

CPAH Life & Intelligence

Science Journal

ISSN XXXX-XXXX

vol. 1, n. 2, 2026

●●● ARTICLE 5

Acceptance date: 20/03/2026

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

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ABSTRACT: Introduction: Notably, a phenomenon of increasing early-onset incidence of certain diseases remains uncontrolled and poorly understood, affecting young adults and adolescents, as in the case of obesity, colon cancer, metabolic syndrome, and acute myocardial infarction (AMI). Although the mortality rate from AMI has decreased, it is increasingly common to find young people diagnosed with AMI, and studies have already demonstrated this increase in incidence in this age group. **Objective:** The integration of intricate genetic pathways related to lipid metabolism, inflammation, and coagulation aids in the understanding and identification of early AMI (eAMI), in addition to guiding primary prevention strategies. **Methodology:** A clinical synthesis with theoretical implications was conducted, grounded in neurobiological and neurogenomic mechanisms, presenting the integration of maladaptive neuroscience with cardiology. **Results:** Upon reviewing data on risk factors for PE, whose pathophysiological processes are poorly understood, we identified a possible relationship with psychosocial stress, which can currently be assessed through a clinical approach focused on stress-related clinical biomarkers and emotional dysfunctions attributed to neuro-maladaptive biobehaviors. To provide a better understanding, we integrated the clinical and pathophysiological components related to cardiology and psychosocial neuropsychology. **Discussion:** Stressful events have long been implicated in stroke, yet there has never been a methodology to objectively assess the neuropsychological clinical picture. Furthermore, there is a lack of integration of the various underlying and intricate pathophysiological mechanisms, which must be evaluated for the strength of their causal effect through new population-based studies. **Conclusion:** We present a clinical model addressing stress-

-related effects through an unprecedented clinical approach to maladaptive biobehaviors, which involves objective and assessment using clinical neuromarkers. This model enables a new organization of research and insights, as well as an attempt to elucidate the origins of DCNTs and IAMP.

KEYWORDS: Neurocardiology, early myocardial infarction, neurosciences, inflammatory biomarker.

Introduction

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

Notably, a phenomenon of increasing early-onset incidence of certain diseases remains uncontrolled and poorly understood, affecting young adults and adolescents, as in the case of obesity, colorectal cancer, metabolic syndrome, and acute myocardial infarction (AMI)¹⁻²

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

The terms “myocardial infarction in young patients” or “early acute myocardial infarction” (EAMI) are not defined by guidelines or protocols; most studies use a cutoff of under 40 to 50 years of age to identify this group of patients.¹⁻²

The few studies addressing this topic have shown that 6–12% are under 45 years of age, 3.4–5.6% are under 40 years of age, and 1.6% are under 35 years of age; thus, AMI in young adults is accounting for a considerable proportion of total CVD events.^{3–7}

The young adult population has undergone lifestyle changes over the decades, favoring the onset of atherosclerosis at earlier stages and, consequently, the occurrence of cardiovascular events at an earlier age.^{3–7}

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

Classic risk factors for atherosclerosis include psychosocial factors, smoking, alcohol consumption, diet, physical inactivity, obesity, hypertension, diabetes, and dyslipidemia, and they account for more than 90% of the risk of CVD.^{3–7}

The differences already identified in the risk factor profile for AMI include higher prevalence of smoking, a family history of premature coronary artery disease (CAD), and male gender.^{3–7}

In addition, IAMP may be associated with illicit substance use, stimulants, psychosocial stress, addiction, and, indirectly, new genetic dysfunctions caused by mutations, particularly in coagulation and lipid metabolism pathways (elevated lipoprotein-a).^{3–7}

Patients with IAMP generally have eccentric atherosclerotic plaques with inflammatory features and fewer lesions; the lack of a true clinical and pathophysiological understanding may lead to the underestimation of important differences, which contributes to delayed or missed diagnosis.²

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

The short-term prognosis for young patients with MI is better than for older patients; however, current data raise concerns regarding long-term outcomes, particularly in those with reduced left ventricular systolic function, as the tendency for progressive complications is heart failure.³

Nevertheless, there remains a significant knowledge gap regarding modifiable risk factors that could help alter the course of this extreme end of the CAD spectrum among young patients.³

AMI is a significant problem, yet there is a scarcity of illuminating data; in this review, we present an integrative approach combining neurocardiology and that addresses various risk factors intertwined with the pathophysiological processes in AMI.^{2–4}

Objective

To highlight the neuropsychological clinical features of common biobehaviors, which are integrated into the intricate processes of inflammatory, immunological, genetic, and epigenetic pathways that contribute to the destabilization of an atherosclerotic plaque, leading to an acute cardiovascular event, as well as their direct relationships that sustain the epidemic of obesity and addictive disorders, which may be associated with certain early-onset diseases that share common risk factors, such as AMI, thereby organizing and guiding new prevention and treatment strategies.

