Review

COVID-19 Mrna Vaccines: from Inflammation to Hyperinflammation.

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Abstract: Each injection of any known vaccine results in a strong expression of pro-inflammatory cytokines. This is the result of the innate immune system activation, without which no adaptive response to the injection of vaccines is possible. COVID-19 mRNA vaccines would not escape this rule. Unfortunately, the degree of inflammation produced by these vaccines is variable, probably depending on the genetic background and previous immune experiences, which through epigenetic modifications, could have made the innate immune system of each individual tolerant or reactive to subsequent immune stimulations.We hypothesize that we can move from a limited pro-inflammatory condition to conditions of increasing expression of pro-inflammatory cytokines that can culminate in multisystem hyperinflammatory syndromes following COVID-19 mRNA vaccines (MIS-V). We have graphically represented this idea in a hypothetical inflammatory pyramid (IP) and we have correlated the time factor to the degree of inflammation produced after the injection of vaccines. Furthermore, we have placed the clinical manifestations within this hypothetical IP, correlating them to the degree of inflammation produced. Surprisingly, excluding the possible presence of an early MIS-V, the time factor and the complexity of clinical manifestations are correlated to the increasing degree of inflammation: symptoms, heart disease and syndromes (MIS-V).

Keywords: COVID-19 mRNA vaccines; Myo-pericarditis and COVID-19 mRNA vaccines; Multisystem-Inflammatory-Syndrome and COVID-19 mRNA vaccines; arrhythmias and COVID-19 mRNA vaccines; Pathogenesis of myocarditis following COVID-19 mRNA vaccines; MIS-A; MIS-C; MIS-V; Myocarditis; COVID-19 mRNA vaccine Adverse Events.

1. Introduction

In the post-marketing period, some adverse events (AEs) were temporally associated with the injection of COVID-19 mRNA vaccines. Starting from the evidence that up to now no studies have been published on the pathogenetic mechanisms that could determine cardiac AEs, we have conducted a research focused on the molecular effects determined by the Spike protein that have allowed us to propose a unifying mechanism that includes at least four groups of AEs: 1- Systemic Symptoms; 2- Arrhythmias; 3- Mio-pericarditis; 4- Multisystemic Hyperinflammatory Syndromes (MIS).

Considering the clinical relevance of cardiac AEs (arrhythmias, myo-pericarditis), in this study we have devoted ample space to a series of pathophysiological mechanisms that can be influenced by the administration of lipid nanoparticles (LNPs) containing mRNA encoding Spike protein.

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2. Human heart

In the human heart there are several cell types: cardiomyocytes (CMs), cardiac fibroblasts (CFs), cardiac endothelial cells (CECs), macrophages, smooth muscle cells, pericytes and other cells [1-4], but CMs are about one third of the entire cell population [4-8]. In CMs there is an axis Toll-Like Receptor 4 (TLR4) / Nuclear Factor kappa B (NF-kB) which is important in cardiac inflammation [9]. TLR4 activation triggers inflammatory immune response via TLR4 / MyD88 / NF-κB signaling pathway [10]. SARSCoV-2 Spike protein S1 subunit (CoV-2-S1) induces high levels of NF-κB activation [11].

CFs are the primary cell type responsible for deposition of extracellular matrix (ECM) in the heart, providing support to the contracting myocardium and contributing to a myriad of physiological signaling processes [12]. CFs contributes to both electrical and structural remodeling of the heart, which ultimately leads to decreased cardiac function, heart failure, and arrhythmias [13-16]. Myocardial interstitium is a complex and dynamic microenvironment [17], and ECM synthesis contributes to myocardial fibrosis [18]. When ECM expands, the extracellular space expands and signals a process of myocardial fibrosis which can be detected with Cardiac Magnetic Resonance (CMR) imaging, where an excess of gadolinium is retained and deposited in the extracellular space [19], producing the phenomenon of Late Gadolinium Enhancement (LGE).

CECs form a barrier to the movement of fluids and molecules [20] and during inflammation the junctional proteins of the paracellular pathway are modified with subsequent interruption of the integrity of this barrier [21]. CECs organize recruitment of immune cells and regulate leukocyte extravasation at places of inflammation by inducible expression of adhesion molecules, and maintain appropriate hemostasis or coagulation.

Several cardiac cells express Angiotensin-Converting Enzyme 2 (ACE2) [22], but pericytes have the highest concentration of ACE2 and their injury may result in microvascular dysfunction [23], which facilitates the transit of neutrophils and macrophages in a proinflammatory environment [23].

3. Systemic Symptoms

In our representation of the hypothetical IP, at the first level we have placed the systemic symptoms that arise after the injection of the vaccine (muscle aches, chills, asthenia, fever, headache, pain at the injection site), symptoms generated by the strong production of pro-inflammatory cytokines, species interleukin (IL)-1 IL-1β, IL-6 and Tumor Necrosis Factor (TNF)-α. In our previous studies we have described the mechanism of action of common infant vaccines and found that there is no adaptive immune response to vaccine injection if the innate immune system is not activated, which also leads to strong expression and secretion of various pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α [24, 25].

4. Inflammatory cardiac channelopathies and arrhytmias

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Immune system can promote cardiac arrhythmias by means of autoantibodies and / or inflammatory cytokines that directly affect the function of specific ion channels on the surface of CMs [26-29].

5. The cardiac Action Potential (AP)

Normally, a cardiac muscle cell, in a resting state, has a negative electric charge of about 90 mV on the inner side of its cell membrane, compared to the surrounding medium. When an electrical stimulus excites a ventricular cell, the cell membrane rapidly depolarizes and the potential difference now becomes positive inside with a value of about 20mV (positive overshoot). Now we are at the 0 phase of Action Potential (AP). This is followed by phase 1 which consists of a short phase of partial repolarization that is followed by phase 2, which is that of the plateau that signals a period of intense and sustained depolarization of the membrane. The repolarization process starts at stage 3 and it is a slower process. The interval from the end of repolarization until the beginning of the next AP is designated as phase 4 [30].

