with mutations in TET2, ASXL1, and JAK2, of which preclinical patients demonstrate signs of accelerated atherosclerosis with TET2 mutation. [45] Current data point to an association between inflammation and socioeconomic and psychosocial stressors, although this has not yet been evaluated. [45]

5. Discussion

Stressful events have been involved in CVD for a long time, and there has never been a methodology to objectively assess the neuropsychological clinic, in addition to the lack of integration of the various underlying and intricate pathophysiological mechanisms, which should be evaluated in light of the causal effect through new population research. [46]

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study that evaluated the significance of subclinical cardiovascular injury, focusing on the relationship between smoking intensity and proximal biomarkers of cardiovascular injury in a large, multi-ethnic, gender-balanced cohort of 6814 participants, and it was shown that high-sensitivity C-reactive protein (hsCRP) was the most sensitive biomarker of smoking and CVD. [46]

In CVD prevention studies in children, several conditions must be met before recommending screening for CVD risk factors in children, but the risk factors evaluated are the same as in adults.

However, we draw attention to reflect on the objective neuropsychological assessment in children, especially in childhood obesity, with assessment of childhood adversity, such as Adverse Childhood Emotions (ACE) and PTSD, which are involved in the development of common neuromaladaptivebiobehaviors, as direct factors of emotional regulation deficit and psychosocial stress, in addition to presenting the same inflammatory biomarkers and voluminous evidence that predict CVD in adulthood. [47-48]

Regarding genetics and IAMP studies, most studies present a population of older adults, and the validity of the results depends on the assumption of relevance, that is, the genetic variants must exhibit a strong association with the exposure of interest, the assumption of independence, that is, the genetic variants must be independent of confounding factors, and the exclusion restriction, that is, the genetic variants must only impact the result through exposure. [47-48]

In medicine, clinical practice is the ability to identify the effect according to the cause in an assertive, observational way that requires an understanding of the pathophysiological processes that are dynamic.

Clinical neuroscience was developed according to the traditional scientific methods of observing a change in nature (cause) that presents a pathophysiological causal link with assertiveness that generates the effect. Current studies present heterogeneity of causal effects that can generate bias in the estimates due to the various risk factors of average effects that are underlying.

The clinical use to select populations with PMI and involvement of the mental health of stress can be considered through the systematized clinical organization of common biobehaviors—ONCs. [36]

6. Conclusion

We present a clinical model with an approach to stressful effects through an unprecedented clinical approach to maladaptive biobehaviors, which

involves objective assessment through clinical neuromarkers and enables a new organization of research and insights, in addition to the attempt to elucidate the origins of NCDs and PMI. We would like to point out that the current psychosocial neurocardiology model assesses psychological components in an unprecedented way, in addition to identifying causal factors such as ACE and PTSD that are fundamental to the development of common neuromaladaptivebiobehaviors, and may assist with new strategies for controlling and preventing the current epidemics of obesity, TM, and NCDs. This work has the limitation of being in its early stages of development, but it was constructed through clinical empiricism guided by theory, through accumulated data from functional neuroimaging research, and must be tested and proven by larger studies.

Cause and effect studies in genomics are more effective when guided by clinical practice. As in the case of Keneth Blum's group, which described the Reward System Dysfunction Syndrome (RDS) in 1996, which brought several advances and which must be considered in future integrative research on obesity and CVD.

7. Declaration of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

8.References

1.Budreviciute A, Damiati S, Sabir DK, Onder K, Schuller-Goetzburg P, Plakys G, et al. Estratégias de gestão e prevenção para doenças não transmissíveis (DNTs) e seus fatores de risco. Front Public Heal. 2020;8: 574111. doi: 10.3389/fpubh.2020.574111

2.Sagris M, Antonopoulos AS, Theofilis P, Oikonomou E, Siasos G, Tsalamandris S, Antoniades C, Brilakis ES, Kaski JC, Tousoulis D. Risk factors profile of young and older patients with myocardial infarction. Cardiovasc Res. 2022 Jul 27;118(10):2281-2292. doi: 10.1093/cvr/cvab264. PMID: 34358302.