Methodology

A literature search was conducted in the PubMed and Web of Science databases. The inclusion criteria were studies demonstrating clinical evidence associated with neurobiological mechanisms linked to cardiovascular diseases, acute myocardial infarction, and myocardial infarction in young adults, as well as genetic alterations associated with AMI.

Convenience studies were also selected, which presented data on adverse childhood emotions.

A clinical synthesis with theoretical implications was conducted, grounded in neurobiological and neurogenomic mechanisms, presenting the integration of maladaptive neuroscience with cardiology.

Results

Upon reviewing the data on IAMP risk factors and its poorly understood pathophysiological processes, we identified a possible relationship with psychosocial stress, which can currently be assessed through a clinical approach focused on stress-related clinical biomarkers and emotional dysfunctions attributed to neuro-maladaptive biobehaviors.

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

We present the summaries of the cardiological and neurological components, followed by an exploration of the pathophysiological mechanisms and findings of genetic alterations related to IAMP.

Cardiological Component

Pathophysiology of Atherosclerosis

Typical atherosclerotic disease is characterized by chronic and local traumatic immuno-inflammatory mechanisms, which can progress with an acute exacerbation of these same mechanisms, triggering a new event; as the plaque becomes unstable and ruptures, molecules and coagulation factors are exposed to the arterial lumen, immediately leading to thrombus formation, causing occlusion of blood flow and thus producing an ischemic event, such as AMI.⁶⁻⁸

Such a cardiovascular event is more common in older individuals (>55 years), as atherosclerosis has a slow and insidious onset.⁶⁻⁸

The pathophysiology of atherosclerosis begins after lipid intake and proceeds to the accumulation of oxidized lipoproteins in the intima, resulting in lipid-rich macrophages or foam cells.⁶⁻⁸

Smooth muscle cells migrate to the intima after forming the fibrous cap, which may calcify. This indicates that, initially, the atherosclerotic lesion grows toward the vessel lumen, characterizing arterial remodeling.⁶⁻⁸

It is noted that at bifurcations and in sinuous arterial segments, there is a higher prevalence of atherosclerotic lesions, as these areas create a division in blood flow, which tends to increase blood turbulence, associated with an increase in the shear stress mechanism.⁶⁻⁸

This mechanism—an increase in blood flow stress on the endothelium—activates local inflammatory processes, such

as the release of the vasodilator nitric oxide and inflammatory cell adhesion molecules, thereby modulating endothelial function and vessel diameter.⁶⁻⁸

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

Classic Risk Factors

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

The burden of NCDs is increasing among adolescents and young adults in both developed and developing countries. Data from the Global Burden of Disease Study (2019) of European Union member states revealed that NCDs accounted for 38.8% of all deaths among individuals aged 10 to 24.¹³

Despite the multifactorial nature of NCD etiology, the main determinants of these diseases are behavioral risk factors, including smoking, alcohol use, unhealthy diet, physical inactivity, overweight, and obesity, which can lead to high blood pressure, elevated serum cholesterol levels, and hyperglycemia.¹³

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

A recent study evaluating factors associated with risk factors for chronic non-communicable diseases in adolescents and

young adults in Brazil assessed 10,460 individuals and found that young adult males with lower educational attainment, of Black race/skin color, with lower household income, and residing 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 showed a higher prevalence of most risk factors.¹³

According to *Estivaleti JM et al.*, the prevalence of overweight is higher among middle-aged adults compared to adolescents and adults, and they demonstrated a sustained increase in the obesity epidemic across all sociodemographic subgroups in Brazil.⁶

Furthermore, the prevalence of obesity increased from 11.8% in 2006 to 20.3% in 2019. Projected prevalences by 2030 are estimated at 68.1% for overweight, 29.6% for obesity, and 9.3% for obesity classes II and III. In the current Brazilian study, the prevalence of overweight was 32.5%. In the general population, it was found that stress increases the risk of CVD through direct and indirect behavioral pathways mediated by biological processes, such as hormonal, immunological, and inflammatory dysfunctions.⁷⁻¹¹