6. The ionic basis of AP

The changes in the permeability of the cellular membrane are associated with the various phases of the AP and essentially involve three ions: Na^+, K^+, and Ca^{2+}. These permeability changes alter the rate of ionic movements across the membrane [30]. Apart from the movement of sodium of the 0 phase of AP, the movements of potassium and calcium can be influenced by pro-inflammatory cytokines which act precisely on certain ion channels. In table 1, we present a series of characteristics of some channels of the cardiac muscle fibrocells, relating them to the specific AP phase and we indicate the documented interferences that pro-inflammatory cytokines produce on ion channels and currents.

Channel	Current	Current type	Ion	AP phase	Interference
K_v 4.3	I_{to}	Outward	K^+	1	IL-1β, TNF-α
L-type	$I_{Ca,L}$	Inward	Ca^{2+}	2	IL-1β, IL-6
K_v 11.1 hERG	I_{Kr}	Outward	K^+	3	IL-6, TNF-α
K_v 7.1	I_{Ks}	Outward	K^+	3	TNF-α
Kir 2.1/2.3	I_{K1}	Inward	K^+	4	

Table 1. Kv 4.3, Kv 11.1 or hERG, and Kv 7.1 are Voltage-Gated Potassium Channels. They produce three outward currents of K+: one in AP 1 (Ito), and two in AP 3 (IKr,IKs). Conversely, Kir 2.1 / 2.3 channels produce inward current in AP 4 (IK1). Proinflammatory cytokines interfere with the physiological function of all the currents represented here, excluding the inward current IK1.

Several studies have demonstrated the importance of Voltage-Gated Potassium Channels in the genesis of cardiac arrhythmias [31-35]. Loss-of-function mutations in K_v 7.1 channel, lead to long-QT syndrome type 1 (LQTS1), which is the most frequent type of

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the long-QT syndromes [36]. The link to physiology is exemplary: patients with LQTS1 most frequently have arrhythmic events during exercise, where the sympathetic drive increases heart rate but fails to reduce repolarization time, because Kv 7.1 channel is dysfunctional [37]. Furthermore, TNF-α causes a functional inhibition of the K_v 7.1 channel which reduces the current I_k [38]. KV11.1 is essential for normal cardiac electrical activity and rhythm [39]. IL-6 produces an inhibition on the rapid delayed rectifier current Ikr. The consequent prolongation of the duration of AP results in QT interval prolongation [40]. Finally, Kir 2.1 / 2.3 channels also determine effects on AP [41-43].

Voltage-activated Ca^{2+} channels represent the major route of Ca^{2+} entry into CMs in response to depolarizations of the cellular membrane potential [44]. These channels are important in the AP plateau phase and are important for the electrical and mechanical properties of the heart [45-50].

7. Proinflammatory cytokines

Inflammatory factors can cause cardiac K^+ channel dysfunction and arrhythmias in the setting of a structurally normal heart [51]. Emerging experimental evidence has shown that inflammatory responses, mainly via IL-1β, IL-6 and TNF-α, regulate CMs electrophysiological properties [51-56]. Proinflammatory cytokines can be arrhythmogenic and cytokines can promote the development of LQTS [27]. Some studies report in detail the effects of proinflammatory cytokines on cardiac ion currents [29, 40,46,57-59].

8. Myo-pericarditis

The mean monthly number of cases of myocarditis or myopericarditis during the pre-vaccine period was 16.9 vs 27.3 during the vaccine period [60]. Although it doesn't seem like it, the monthly increase in cases is statistically significant, practically doubling. Myocarditis incidence after RNA vaccines is very rare (0.0035%) and has a very favorable clinical course [61]. But not all cases are benign and critical or fatal cases have been reported [62-65]. There is an excess of cases with a substantial burden of both myocarditis and pericarditis in all ages [66]. Increased risk of myocarditis / pericarditis has been associated with the second dose of BNT162b2 and both doses of mRNA-1273 [67]. In one study the highest risks were observed in males of 12 to 39 years [67], while Wong and colleagues [68], demonstrated that an increased risk of myocarditis or pericarditis was observed after COVID-19 mRNA vaccination and was highest in men aged 18–25 years after a second dose of the vaccine.

8.1. Probable pathogenesis of myocarditis

Husby and Kober [69], argue that the disease mechanism is specific neither to the newly developed mRNA vaccines nor to exposure to the SARS-CoV-2 Spike protein. However, we try in this study to elaborate a pathogenetic hypothesis on the basis of extensive scientific documentation in support of our thesis.

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Before proceeding it is necessary to understand that the two vaccines have a partly different composition, both in the quantity of Lipid Nanoparticles (LNPs) and in the excipients. There is a difference in the amount of LNPs contained in the two vaccines: in the dose of Comirnaty (BNT162b2 - Pfizer / Biontech), to be administered to subjects aged> 12 years, there are 30 micrograms / dose [70]; while in the Moderna vaccine (mRNA-1273) there are 100 micrograms / dose [71]. As it is evident, the content of LNPs is three times higher in the Moderna vaccine, compared to Pfizer / Biontech, and could probably affect the timeline of the onset of these adverse events (AEs). In addition, the vaccination schedule provides an interval between the first and second dose of 21 days for the Pfizer / Biontech vaccine [70]; while this interval is 28 days if the Moderna vaccine is used [71].

8.1.1. One or two shots?

In several studies, myocarditis / pericarditis are more frequent after injection of the second dose of Pfizer / Biontech mRNA vaccine; while myocarditis / pericarditis can occur both after the first and second injection of Moderna's mRNA vaccine. Considering the time interval between the two vaccine doses; one would think that it takes less than 28 days to produce this AEs (about 23-27 days for the BNT162b2 vaccine).

We must develop our hypotheses starting from the fact that there are two different formulations of COVID-19 mRNA vaccines and two different vaccination schedules. Furthermore, our immune system must produce dose-dependent inflammatory responses after the administration of two different doses of LNPs (30 micrograms / dose vs 100 micrograms / dose). In addition, the immune response is complex and affects the entire LNP.

It was demonstrated that if the antigenic stimulus persists for over a week at low levels cause chronic low-level stimulation of T cells, keeping them in a partially activated state and leading to their accumulation over time [72-74].

Li and colleagues [75] conducted a study in a Balb / c mouse model and found that intravenous injection of a COVID-19 mRNA vaccine rapidly resulted in multifocal myopericarditis, while intramuscular injection produced signs 7 days after injection. (myocardial edema, and occasional foci of cardiomyocyte degeneration). However, these histopathological changes worsened after the second dose. Since the injected vaccine was BNT162b2, this study may indicate that two shots are needed with this vaccine to produce myopericarditis, as occurs predominantly in humans.