3.Shah N, Kelly AM, Cox N, Wong C, Soon K. Myocardial Infarction in the "Young": Risk Factors, Presentation, Management and Prognosis. Heart Lung Circ. 2016 Oct;25(10):955-60. doi: 10.1016/j.hlc.2016.04.015. Epub 2016 May 16. PMID: 27265644.

4. Gurel NZ, Hadaya J, Ardell JL. Stress-related dysautonomias and neurocardiology-based treatment approaches. AutonNeurosci. 2022 May;239:102944. doi: 10.1016/j.autneu.2022.102944. Epub 2022 Jan 20. PMID: 35158161.5.

5.Estivaleti JM, Guzman-Habinger J, Lobos J, Azeredo CM, Claro R, Ferrari G, et al. Tendências temporais e projeção de epidemia de obesidade em adultos brasileiros entre 2006 e 2030. Sci Rep. 2022;12: 1–8. doi: 10.1038/s41598-022-16934-5

6. ML Furlanetto, EFB Chagas, Payão SLM. Atherosclerotic Extension of the Carotid Arteries: An Insertion into Clinical Practice.Revista Internacional de Medicina Vascular.2020-06-2.DOI: 10.1155/2020/3120327

7.Caceres BA, Makarem N, Hickey KT, Hughes TL. Cardiovascular Disease Disparities in Sexual Minority Adults: An Examination of the Behavioral Risk Factor Surveillance System (2014-2016). Am J Health Promot. 2019 May;33(4):576-585. doi: 10.1177/0890117118810246. Epub 2018 Nov 5. PMID: 30392384; PMCID: PMC6476632.

8.Associação Americana de Psicologia. Estresse e Disparidades de Saúde: Contextos, Mecanismos e Intervenções entre Populações de Minorias Raciais/Étnicas e Baixo Status Socioeconômico. Washington DC; 2017. http://www.apa.org/pi/health-disparities/resources/stress-report.aspx

9.Ippoliti F, Canitano N, Businaro R. Estresse e obesidade como fatores de risco em doenças cardiovasculares: uma perspectiva neuroimune. J NeuroimmunePharmacol. 2013;8(1):212–226. doi: 10.1007/s11481-012-9432-6.

10.Richardson AS, Arsenault JE, Cates SC, Muth MK. Estresse percebido, comportamentos alimentares pouco saudáveis e obesidade grave em mulheres de baixa renda. Nutr J. 2015;14(1):1–10. doi: 10.1186/s12937-015-0110-4.

11.Keyes KM, Hatzenbuehler ML, Grant BF, Hasin DS. Estresse e álcool: evidências epidemiológicas. Alcohol Res. 2012;34(4): 391–400. doi: 10.3109/10826088509044926

12.Al Rifai M, DeFilippis AP, McEvoy JW, Hall ME, Acien AN, Jones MR, Keith R, Magid HS, Rodriguez CJ, Barr GR, Benjamin EJ, Robertson RM, Bhatnagar A, Blaha MJ. The relationship between smoking intensity and subclinical cardiovascular injury: The Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2017 Mar;258:119-130. doi: 10.1016/j.atherosclerosis.2017.01.021. Epub 2017 Jan 19. PMID: 28237909; PMCID: PMC5404388.

13.Pedroso CF, Pereira CC, Cavalcante AMRZ, Guimarães RA. Magnitude of risk factors for chronic noncommunicable diseases in adolescents and young adults in Brazil: A population-based study. PLoS One. 2023 Oct 19;18(10):e0292612. doi: 10.1371/journal.pone.0292612. PMID: 37856487; PMCID: PMC10586685.

14. Kim S, Lee S, Kim JB, Na JO, Choi CU, Lim HE, Rha SW, Park CG, Oh DJ, Yoo H, Kim JW. Concurrent Carotid Inflammation in Acute Coronary Syndrome as Assessed by (18)F-FDG PET/CT: A Possible Mechanistic Link for Ischemic Stroke. J Stroke Cerebrovasc Dis. 2015 Nov;24(11):2547-54. doi: 10.1016/j.jstrokecerebrovasdis.2015.07.004 . Epub 2015 Aug 22. PMID: 26306455.