Smoking

Subclinical cardiovascular damage 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- α)] 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- α , and Interleukin-6.⁶⁻⁸

Smoking promotes prothrombotic changes through platelet activation, as exposure to tobacco increases platelet-activating factor levels and inhibits nitric oxide formation (due to oxidative stress), thereby influencing vascular tone balance.⁶⁻⁸

Subclinical Cardiovascular Disease

CVDs related to atherosclerosis can be clinically considered secondary conditions resulting from primary conditions such as obesity, diabetes mellitus, dyslipidemia, smoking, and hypertension, along with other risk factors, as they are initially asymptomatic or subclinical and may progress to chronic or 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 burden of atherosclerotic plaque instability and future CVD events.⁹⁻¹⁴

Hamada S et al. demonstrated via T1-weighted magnetic resonance imaging that high-signal-intensity carotid plaques predict the risk of CAD, and that the charac-

teristics of an unstable plaque correlate with increased levels of many pro-inflammatory molecules, such as Interleukin-6 (IL-6), and Tumor Necrosis Factor- α (TNF- α).¹⁸

Kim S, Lee S et al. assessed inflammation in carotid plaques of 74 patients with AMI using fluorodeoxyglucose positron emission tomography/computed tomography ((18)F-FDG PET/CT) within 1 week of the AMI diagnosis, and demonstrated in vivo that carotid artery inflammation occurs concurrently with coronary artery inflammation. In this group of patients who suffered AMI, 3 patients experienced a carotid-origin stroke.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 associated with inflammatory activity.¹⁵

Thus, evidence suggests that acute inflammatory conditions occurring during thrombotic and intraplaque events in the cardiac region can induce inflammation and plaque destabilization in another region, such as the carotid region, over a certain period, leading to an acute local event and resulting in a stroke.¹⁵

In the field of vascular and endovascular surgery, large studies evaluating treatments for carotid atherosclerosis—whether via endovascular procedures, which cause rupture of the atherosclerotic plaque during angioplasty, or via surgical endarterectomy, in which plaque injury and rupture also occur during the surgical procedure—the monitoring of AMI occurrence 30 days after 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 extremities, whether via endovascular procedures or bypass surgery, with AMI being the primary clinical complication following these treatments. Thus, unequivocally, there is a mechanistic link between the role of systemic immune and inflammatory activation and its contribution to multi-arterial instability in symptomatic atherosclerosis, particularly in AMI.⁶⁻⁸ According to *Peter Libby et al.*, an unstable plaque may represent the phenotype of systemic inflammation, which 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 evident symptomatic CVD, thus requiring the identification of validated biomarkers that can provide data over 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; these can be identified mechanistically through neurocardiology by the clinical and pathophysiological integration of common maladaptive neuro-emotional mechanisms of a psychosocial nature, which are central to all stress medicine, and significantly influence subclinical CVD and the onset of an acute cardiovascular event.¹⁷

Neuropsychological Component

Currently, some mental disorders (MDs), such as anxiety, depression, burnout, and various addictions (such as internet addiction, for example), also tend to worsen progressively and uncontrollably.

Following the COVID-19 pandemic, scientists have identified a “silent epidemic” linked to the decompensation of MDs, loneliness, stress, and interpersonal conflicts as intertwined factors.

Studies have shown that 70% of potentially preventable deaths from NCDs in adults result from health-related behaviors that begin in childhood and adolescence.

Stress and Inflammation

Inflammatory and immunological processes play a key role in the onset and progression of a wide range of diseases, and currently, several clinical models 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 impaired wound healing. Although these associations are often attributed to stress-induced dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, few studies comprehensively evaluate stressful events and their altered HPA axis responses, which are associated with immuno-inflammatory and genetic mechanisms.²¹⁻²²

This lack of a comprehensive approach is attributable to the absence of a complete and well-defined understanding of the neurobiological effects of prolonged stress in humans, as well as its practical and systematic identification, in addition to determining which stress-induced changes play a subsequent role in disease risk.²¹⁻²²

Currently, studies have shown that the way target tissues respond to cortisol may be more significant than the simple increase in hormone levels itself.²¹⁻²²