8.1.2. Inflammatory infiltration of myocardium

Verma and colleagues [64] described two cases (one fatal) with multifocal myocardial damage (biopsy and autopsy) associated with mixed inflammatory infiltration. The surviving subject presented at the endomyocardial biopsy (EMB) an infiltration of T cells, macrophages, eosinophils, B cells and plasma cells. Conversely, the fatal case presented at the autopsy an infiltrate that was similar but did not contain plasma cells. Oka and colleagues [78] described a case of fulminant myocarditis after the second dose of COVID-19 mRNA vaccination. The inflammatory infiltrate was identical to the non-fatal case described by Verma and colleagues [64]. Kazama and colleagues [79] described the case of a

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woman with fulminant myocarditis following the second dose of Moderna COVID-19 vaccine. Again, EMB revealed lymphocytic infiltration with predominant immunostaining for CD8 and CD68-positive cells (macrophages). Two other cases with acute myocarditis following COVID-19 mRNA vaccination, at EMB analysis, have elevated CD3 T cells and CD68 macrophages [80]. The activation of T lymphocytes and macrophages [81-85] is believed to play a fundamental role in myocardial inflammation [81], and cardiac macrophage populations are markedly perturbed by inflammation [82].

Since COVID-19 mRNA vaccine-related myocarditis develops rapidly in 3 to 4 days after vaccination, innate immunity more likely contributes to the pathogenesis of vaccine-related myopericarditis than adaptive immunity [76]. It is useful to remember that any vaccine determines a strong expression of proinflammatory cytokines (including IL-18) by DCs, which is associated with an evident activation of NFκB [24,25]. In an inflammatory microenvironment, caspase-1 is regulated by NF-κB [77], and this enzyme facilitates the conversion of pro-IL-18 in IL-18. Patient with myo-pericarditis following COVID-19 vaccination had excessive Th1-type immune responses over vaccine-induced immune activation. Diffuse myocardial macrophages infiltration in the patient biopsy sample, suggest an increased level of IL-18 produced by monocytes and macrophages in the heart with COVID-19 vaccine-related myo-pericarditis [76].

8.1.3. Who opens the gate?

Now it is necessary to understand how the injection of the vaccine determines a series of immune events that can open a passage in the endothelial line of the heart vessels through which inflammatory cells will then infiltrate and can cause damage to the myocardium. We have identified at least 4 main actors: 1- DCs derived exosomes; 2- proinflammatory cytokines; 3- Adhesion molecules; 4- Spike protein. The framework is then integrated by the activation of the TLRs and the TLR4 / NFκB axis.

8.1.4. Exosomes

Exosomes are cell-derived small extracellular membrane vesicles, with 50–100 nm in diameter, that are actively secreted and released both in physiological and pathological conditions. Exosomes contain and transport multiple types of biological macromolecules that maintain their whole activity when delivered to target cells. This bioactive cargo, include nucleic acids, lipids, and soluble or membrane-bound proteins [86]. Exosomes, produced by mature DCs, can produce inflammation in endothelial cells through their TNF-α content in their membrane, via transcription factor NF-κB, which also induces the transcription of adhesion molecules such as Vascular Cell Adhesion Protein 1 (VCAM-1), Intercellular Adhesion Molecule 1 (ICAM-1) and E-selectin in endothelial cells (ECs) [87]. Furthermore, DCs-derived exosomes contain major histocompatibility complex (MHC) Class I and II molecules and T cell co-stimulatory molecules, which determine direct antigen presentation and CD4 and CD8 T cell activation [21,88]. There is important crosstalk between CMs and CECs that is ensured by means of the cardiomyocytes-derived exosomes that are up-taken by CECs. ECs can also actively collaborate with the underlying

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CMs and modulate cardiac function, both under physiological conditions and under proinflammatory conditions [21,89-96].

In summary, after injection of COVID-19 mRNA vaccines, DCs-derived exosomes may contain a variable amount of what is found in their cytosol: Spike protein-encoding mRNA, Spike protein, Spike protein peptides, proinflammatory cytokines, MHC Class I and II molecules, and T cell co-stimulatory molecules that make the particle capable of initiating and maintaining an inflammatory process in the target tissue.

8.1.5. Spike protein induces endothelial cells (ECs) dysfunction

Spike protein of SARS-CoV-2 alone activates ECs inflammatory phenotype in a manner dependent on integrin α5β1 signaling and induced the nuclear translocation of NF-κB and subsequent expression of leukocyte adhesion molecules (VCAM-1 and ICAM-1), coagulation factors, proinflammatory cytokines (TNF-α, IL-1β, and IL-6), and ACE2. Furthermore, *in vivo*, intravenous injection of the protein Spike increases expression of ICAM-1, VCAM-1, CD45, TNF-α, IL-1β, and IL-6 in the lung, liver, kidney, and eye [97].

Therefore, it emerges with extreme clarity that the protein Spike alone, is able to induce the secretion of pro-inflammatory cytokines (via NF-κB) and adhesion molecules (ICAM-1, and VCAM-1) in ECs.

8.1.5.1. Spike Protein and cardiomyocytes (CM)

CoV-2-S1 interacts with the extracellular leucine rich repeats-containing domain of TLR4 and activates NF-κB [98]. TLR4 initiates the expression of several pro-inflammatory genes, cell surface molecules, and chemokines through the MyD88-dependent pathway, which exacerbates the damage to myocardium [99]. The circulating CoV-2-S1 is a TLR4-recognizable alarmin that may harm the CMs by triggering their innate immune responses [98]. In CMs there is an axis TLR4 / NF-kB [9] and unmitigated TLR4 activation may lead to increased risk for cardiac inflammation [100]. Thus, the TLR4 / NF-kB axis in CMs can also cause cardiac inflammation and myocardial damage, and the Spike protein alone is able of activating this axis in CMs.

Spike protein alone can easily reach the myocardium through these routes: 1- via DCs derived exosomes; 2- via ECs that have ACE2 receptors, and, after uptake, they can produce exosomes to be exported to CMs; 3- via transmigration through the endothelium.