15. Wang LJ, Ergul EA, Mohebali J, Goodney PP, Patel VI, Conrad MF, et al. The effect of combining coronary bypass with carotid endarterectomy in patients with unrevascularized severe coronary disease. J VascSurg [Internet]. 2019 Mar [cited 2019 Mar 31]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0741521419301661

16. Adhikary D, Ranjan R, Mandal S, Hawlader MDH, Mitra DK, Adhikary AB. Prevalence of carotid artery stenosis in ischaemic heart disease patients in Bangladesh. SAGE Open Med [Internet]. 2019 Jan 15 [cited 2019 Mar 31];7:205031211983083. Available from: http://journals.sagepub.com/doi/10.1177/2050312119830838

17. Habib N, Mahmoodi BK, Suttorp MJ, Kelder JC, Tromp SC, Sonker U, et al. Longterm results of carotid stenting and risk factors in patients with severe carotid artery stenosis undergoing subsequent cardiac surgery. Catheter CardiovascInterv [Internet]. 2019 Feb 15 [cited 2019 Mar 31];93(3):E134–9. Available from: http://doi.wiley.com/10.1002/ccd.27947

18.Hamada S, Kashiwazaki D, Yamamoto S, Akioka N, Kuwayama N, Kuroda S. Impact of Plaque Composition on Risk of Coronary Artery Diseases in Patients with

Carotid Artery Stenosis. J Stroke Cerebrovasc Dis. 2018 Dec;27(12):3599-3604. doi: 10.1016/j.jstrokecerebrovasdis.2018.08.031 . Epub 2018 Sep 13. PMID: 30219630.

19. Libby P, Hansson GK. From Focal Lipid Storage to Systemic Inflammation. J Am CollCardiol. 2019;74(12):1594–607. 9. Gallo D, Bijari PB, Morbiducci U, Qiao Y, Xie Y (Joyce), Etesami M, et al. Segmentspecific associations between local haemodynamic and imaging markers of early atherosclerosis at the carotid artery: an in vivo human study. J R Soc Interface [Internet]. 2018 Oct 10 [cited 2019 Mar 30];15(147):20180352. Available from: http://rsif.royalsocietypublishing.org/lookup/doi/10.1098/rsif.2018.0352 10.

20. Ammirati E, Moroni F, Norata GD, Magnoni M, Camici PG. Markers of Inflammation Associated with Plaque Progression and Instability in Patients with Carotid Atherosclerosis. Mediators Inflamm [Internet]. 2015 [cited 2019 Mar 31];2015:1–15. Available from: http://www.hindawi.com/journals/mi/2015/718329/

21.Cohen S, Janicki-Deverts D, Miller GE. Estresse psicológico e doença. JAMA. 2007;298(14):1685–1687. doi: 10.1001/jama.298.14.1685.

22.Cohen S, Janicki-Deverts D, Doyle WJ, et al. Estresse crônico, resistência ao receptor de glicocorticoide, inflamação e risco de doença. Proc Natl AcadSci US A. 2012;109(16):5995–5999. doi: 10.1073/pnas.1118355109.

23.Miller GE, et al. Uma impressão digital genômica funcional do estresse crônico em humanos: glicocorticoide embotado e sinalização NF-kappaB aumentada. BiolPsychiatry. 2008;64:266–272. doi:10.1016/j.biopsych.2008.03.017.

24.Alam MM, Rana MS, Hayee S, Mahjabeen F, Tasha T, Shakil SS. Comparison of Risk Factors between Younger and Older Patients of Myocardial Infarction among Bangladeshi Rural People: A Hospital Based Study. Mymensingh Med J. 2023 Apr;32(2):567-579. PMID: 37002772.

25.Girotti M, Bulin SE, Carreno FR. Effects of chronic stress on cognitive function - From neurobiology to intervention. Neurobiol Stress. 2024 Sep 2;33:100670. doi: 10.1016/j.ynstr.2024.100670. PMID: 39295772; PMCID: PMC11407068.

26. Koch SBJ, Klumpers F, Zhang W, Hashemi MM, Kaldewaij R, van Ast VA, Smit AS, Roelofs K. The role of automatic defensive responses in the development of posttraumatic stress symptoms in police recruits: protocol of a prospective study. Eur J Psychotraumatol. 2017 Dec 20;8(1):1412226. doi: 10.1080/20008198.2017.1412226. PMID: 29321826; PMCID: PMC5757225.