Cohen S et al. demonstrated a significant effect on the pathophysiology of chronic stress, such as glucocorticoid receptor resistance (GCR), 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 (recent stressful life experiences or major stressful life events associated with a long-term threat) can result in GCR, and consequently, this insufficient control of the inflammatory response leads to a greater expression of symptoms and signs generated by the disease's pro-inflammatory response. They concluded that stress and GCR, associated with increased levels of local pro-inflammatory cytokines, present a higher risk of clinical disease.²¹⁻²²

Studies have shown that stress is associated with CRG, with stressed individuals exhibiting reduced sensitivity of lymphocyte and neutrophil counts to distributional changes associated with higher circulating cortisol levels.²³⁻²⁴

Stress may be associated with the manifestation of various diseases through its effect on the glucocorticoid sensitivity of other immune defense cells, as glucocorticoid receptors (GR) are expressed by cells involved in antigen presentation, such as dendritic cells 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 GR α , the active isoform of the receptor, and there is evidence linking stress and cytokines to higher levels of the dominant negative GR β

receptor for cortisol, and a lower GR α /GR β ratio, which may suppress GR α 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 people reporting high levels of loneliness.

Without sufficient glucocorticoid regulation, the duration and/or intensity of the inflammatory response increases, raising the risk of acute exacerbations, such as those occurring in asthma and autoimmune diseases, as well as the onset and progression of chronic inflammatory diseases, such as CVD and type 2 diabetes (T2D).²³⁻²⁴

Currently, there is consistent evidence that the effects of stress result in an increased risk of CVD due to increased gene expression leading to the production of interleukins and local inflammatory cytokines.²³⁻²⁴

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 significantly to the development of various comorbidities.²⁵

In fact, the stress response is fundamentally an adaptive phenomenon aimed at reallocating 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 termed allostasis. Allostatic load refers to the cost of this rebalancing process to 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 body is weakened, prolonged engagement or overstimulation of allostatic systems causes a physiological burden that can lead to disease.²⁵

This chronic activation of the stress response system has been associated with a range of health disorders, including cardiovascular, immune, and reproductive dysfunction, as well as an increased incidence of stress-related psychiatric disorders.²⁵⁻²⁷

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

Research into the mechanisms of adaptive and maladaptive stress responses, as well as interpersonal interactions, is fundamental and includes effects on cognitive and translational function.²⁵⁻²⁷

Acute stress can be defined as a real or perceived temporary challenge to the body'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 nervous system releases epinephrine (E, secreted by the adrenal medulla) and norepinephrine (NE, from the adrenal medulla and sympathetic nerves), which 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 controlled by the hypothalamic-pituitary-adrenal (HPA) axis, which is the system of glucocorticoids (cortisol) released by the adrenal cortex in response to circulating adrenocorticotrophic hormone (ACTH), released by the anterior pituitary.²⁵⁻²⁷

In contrast to catecholamine-induced responses, the effects of glucocorticoids can be rapid (minutes after the stimulus) and long-lasting.²⁵⁻²⁷

Long-term effects develop over several hours and include transcriptional effects of 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 restoring homeostasis can produce harmful consequences for the body. 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 the 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 and animal studies analyzed using molecular markers of glutamatergic transmission. It is suggested that similar adaptations may also underlie HPA axis dysfunction.²⁵⁻²⁷

Development of the Set of Common Maladaptive Biocomportments

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 serving exclusively the function of emotional homeostasis.³⁶

The first level represents individual characteristics, where adverse (exposure to toxins, physical abuse) and protective exposures are assessed starting 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 incidents).³⁶

The third level represents characteristics of out-of-home environments, such as socioeconomic status, social organization, and crime.³⁶

The model begins with the formation of the first group of the system, which is essentially composed of clinical alterations in objective neuropsychological factors, attributed to common neuro-maladaptive elements that develop through social

interactions among family members early in life, and initiates the dysfunction of the first neurological mechanism of family synchrony.²⁶⁻³⁵

Dysfunctions of the family synchrony system can generate a constellation of typical subclinical signs and symptoms, such as emotional and affective neglect, deficient interpersonal communication, stress, anxiety, depression, and addictions that begin, worsen, or persist following family triggers and errors in perceptual processes, due to dysfunction of the initial Pre-cueing neurological mechanism of perception, which leads to limitations in perception and attention.³⁹⁻⁴²

Perceptual errors involving a mismatch between Pre-cueing and emotional value limit cognitive intelligence and are responsible for many cases of irrational family conflicts, including prejudice, ableism, emotional abuse, and even domestic violence.³⁹⁻⁴²