Baumeier and colleagues [101], studied 15 cases of myocarditis after COVID-19 mRNA vaccine using EMB and immunohistochemical analysis. In 9 of these patients the Spike protein was found in CMs. Furthermore, CoV-2-S1 activates TLR4 signaling to induce pro-inflammatory responses in murine and human macrophages [102]. Finally, SARS-CoV-2-induced myocarditis and multiple-organ injury may be due to TLR4 activation, aberrant TLR4 signalling and hyperinflammation in COVID-19 patients [103].

8.1.6. Young males: the favorite target.

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Adolescence is accompanied by increased exposure to stressors [104,105] and it is a time of many psychosocial and physiological changes [106]. Change also the stress response system (SRS). Acute stress prepares the body for the stressful situation [107]. Briefly, autonomic nervous system (ANS) responding to stress within milliseconds to minutes and the HPA axis responding over minutes to hours following stressor onset [108,109]. The stress response to physical and / or psychological stressors is initially produced by ANS which introduces the catecholamines epinephrine (E) and nor-epinephrine (NE) into the circulation [110].

Acute stress induces inflammatory response and raises the circulatory levels of inflammatory cytokines [111], such as IL-6 and TNF-α, also results in platelet activation and endothelial stimulation [112]. Mental stress induces prolonged endothelial dysfunction [113]. Adrenaline released during acute stress greatly increases both the inotropic and chronotropic effects in the heart via the β_2 receptors [114]. B_2-receptor activation has effects on a calcium current (I_{CaL}) and a potassium current (I_{Ks}) which exert opposite effects on the AP. When I_{Ks} is dysfunctional, as in LQT1, the resulting unbalanced I_{CaL} effect causes excess AP prolongation [115].

Overall, acute stress creates a pro-inflammatory and pro-arrhythmic condition that can worsen if eating disorders (typical of adolescents) coexist. For example, repeated vomiting leads to a loss of potassium and consequent hypokalemia, resulting in effects on other potassium ion currents, delays repolarization and promote LQTS by suppressing K^+ currents like I_{Kr} and the background inward rectifier I_{K1} [116]. Chronic stress is more harmful, and in an animal under chronic stress, a new stressful stimulus determines a strong response of the ANS with high secretion of catecholamines [117,118].

Stress reactions in Italian adolescents in response to the COVID-19 pandemic during the peak of the outbreak seem to be considerable [119]. Furthermore, we must not forget that young people practice sports of varying intensity. Combined stress (psychological and physical) can exacerbate cardiovascular responses to stress [121].

8.1.7. Other pathological mechanisms triggered by the Spike protein

ACE2 is expressed throughout the cardiovascular system [122]. When the Spike protein binds to the ACE2 receptor, the typical enzymatic function (carboxypeptidase) is replaced by a receptor function which activates intracellular signaling pathways [123-125]. As a result, normal ACE2 activity in the Renin - Angiotensin - Aldosterone System (RAAS) is lost and excess angiotensin II occurs.

8.1.7.1. Renin–Angiotensin–Aldosterone System (RAAS)

Renin, angiotensin, and aldosterone represent the core of a complex hormonal axis, referred to as RAAS, which contributes to blood pressure control, sodium reabsorption, inflammation, and fibrosis [126]. The renin enzyme degrades angiotensinogen producing angiotensin I (Ang I). ACE catalyzes the transformation of Ang I to Ang II. Ang II, the primary physiological product of the RAAS system, is a potent vasoconstrictor [127]. ACE2 converts Ang II into Ang-(1–7) and activates the protective axis AT_2R. Conversely,

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if the action of ACE2 is reduced, the AT_1R axis is enhanced, which is pro-inflammatory, pro-apoptosis and pro-fibrosis. The Ang II / AT_1R axis is also involved in oxidative stress that stimulates endothelial dysfunction, inflammation of the vessels and thrombosis [128-130]. Furthermore, the upregulated expression of AT_1R is linked with arrhythmias [131] and cardiac remodeling [132].

It is interesting to remember that the Ang II / AT_1R axis mediates a cascade of signals that induce transcriptional regulatory molecules NF-κB and AP-1 / c-Fos via MAPK activation, and increased IL-6 release [133]. In addition, Angiotensin II also promotes the expression and production of adhesive and proinflammatory molecules (VCAM-1, ICAM-1, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and IL-8) on the endothelial and vascular smooth muscle cells [134-139]. The functional deficit of the Ang II / AT_2R / Mas receptors axis does not produce the normal beneficial effects during stressful situations, lacking the ability to effectively modify sympathetic nervous activity during stressful conditions [139].

8.1.7.2. Toxicity of lipid nanoparticles (LNPs)

LNPs are composed of cholesterol, a helper lipid, a Polyethylene glycol (PEG) lipid and an ionizable amine-containing lipid [140]. Some cationic / ionizable lipids contained in the LNPs of COVID-19 mRNA vaccines, pose toxicity problems [141]. Overall, LNPs exhibit a powerful proinflammatory action [142,143]. Small amounts of double-stranded RNA (dsRNA) can occasionally get packaged within mRNA vaccines [144]. LNPs evoke a strong proinflammatory response by activating TLR pathways [143-147], and the inflammatory milieu induced by the LNPs could be partially responsible for reported side effects of COVID-19 mRNA vaccines in humans [148]. Furthermore, the Spike protein present on plasma membranes could expose these cells to attack by anti-Spike antibodies, generating an antibody-dependent cellular cytotoxicity (ADCC) [149].

BioNTech / Pfizer Comirnaty vaccine contains two novel LNP-excipients: ALC-0315 (aminolipid) and a Polyethylene glycol lipid (PEG) ALC-0159 [150]. Saadati and colleagues [151] have recently described a new and clean way to produce ALC-0315, which contrary to the public-domain route, does not use dangerous reagents, such as hexavalent chromium Cr (VI) which is cardiotoxic [152,153].