27.Bernardi S, Benna MK, Rigotti M, Munuera J, Fusi S, Salzman CD. The Geometry of Abstraction in the Hippocampus and Prefrontal Cortex.Cell. 2020 Nov 12;183(4):954-967.e21. doi: 10.1016/j.cell.2020.09.031. Epub 2020 Oct 14. PMID: 33058757; PMCID: PMC8451959.

28.Furlanetto Jr ML, Vinicius LL, Kurlander PA, Freschi S, Francisco AJ, Melo SL and Vieira L. Treatment and the Current Concept of Relapse, in Substance Use Disorder. IntClinImg and Med Rew. 2022; 1(1): 1026

29.FurlanettoMLJr.(2023). Dialectical Medicina: Syndrome Z and Use of Pathological Substances. J. Integrated Health.2(1),1-202 ISSN:2583-5386

30.FurlanettoM.L.Jr.(2023). Clinical Neurogenetics of syndrome Z and

Scientific Evidence Based Clinical Evaluation. J Health Integrated. 2(1), 21-25.DOI: http//: doi.org/10.51219/JIH/Furlanetto-M-L-Jr/5

31.FurlanettoM.L.Jr(2023).Stakehold ZXSY Brazil,PrecisionMediicine in Pediatric Clinic: Reward Deficiency Syndrome (RDS)is surprisingly Evolving and Found Everywhere: Is It ´´lowing in the Wind? Yes, but how Syndrome Z.J. Integrated Health,2(2),26-38.DOI:doi.org/10.51219/JIH/Furlanetto-M-L-Jr-6

32. Ivan T., et al (2023).Precision Medicine in Pediatrics: Infantile Z Syndrome, Familial Sync Neurological Deficit, ANAAS Syndrome, Zoé Syndrome, RDS Spectrum Disorder. J Medical Case Repo, 5(2):1-15.

33.M. L. Furlanetto Junior (2023). Stakehold ZXSY: Disorder Deficit Familial Asynchrony and Syndrome Z. J Medical Case Repo, 5(1):1-24. DOI: https://doi.org/10.47485/2767-5416.1032

34.Detrigiachi E, Sukorski JP, de Oliveira MTM, Lima LA,Furlanetto Junior ML (2023):Medicine,Law and Collective Mental Health:New Therapeutic for pré-parental and Pré-addiction.J.Integrated Health20223;2(4)91-99.DOI:doi.org/10.51219/Mario-Luiz-16

35.LuizFurlanetto Junior et al.Diagnostic Methodologic and Prevention on Internal Medicine and common Neurobehavior:Target of prevention of cardiovascular events and Metabolic syndrome.CardiolArch 2023; 1(1):5-11.

36,M.L.Furlanetto Junior, F. de A. A. Rodrigues (2025).EMOTIONAL SURVIVAL PERSONALITY MICROSTRUCTURE ONCS: THE NEUROBIOLOGICAL ORIGINS OF PERSONALITY DISORDERS AND DYSFUNCTIONAL PARENTING. J.Bio.Innov14(1), pp: 45-84, 2025 |ISSN 2277-8330 (Electronic). https://doi.org/10.46344/JBINO.2025.v14i01.04

37.Hoyniak CP, Quiñones-Camacho LE, Camacho MC, Chin JH, Williams EM, Wakschlag LS, Perlman SB. Adversity is Linked with Decreased Parent-Child Behavioral and Neural Synchrony. Dev CognNeurosci. 2021 Apr;48:100937. doi: 10.1016/j.dcn.2021.100937. Epub 2021 Feb 19. PMID: 33639519; PMCID: PMC7910510.

38. Feldman R. Parent-infant synchrony and the construction of shared timing; physiological precursors, developmental outcomes, and risk conditions. J Child Psychol Psychiatry. 2007 Mar-Apr;48(3-4):329-54. doi: 10.1111/j.1469-7610.2006.01701.x. PMID: 17355401.

39.Sagris M, Theofilis P, Mistakidou V, Oikonomou E, Tsioufis K, Tousoulis D. Young and older patients with acute myocardial infarction: differences in risk factors and angiographic characteristics. Hellenic J Cardiol. 2024 May 10:S1109-9666(24)00112-X. doi: 10.1016/j.hjc.2024.05.008. Epub ahead of print. PMID: 38734305.