Biobehavioral Aspects of Family Synchrony

Family synchrony is a subtle biobehavioral phenomenon that is fundamental to the initiation and effectiveness of parent-infant interactions, which depend on the proper functioning of the mechanisms of oxytocin and peripheral oxytocinergic and dopaminergic neurons, which develop during the first three years of life, and depends on the synchrony and effectiveness of interactions between biological parents, involving the babies' physical senses and reactions.²⁸⁻²⁹

Parent-child synchrony is defined as an observable pattern of dyadic interaction characterized by social reciprocity, contingent responsiveness, and dyadic behavioral

correspondence; the presence of a deep and effective bond in the interpersonal relationship; the capacity for mentalism (identifying the emotional state of the dyad); and the involvement of biological rhythms.²⁸⁻²⁹

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, symbol use, and empathy throughout childhood and adolescence.²⁸⁻²⁹

The ability to engage in temporally matched interactions is based on physiological mechanisms, particularly oscillatory systems such as the biological clock and the cardiac pacemaker, and hormones related to attachment, such as oxytocin.²⁸⁻²⁹

The bio-behavioral synchrony within the family develops through maternal tactile stimulation and via other physical senses between biological parents and the newborn (NB), which is involved in interpersonal emotional and affective behaviors.²⁸⁻²⁹

These dyadic processes observed in early childhood contribute to the development of self-regulation and children's overall socio-emotional outcomes.²⁸⁻²⁹

Family Synchrony Biobehavior 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 relieving (amygdalan) behaviors or Family Schemas (FSs).²⁸⁻²⁹

Peripheral oxytocinergic and dopaminergic neurons (NODP) are responsible for the mechanisms of effective, or deep, attention, which are essential for identifying a family member's emotional and affective state—a process currently referred to as mentalism.²⁸⁻²⁹

Throughout childhood and early childhood, parent-child synchrony facilitates the child's autonomy, self-regulatory behaviors, and social skills, and supports attachment and the formation of bonds between parents and children. Examining the neurobiological foundations of observable parent-child synchrony and how they can be disrupted by stress will provide critical insight into how stress, broadly interpreted, influences parent-child outcomes.²⁸⁻²⁹

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.²⁸⁻²⁹

Higher levels of parenting-related stress were associated with lower behavioral synchrony between parents and children aged 3 to 14, and higher levels of chronic maternal physiological stress were associated with decreased behavioral synchrony between parents and children.²⁸⁻²⁹

Studies have shown that disruption of the neural circuit underlying behavioral synchrony (the mentalization network) may be a mechanism through which stress affects synchrony between parents and children.²⁸⁻²⁹

The mentalization network consists of several regions across the frontal, parietal, and temporal cortices that co-activate during social cognition.²⁸⁻²⁹

Specifically regarding 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.²⁸⁻²⁹

Nguyen et al. (2020) found that higher levels of stressors reported by parents, such as stress related to family, relationships, and finances, as well as difficulties with child-rearing, were associated with reduced neural synchrony between parents and children in the bilateral prefrontal cortex during a problem-solving task and in the left anterior prefrontal cortex during a joint passive attention task.²⁸⁻²⁹

Gubhaju et al. (2013) identified that the 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 difficulties, etc.) and psychosocial disadvantage (which included parent relationships and parental well-being).²⁸⁻²⁹

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.²⁸⁻²⁹

Adversity, across all domains, was significantly associated with lower behavioral synchrony between parents and children in all task conditions.

Several studies show that stress/adversity has a disruptive effect on behavioral synchrony between parents and children.²⁸⁻²⁹

Hoyniak CP et al. demonstrated that parent-child neural synchrony in the context of induced adversity and stress, with a frustration effect, 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.²⁸⁻²⁹

This study assessed the regions comprising the emotional regulation and executive control networks, and disruptions in one or both networks contribute to deficits in their functioning.²⁸⁻²⁹

Furthermore, dyads who experienced higher levels of sociodemographic risk were employing adaptive regulation strategies that allowed them to overcome disruptions in synchrony, which is consistent with research data demonstrating increased activation of limbic and subcortical regions during socioemotional cognition in individuals who have experienced high levels of adversity, and which, in clinical practice, is expressed through coping 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.²⁸⁻²⁹

(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.*)

Neurocardiology and Stress

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

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

Early Acute Myocardial Infarction (EAMI)