8.1.8. TCD8, TCD3/CD45R0 and Macrophages CD68 in Myo-pericarditis

Human T-cell differentiation should be delineated using a minimum set of canonical markers, i.e. CD45R0 (or CD45RA), CCR7, CD28, and CD95 [154]. $CD45RA^-CD8^+$ memory T cells expressing CD27 produce both IL-2 and IFN-γ but lack immediate killing activity (T memory cells); while effector T cells ($CD45RA^-CD8^+CD27^-$) produce mostly IFN-γ and TNF-α, but not IL-2 and are capable of immediate cytotoxicity ex vivo [155]. CD45R0 being preferentially expressed on memory cells [156,157].

Under normal conditions, T lymphocytes also exercise immune surveillance on the heart with a continuous trafficking of T cells through blood, lymphoid organs, and the heart [158]. Human CD8 T cell subset contains two distinct and separate entities: memory-

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and effector-type T cells, and the degree of systemic inflammation produced by vaccination affects the phenotype of secondary memory CD8 T cells [159]. Upon the second encounter with the cognate antigen, memory T cells are ready to proliferate and perform cytotoxic functions [160].

8.2. Diagnostic Items

The definition of myocarditis has been more recently enumerated by the ESC Working Group on Myocardial and Pericardial Diseases [161]. In patients with myocarditis main inflammatory populations consisted of macrophages and T cells [162-164].

Diagnostic tools include clinical signs and symptoms (difficulty breathing, chest pain), auscultation, ECG, echocardiography, cardiac MRI (to detect late gadolinium enhancement or LGE) and EMB, when indicated. Among the laboratory markers are useful: creatine kinase MB, troponin I and PCR [165]. For all the details, see the position statements [161, 165].

Autoimmune forms of myocarditis excluded [166,167], immunohistochemical examinations [168-169] uniformly confirm that the inflammatory infiltrate is composed of activated CD3 T lymphocytes and CD68 macrophages (human heart contains distinct macrophage subsets) [170]. Conversely, in the autoimmune forms cardiac antigen-specific CD8 T lymphocytes could also be produced due to the molecular mimicry between Spike peptide and myocardial antigens [171].

8.3. Trans-endothelial migration towards heart tissue

Leukocyte homing and recruitment require the adhesion of leukocytes to the endothelial lining of postcapillary venules, a process that involves molecules on the surfaces of both the leukocytes and endothelial cells [172-174].

8.4. Immune Black Hole

We presume to know a series of events following the injection of the vaccine and to predict reasonably enough what happens after the second injection; while we do not know how the immune system behaves in the period of time between the injection of the vaccine and the clinical onset of myo-pericarditis. We know that a few hours after the injection of the vaccine there is a strong production of pro-inflammatory cytokines and the synthesis of adhesion molecules is enhanced. All this makes it easy for T lymphocytes and macrophages to migrate towards the myocardium. Memory CD8 T cells, upon reinfection and antigenic stimulation, they have the capacity to rapidly proliferate and differentiate into secondary effector CD8 T cells [175-177].

8.5. Experimental myocarditis

There are two different study models of myocarditis: infectious and non-infectious. In non-infectious models, myocarditis is typically triggered by an autoimmune response

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against heart-specific antigens [178]. α-isoform of cardiac myosin heavy chain (α-MyHC) is not expressed in cells implicated in T cell tolerance. This results in undisturbed development of α-MyHC-specific T cells in human [179] due to the molecular mimicry between Spike protein and α-MyHC. In fact, antibodies directed to SARS-CoV-2 Spike glycoproteins might cross-react with structurally similar human protein sequences, including myocardial α-MyHC [179].

In summary, these two experimental models do not add contributions to our understanding because the cases following the injection of vaccines are not of an infectious nature and there are few cases of autoimmune etiology.

9. Multisystem Inflammatory Syndromes (MIS)

Multisystem Inflammatory Syndrome in children (MIS-C) is a new pediatric illness that is a late complication of SARS-CoV-2 infection. Myocardial dysfunction with or without mild coronary artery dilation can occur in MIS-C [180]. MIS-C is characterized by fever, systemic inflammation, and multisystem organ involvement [181-183] with particular interest in the gastrointestinal, cardiovascular and neurological system, associated with elevated markers of inflammation and altered coagulation [184]. MIS in adult (MIS-A) is a serious hyperinflammatory condition that presents approximately 4 weeks after onset of acute COVID-19 with extrapulmonary multiorgan dysfunction [185].

MIS following COVID-19 vaccination (MIS-V) remain rare event [186], but it is a serious adverse event. There have been identified 12 cases of hyper-inflammatory syndrome following COVID-19 mRNA vaccines (now MIS-V) in 12-17-year-old children in France, with multisystemic involvement [187], and two pediatric cases with neurological involvement in Italy [186]. Two other cases have recently been described and both children presented with MIS-V within 4 and 5 weeks of receiving their first and only dose of Pfizer/BioNTech's SARS-CoV-2 vaccine [188]. There are other MIS-V case reports and case series.

It follows that the cases of hyperinflammatory syndromes triggered by the injection of the COVID-19 mRNA vaccines must now be indicated by the acronym MIS-V.

10. Discussion

The injection of COVID-19 mRNA vaccines results in a strong expression and secretion of pro-inflammatory cytokines associated with a wide and variable cellular activation, both immune and vascular. In relation to the degree of inflammation produced by each subject, depending on its genetic status and the acquired condition of epigenetic modification of the innate immune system; systemic symptoms, heart disease and hyperinflammatory syndromes can be produced as AEs.

In table 2, some effects determined by the injection of COVID-19 mRNA vaccines are listed.

Potential effects after COVID-19 mRNA vaccination.	Ref.