40.Matsis K, Holley A, Al-Sinan A, Matsis P, Larsen PD, Harding SA. Differing Clinical Characteristics Between Young and Older Patients Presenting with Myocardial Infarction. Heart Lung Circ. 2017 Jun;26(6):566-571. doi: 10.1016/j.hlc.2016.09.007. Epub 2016 Nov 11. PMID: 28089789.

41.Egred M, Viswanathan G, Davis GK. Myocardial infarction in young adults.PostgradMed J. 2005 Dec;81(962):741-5. doi: 10.1136/pgmj.2004.027532. PMID: 16344295; PMCID: PMC1743402.

42.Yu, S. · Yang, H. · Guo, X. A hiperuricemia está independentemente

associada à hipertrofia ventricular esquerda em mulheres na pós-menopausa, mas não em mulheres na pré-menopausa no nordeste rural da China.*GinecolEndocrinol.* 2015; **31** :736-741

43.Yang F, Lu Y, Chen S, Wang K, Hu T, Cui H. Sex-specific effect of serum urate levels on coronary heart disease and myocardial infarction prevention: A Mendelian randomization study. NutrMetabCardiovasc Dis. 2022 May;32(5):1266-1274. doi: 10.1016/j.numecd.2022.01.022. Epub 2022 Jan 22. PMID: 35197211.

44.Yang F, Xu F, Zhang H, Gill D, Larsson SC, Li X, Cui H, Yuan S. Proteomic insights into the associations between obesity, lifestyle factors, and coronary artery disease. BMC Med. 2023 Dec 5;21(1):485. doi: 10.1186/s12916-023-03197-8. PMID: 38049831; PMCID: PMC10696760.

46.Al Rifai M, DeFilippis AP, McEvoy JW, Hall ME, Acien AN, Jones MR, Keith R, Magid HS, Rodriguez CJ, Barr GR, Benjamin EJ, Robertson RM, Bhatnagar A, Blaha MJ. The relationship between smoking intensity and subclinical cardiovascular injury: The Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2017 Mar;258:119-130. doi: 10.1016/j.atherosclerosis.2017.01.021. Epub 2017 Jan 19. PMID: 28237909; PMCID: PMC5404388.

47.Zeitouni M, Nanna MG, Sun JL, Chiswell K, Peterson ED, Navar AM. Performance of Guideline Recommendations for Prevention of Myocardial Infarction in Young Adults. J Am CollCardiol. 2020 Aug 11;76(6):653-664. doi: 10.1016/j.jacc.2020.06.030. PMID: 32762899; PMCID: PMC7444655.

48.Liu M, Wang M, Peng T, Ma W, Wang Q, Niu X, Hu L, Qi B, Guo D, Ren G, Geng J, Wang D, Song L, Hu J, Li Y. Gut-microbiome-based predictive model for ST-elevation myocardial infarction in young male patients. Front Microbiol. 2022 Dec 1;13:1031878. doi: 10.3389/fmicb.2022.1031878. PMID: 36532426; PMCID: PMC9756097.

49.Chen S, Melara RD. Sequential effects in the Simon task: conflict adaptation or feature integration? Brain Res. 2009 Nov 10;1297:89-100. doi: 10.1016/j.brainres.2009.08.003. Epub 2009 Aug 8. PMID: 19666010.

50.Clark A. Attention alters predictive processing. Behav Brain Sci. 2016 Jan;39:e234. doi: 10.1017/S0140525X15002472. PMID: 28355839.

51.Raftopoulos A. Studies on cognitively driven attention suggest that late vision is cognitively penetrated, whereas early vision is not. Behav Brain Sci. 2016 Jan;39:e256. doi: 10.1017/S0140525X15002484. PMID: 28355840.

52.Raftopoulos A. Pre-cueing, the Epistemic Role of Early Vision, and the Cognitive Impenetrability of Early Vision. Front Psychol. 2017 Jul 10;8:1156. doi: 10.3389/fpsyg.2017.01156. PMID: 28740474; PMCID: PMC5502256.

.