Through clinical empiricism and inductive reasoning guided by specific risk factors associated with immunological, inflammatory, and genetic mechanisms, as well as the neurocardiology of psychosocial stress, an assertive and plausible hypothesis is generated for understanding and explaining the development of EMMI.³⁰

Sagrís M et al. demonstrated through angiographic studies the presence of different vascular lesions between young and elderly patients with MI. In young patients, they found a higher propensity for no disease or single-vessel disease, lower pulse wave velocity, and a lower central augmentation index compared to the elderly, who frequently presented with disease involving multiple lesions in three or more vessels.³⁰

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 sex, obesity, and a family history of early CAD. Within the young MI group, 36% had no or only one traditional risk factor for MI and would have been classified as low risk prior to the index event.³¹

Zeitouni M et al. evaluated 6,639 patients with MI; 41% were <55 years of age (“younger”). Compared to older adult groups (>55 years), younger adults had higher prevalences of smoking (52%), obesity (42%), metabolic syndrome (21%), and dyslipidemia with higher levels of low-density lipoprotein cholesterol.³²

To conduct an unprecedented and comprehensive evaluation of the various mechanisms of stress through family psychoso-

cial neuroscience, by measuring inflammatory, immunological, and neurogenomic markers in patients who have suffered acute myocardial infarction, with systematic and objective clinical identification of maladaptive neuromarkers.³³

Neurocardiology, which utilizes the recent clinical approach to common maladaptive biobehaviors, now encompasses new pathophysiological mechanisms to be evaluated, which is of fundamental importance for both AMI and MI in elderly patients.³⁴

Genetic Alterations Associated with Myocardial Infarction

In recent years, there has been a steady trend toward uncovering the genetic basis of Gout, resulting in the identification of approximately 60 distinct genetic loci.^{33–35}

Currently, the study of genomics associated with AMI is very broad and heterogeneous. Large gene banks and large-scale studies are currently investigating serum urate levels, which are elevated by various genes and have been associated with increased risks of MI.^{33–35}

Serum urate can cause platelet activation, adhesion, and aggregation, and participate in the production of inflammatory interleukins. However, the combined effects of the various AMI risk factors have not yet revealed 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 the *AGER* and *MST1* genes; together with *PCSK9* and *C1S*, these proteins exhibited the highest frequency among the causal mediator networks involved in CAD pathogenesis.^{33–35}

Circulating proteins play a key role in mediating the link between modifiable factors and susceptibility to CAD. The deleterious effect of obesity on CAD appears to be mediated primarily by MAP1LC3A, ANGPTL4, RPS6KA1, PCSK9, ITPKA, and AGER.^{33–35}

Somatic mutations in clonal hematopoiesis of undetermined potential (CHIP)

Clonally derived hematopoietic progenitor cells of undetermined potential (CHIP) are associated with an increased risk of cardiovascular events.⁴⁵

It is defined as a hematopoietic cell with somatic mutations 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 may progress to 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 group.⁴⁵

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

These functional alterations in CHIP are involved in increased gene expression of inflammatory interleukins, which in turn may stimulate the progression of atherosclerosis.⁴⁵

Currently, the results remain heterogeneous; however, the patterns depend on the underlying mutations, as those with *TET2*

mutations exhibited increased inflammatory signaling, while *ASXL1* mutations had selective effects on metabolic pathways.⁴⁵

Most studies have shown that the presence of CHIP involving the *JAK2* locus is associated with a significant increase in the risk of coronary artery disease.⁴⁵

A study of 7,245 participants evaluated the association between CHIP and early-onset myocardial infarction, revealing a fourfold higher risk of atherothrombosis among CHIP carriers compared to the control group.

IAMP was strongly associated with mutations in *TET2*, *ASX1*, and *JAK2*, with preclinical cases showing signs of accelerated atherosclerosis linked to the *TET2* mutation.⁴⁵

Current data point to an association between inflammation and socioeconomic and psychosocial stressors, although this has not yet been evaluated.⁴⁵

Behavioral Genetics as an Integrative Mechanism in Psychosocial Cardiology

Advances in behavioral genetics offer a new pathway to understanding the causal factors involved in the genesis of early acute myocardial infarction (AMI), particularly by linking maladaptive neuropsychological characteristics to functional genetic variants. Susceptibility to chronic stress, alterations in emotional regulation, and addictive behavior—mechanisms already implicated in atherosclerotic plaque instability—is supported by genomic studies that associate polymorphisms with behavioral traits that directly modulate cardiovascular risk.⁵³