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Endothelial dysfunctions produced by the Spike protein.	97
Actions of the Spike protein on the Angiotensin II / AT_1 axis.	127-138
Excessive Th1-type immune responses.	199
Persistence of the Spike protein in circulation for a prolonged period of time.	190
Prolonged immune and inflammatory response against the Spike protein.	189,190
Strong pro-inflammatory activity of LNPs.	141-148
Spike protein alone can easily reach the myocardium.	98,101
Spike protein was found in Cardiomyocytes (CMs).	101
Different levels of expression of pro-inflammatory cytokines over time.	189,198
Circulating CoV-2-S1 is a TLR4-recognizable alarmin that may harm the CMs by triggering their innate immune responses.	98
TLR4 initiates the expression of several pro-inflammatory genes, cell surface molecules, and chemokines through the MyD88-dependent pathway, which exacerbates the damage to myocardium.	99
Activation of TLR4 and the TLR4 / NFκB axis in cardiomyocytes by the Spike protein.	11
Unmitigated TLR4 activation may lead to increased risk for cardiac inflammation.	100
CoV-2-S1 activates TLR4 signaling to induce pro-inflammatory responses in murine and human macrophages.	102
Diffuse myocardial macrophages infiltration in the patient biopsy sample, suggest an increased level of IL-18 produced by monocytes and macrophages in the heart with COVID-19 vaccine-related myo-pericarditis.	76
In an inflammatory microenvironment, caspase-1 is regulated by NF-κB, and this enzyme facilitates the conversion of pro-IL-18 in IL-18.	77
Lymphocytic infiltration with predominant immunostaining for CD8 and CD68-positive cells (macrophages) is present in myocarditis following COVID-19 mRNA vaccines.	79
Vaccinated mice showed signs of myocarditis 2 days after injection of the second dose of BNT162b2 vaccine.	75
Free spike antigen was detected in the blood of adolescents and young adults who developed post-mRNA vaccine myocarditis.	235

Table 2. Summary of some effects determined by the injection of COVID-19 mRNA vaccines.

Different levels of expression of pro-inflammatory cytokines over time, after COVID-19 mRNA vaccination [189], the persistence of the Spike protein in circulation for a prolonged period of time [190], the prolonged immune and inflammatory response against the Spike protein [189,190], the strong pro-inflammatory activity of LNP [141-148], the actions of the Spike protein on the Angiotensin II / AT_1 axis [127-138], the activation

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of TLR4 and the TLR4 / NFκB axis in cardiomyocytes by the Spike protein [11], the endothelial dysfunctions produced by the Spike protein [97], all together represent a series of subsets that can contribute with variable expression, especially to the pathogenesis of myocarditis and multisystem syndromes.

Biochemical studies revealed that Spike protein triggers inflammation via activation of the NF-κB pathway and induction of proinflammatory cytokines, such as IL-6, TNF-α, and IL-1β [189]. Furthermore, the expression of cytokines and chemokines, in response to Spike protein, was dose dependent and this agrees with the different timeline of myo-pericarditis following COVID-19 mRNA vaccines (onset after second dose of Pfizer vaccine or at first and second dose of Moderna vaccine). After the first dose of BNT162b2 vaccine, the human organism produces systemic inflammation which is accompanied by upregulation of TNF-α and IL-6 after the second dose [191].

Furthermore, the S1 subunit of the Spike protein produces an endothelial lesion that is amplified by simultaneous exposure to the inflammatory cytokine TNF-α and the male hormone dihydrotestosterone [192]. This condition of endothelial lesion, amplified by simultaneous exposure to TNF-α and androgens, may allow us to resolve some controversies. There is growing evidence that suggests that males have a higher risk of outcomes in case of myocarditis [193], despite the fact that they are able to suppress the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and increasing the production of anti-inflammatory cytokines [194]. Since the effects of testosterone may be different under normal physiological conditions and in pathological states [195], in the presence of an endothelial lesion and/or myocarditis these effects may be different from the physiological conditions. Indeed, generally, androgens have been found to increase Th1 responses [196] and, in acute myocarditis, testosterone promotes the pro-inflammatory Th1 and/or Th17-type immune response [197] and increases the activity of the inflammasome and TLR4 signaling pathways [198].

This synergy of effects could explain why myo-pericarditis is more frequent in males; while the concomitant proinflammatory action of stress and its ability to induce endothelial dysfunction could explain why young males are more affected by myo-pericarditis.

Exosomes with Spike protein, Abs to SARS-CoV-2 Spike, and T cells secreting IFN-γ and TNF-α increased following the booster dose [190]. Miyashita and colleagues [189] investigated the correlation between proinflammatory cytokine levels in sera and AEs after COVID-19 vaccination, and they found that systemic TNF-α levels were connected with the systemic scores after the second dose. This observation also supports the notion that proinflammatory cytokines are a cause of AEs after vaccination [199-202]. Furthermore, Miyashita and colleagues [189], in the same study, measured serum proinflammatory cytokine levels after vaccination. IL-6 levels one day after the first dose were elevated compared with the levels before vaccination, and the levels were further elevated after the second dose. Serum TNF-α levels did not increase after the first dose but increased significantly after the second dose. It follows that after the second dose of vaccine there are markedly increased concentrations of IL-6 and TNF-α, in the serum,

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already only after the first day following the second vaccine dose. Finally, there would be a significant linear correlation ($p < 0.05$) between the level of proinflammatory cytokine TNF-α and the degree of symptoms (Systemic Scores) occurring one day after the second dose of BNT162b2 vaccine. For these authors, these data suggest that proinflammatory cytokines (IL-6 and TNF-α) were produced in response to BNT162b2 vaccination, especially after the second dose. Murata and colleagues [203] published a study reporting that four subjects died after receiving a second dose of COVID-19 vaccine, with no obvious cause identified at autopsy. RNA sequencing revealed that genes involved in neutrophil degranulation and cytokine signaling were upregulated in these cases, suggesting that immune dysregulation occurred after vaccination.

Flego and colleagues [204] demonstrated that administration of the mRNA-based vaccine BNT162b2 determines, in some subjects, a rapid increase in the systemic concentration of a series of proinflammatory cytokines (including IL-1β, TNF-α and IL-18) within 3- 10 days after the first injection and 10 days after the second dose. Thus, one month after the first dose we have a second wave of pro-inflammatory cytokines expression which coincides with the timeline of the onset of myo-pericarditis. The result of the increase in the serum concentration of IL-18 is relevant, since myo-pericarditis following COVID-19 mRNA vaccination may be associated with increased IL-18-mediated immune responses and cardiotoxicity [76].

Furthermore, anyway, COVID-19 vaccines were associated with rhythm disorders (inflammatory cardiac channelopathies) [205], and vaccination fear, as an acute stress situation, could lead to atrial arrhythmias [206]. Lazzerini and Colleagues [26-29,38] have studied inflammatory cardiac channelopathies in the past and the role of pro-inflammatory cytokines in producing arrhythmias is now well established. Esposito and colleagues [207] believe that among the main mechanisms associated with the development of myocarditis after vaccination with COVID-19 mRNA vaccines, these elements could be considered: activation of natural killer lymphocytes and macrophages and a massive release of cytokines leading to massive damage to the heart tissue.

Acute myocarditis is an inflammatory myocardial disease, which can be complicated by adverse cardiac events, including sudden cardiac death and heart failure [208].

From a series of epidemiological studies [60-62,66-69] it emerges that there is an evident excess of myo-pericarditis in all ages, especially in young people who have been vaccinated with COVID-19 mRNA vaccines, compared to the pre-vaccination period. Oster and colleagues [209] studied 1626 cases of myocarditis reported in a national passive reporting system. The rates of myocarditis cases were highest after the second vaccination dose in males aged 12 to 24 years with the highest incidence in the age group 16-17 years (105.9 per million doses of the BNT162b2 vaccine). In Israel, 136 cases of definite or probable myocarditis were recorded that had occurred in temporal proximity to the receipt of two doses of the BNT162b2 mRNA vaccine, a risk that was more than twice that among unvaccinated persons. This association was highest in young male recipients within the first week after the second dose. Approximately 1 case in every 6637

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male recipients occurred over the age range 16-19 years [210]. Buchan and colleagues [211] found that vaccine products and interdose intervals, in addition to age and sex, may be associated with the risk of myocarditis or pericarditis after receipt of these vaccines. Vaccine effectiveness may be higher with an interdose interval for mRNA vaccinations of 6 to 8 weeks compared with the 3- to 4-week interval [212]. It follows that the intervals adopted between the first and second dose, on the one hand, reduce the effectiveness of the vaccine; while on the other hand they increase the risk of myo-pericarditis, respect to greater intervals between the two doses.

Hence, the number of myo-pericarditis is important and undiagnosed cases could be numerically more important and clinically insidious, since an increase in extracellular matrix deposition could lead to electrical destabilization of the heart [213].

Husby and Kober [69] argue that the disease mechanism of myo-pericarditis is specific neither to the newly developed mRNA vaccines nor to exposure to the SARS-CoV-2 spike protein. However, we have found a number of elements that do not move in the same direction indicated by Husby and Kober [69]. Furthermore, it does not appear from the published statistics that there are such an important number of cases of myo-pericarditis after the injection of a traditional vaccine [214,215]. Myocarditis associated with COVID-19 mRNA vaccines in adult males occurs with significantly higher incidence than in the background population. [216]. The incidence of myo-pericarditis following COVID-19 mRNA vaccines varies from case to case, starting from the lowest data of Das and colleagues [217], which is 0.32 / 100,000, to arrive at the highest data of Nygaard and colleagues [218], which is equal to 5.74 / 100,000.

In a series of report cases of myocarditis following COVID-19 mRNA vaccination [64,78-80], studied with EMB, there is a mixed inflammatory infiltrate in which CD3 T lymphocytes and macrophages CD68 are always present. While $CD4^+$ and $CD8^+$ cell infiltration prevails in typical inflammatory myocarditis, $CD68^+$ cell infiltration is prevalent in SARS-CoV-2 induced myocarditis [219]. The activation of T lymphocytes and macrophages is believed to play a fundamental role in myocardial inflammation [81].

Established that the activation of the innate immune system follows the injection of COVID-19 mRNA vaccines and that the migration of T lymphocytes and macrophages is a real fact in myocarditis; we will now examine the fundamental role of the Spike protein in modifying certain cell physiology events. After injection of COVID-19 mRNA vaccines, the Spike protein is expressed in DCs at the level of the axillary lymph nodes ipsilateral to the injection site (deltoid muscle) [120]. These DCs produce exosomes that circulate in the blood for a long time [190]. Spike protein induces ECs dysfunction. Spike protein of SARS-CoV-2 alone activates ECs inflammatory phenotype and induced the nuclear translocation of NF-κB and subsequent expression of leukocyte adhesion molecules (VCAM-1 and ICAM-1), coagulation factors, proinflammatory cytokines (TNF-α, IL-1β, and IL-6), and ACE2 [97]. CoV-2-S1 interacts with the extracellular leucine rich repeats-containing domain of TLR4 and activates NF-κB [98]. TLR4 initiates the expression of a number of pro-inflammatory genes, cell surface molecules, and

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chemokines through the MyD88-dependent pathway, which exacerbates the damage to myocardium [99]. The circulating CoV-2-S1 is a TLR4-recognizable alarmin that may harm the CMs by triggering their innate immune responses [98]. In CMs there is an axis TLR4 / NF-κB, and unmitigated TLR4 activation may lead to increased risk for cardiac inflammation [100]. Thus, the TLR4 / NF-kB axis in CMs can also cause cardiac inflammation and myocardial damage, and the Spike protein alone is capable of activating this axis in CMs. We have already indicated four different pathways that allow the Spike protein to reach the myocardium.

In summary, the Spike protein is not a mere spectator but the main protagonist in myocarditis. In fact, it causes endothelial dysfunction [97], and activates TLR4 and the TLR4 / NFκB axis in CMs with often unhealthy consequences [98-100]. The concreteness of all these scientific works has been validated by clinical practice. Indeed, Baumeier and colleagues [101] studied 15 cases of myocarditis after COVID-19 mRNA vaccine using EMB and immunohistochemical analysis. In 9 of these patients the Spike protein was found in CMs.

Finally, vaccinated mice showed signs of myocarditis 2 days after injection of the second dose of BNT162b2 vaccine [75].

We are now confident that Spike-specific activated T lymphocytes, macrophages and Spike protein can reach the myocardium after vaccination, but the "Immune Black Hole" prevents us from knowing any interactive modalities between these, and possibly other, cellular components.

Since the natural history of myocarditis does not end after the immediate period following diagnosis, but it can also evolve silently creating the preliminary conditions that could lead to dangerous arrhythmias and sudden death; we would like to bring you some important elements.