Several common genetic variants, such as those associated with the DRD2, COMT, and OXTR genes, have been linked to dopaminergic function and reinforcement and reward mechanisms, influencing risk-taking behaviors, impulsivity, and emotional regulation—factors that act as indirect precursors of endothelial dysfunction and chronic oxidative stress. Such associations have been observed in large-scale genomic studies, such as that by Davies et al. (2011), which highlighted SNPs with a small but cumulative impact on general intelligence, associated with self-regulation and decision-making abilities, and thus indirectly with health behavior.⁵³

Furthermore, recent studies have identified correlations between polygenic intelligence scores and greater stress resilience, lower prevalence of mental disorders, and reduced exposure to cardiovascular risk factors, thereby reinforcing the concept of cardiovascular behavioral genetics. In this sense, the integration of cognitive genomics, affective neuroplasticity, and clinical biobehaviors becomes a central pillar for the development of new diagnostic and preventive methodologies in cardiology.

Understanding these genetic pathways may also aid in risk stratification and the development of personalized interventions that take into account not only traditional clinical factors but also the genetic and behavioral profiles associated with early cardiovascular risk.

Discussion

Stressful events have long been implicated in CVD, yet there has never been a methodology to objectively assess neuropsychological clinical features, compounded by the lack of integration of the various underlying and intricate pathophysiological mechanisms, which must be evaluated in light of causal effects through new population-based studies.³⁶

The Multiethnic Study of Atherosclerosis (MESA) is a prospective cohort study that assessed the significance of subclinical cardiovascular disease, focusing on the relationship between smoking intensity and proximal biomarkers of cardiovascular disease in a large, multiethnic, and sex-balanced cohort of 6,814 participants, and it was shown that high-sensitivity C-reactive protein (hs-CRP) was the most sensitive biomarker for smoking and CVD.³⁶

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

However, we draw attention to the importance of considering objective neuropsychological assessment in children, particularly in cases of childhood obesity, alongside an evaluation of childhood adversity, such as Adverse Childhood Experiences (ACE), and PTSD, which are involved in the development of common neuro-maladaptive biobehaviors; these are direct factors in emotional regulation deficits and psychosocial stress, in addition to presenting the same inflammatory biomarkers and substantial evidence that predict CVD in adulthood.³⁷⁻³⁸

Regarding studies on genetics and IAMP, most studies involve populations of older adults, and the validity of the results depends on the assumption of relevance—that is, genetic variants must show a strong association with the exposure of interest—the assumption of independence—that is, genetic variants must be independent of confounding factors—and the exclusion restriction—that is, genetic variants must influence the outcome solely through the exposure.³⁷⁻³⁸

In medicine, clinical practice is the ability to identify the effect based on the cause in an assertive, observational manner, which requires an understanding of dynamic pathophysiological processes. Clinical neuroscience was developed according to traditional scientific methods of observing a change in nature (cause) that exhibits a pathophysiological causal link with the assertiveness that generates the effect.

Current studies present heterogeneity in causal effects, which may introduce bias in estimates due to the various underlying risk factors for average effects. Clinical application to select populations with IAMP and stress-related mental health issues can be considered through the systematic clinical organization of common biobehaviors—ONCs.³⁶

Conclusion

We present a clinical model that addresses stressors through a novel approach to maladaptive biobehavioral patterns, involving objective assessment using clinical neuromarkers. This model facilitates a new framework for research and insights, as well as an attempt to elucidate the origins of DCNTs and IAMP.

We draw attention to the fact that the current model of psychosocial neurocardiology evaluates psychological components in an unprecedented way, in addition to identifying causal factors such as EAI and PTSD, which are fundamental to the development of common neuro-maladaptive biobehaviors and may aid in new strategies for controlling and preventing the current epidemics of Obesity, TM, and DCNTs.

This work has the limitation of being in an early stage of development; however, it was constructed through theory-guided clinical empiricism, using accumulated data from functional neuroimaging studies, and must be tested and validated by larger studies.

Cause-and-effect studies in genomics are most effective when guided by clinical practice. As in the case of Kenneth Blum's group, which described Reward System Dysfunction Syndrome (RDS) in 1996, these studies have led to several advances and should be considered in future integrative research on obesity and CVD.

Conflict of Interest Statement.

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

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