If we use CRM images we can monitor the LGE pattern over time. In the acute phase, CMR allows to verify if there is inflammation / edema, increased interstitial space, and LGE [220]. LGE on CMR imaging signifies myocardial fibrosis or scar [221]. LGE presence is a strong risk marker in patients with suspected myocarditis [222], and LGE-assessed myocardial fibrosis has been shown to be a predictor for outcome in same patients [223]. Georgiopoulos and colleagues [208] conducted a meta-analysis and demonstrates that the presence and location of LGE may identify a subgroup of patients with acute myocarditis who warrant more intensive clinical surveillance for adverse cardiac events. Indeed, anteroseptal location but not LGE extent was also associated with the clinical outcome. Finally, LGE in basal and mid lateral segments have a better prognosis than cases with LGE localized to the septal segments [208,224,225]. Indeed in milder cases of myocarditis, the subepicardial layer, especially in the posterolateral wall, presents LGE; while in the most severe cases LGE can be more diffuse and circumferential [224,225]. LGE is present in many cases of myocarditis following COVID-19 mRNA vaccine [226-228] and is likely a robust prognostic marker in children and adults with myocarditis [208].

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Among the patients studied by Kracalik et collegues [229], a subgroup of 151 patients were investigated with MRI and over 50% presented abnormal results (LGE and / or edema), after 90 days from the onset of myocarditis. Additionally, two patients with LGE also had atrial or ventricular arrhythmias. Although there are few cases of arrhythmia associated with the LGE phenomenon, this data reinforces our concern as it demonstrates that scarring can be arrhythmogenic. Furthermore, LGE is a strong and independent predictor of cardiac mortality in patients with myocarditis [222]. It must always be remembered that in clinical practice there can be complete healing with restitutio ad integrum (complete restoration of the initial conditions) and healing with scarring results and the two types are not superimposable.

Finally, myocarditis can be a potentially lethal complication following mRNA-COVID-19 vaccination [230], but inflammatory infiltration of the myocardium may be different in autopsy examinations (predominantly composed of lymphocytes CD4), than data provided by the EMB (predominantly composed of macrophage $CD68^{+}$).

Multisystem Inflammatory Syndrome in children (MIS-C) and adult (MIS-A) are late complication of SARS-CoV-2 infection [181-185]. MIS following COVID-19 mRNA vaccines (MIS-V) it is a serious adverse event and there are many pediatric case reports that begin 4-6 weeks after the first vaccine dose [186-188].

We always remember that each vaccination determines a strong production and secretion of proinflammatory cytokines [24,25]. What happens next also depends on how strong this proinflammatory response was. Unfortunately, in many cases of MIS-V the markers of inflammation used are few and often include only C-reactive protein, ferritin and procalcitonin [231]. We have not been able to find MIS-V studies that test the three main pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), although we did find a case report in which serum IL-6 values were of 566.0 pg / mL [232], while an IL-6 concentration higher 37.65 pg / mL was predictive of in-hospital death, in patients with SARS-CoV-2 infection [233]. In 16 cases of MIS-C, levels of 14 of 37 cytokines / chemokines (including IL-6, IL-18 and TNF-α), were significantly higher in children with MIS-C compared to those without, irrespective of age or sex [234].

Conclusion

We think that a series of post-vaccination adverse events (early systemic reactions, arrhythmias, myo-pericarditis and multisystem syndromes) can be integrated into a new paradigm that we have called “Inflammatory Pyramidis (IP)”, following COVID-19 mRNA Vaccines (Figure 1). The different degrees of IP, express the levels of inflammation determined by vaccination which persist over time due to a prolonged antigenic stimulation by the Spike protein that determines a prolonged and differentiated production of cytokines associated with an immune and non-immune cellular activity that now we will describe in detail.

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In our hypothesized IP, the level of pro-inflammatory cytokine production and secretion underlies the correlation between the time elapsed since the injection of the vaccine and the progressive level of inflammation, which starts from the base (low-grade inflammation), where we find the common systemic reactions to the injection, to its apex where MIS (high-grade inflammation) are located. The progression of the degree of inflammation over time, starting from the date of injection of the first vaccine dose, is related to the severity of the disease, as MIS begin one month after the initial stimulus (infection or vaccination). In this IP, we compared the times of clinical onset of the syndromes with the theoretical level of production and secretion of pro-inflammatory cytokines. For this reason we believe that systemic reactions are the result of the production of pro-inflammatory cytokines which are also capable of triggering inflammatory channelophaties even at a low-grade of inflammation.

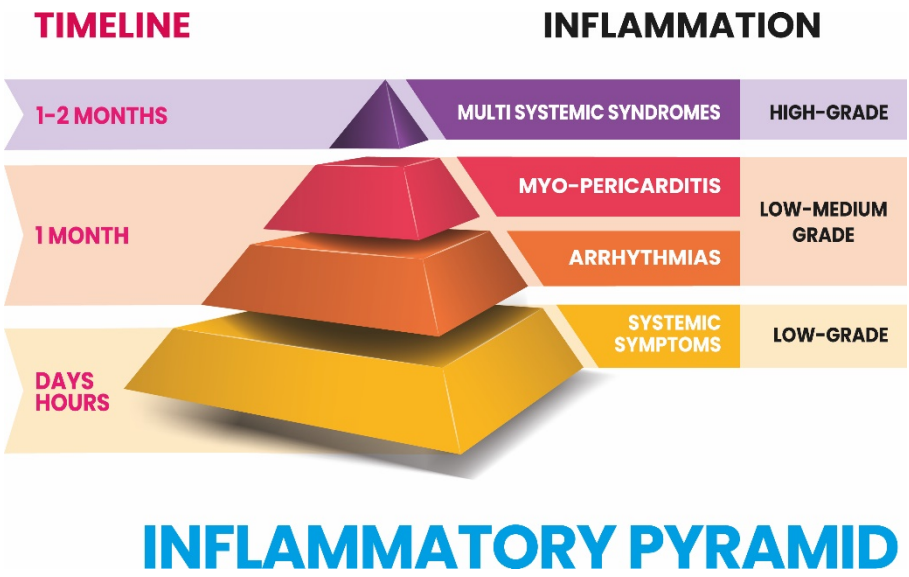

Figure 1. Inflammatory Pyramid (IP) following COVID-19 mRNA Vaccines. In our hypothesis, we correlated the timeline of COVID-19 mRNA vaccines adverse events to the degree of inflammation that can occur after their injection. On the left side, we have diversified the time of onset of adverse events, based on the scientific literature presented here. On the right side, we stratified the degree of inflammation into three progressive levels starting from the base of the IP to reach its apex: low-grade, low-medium grade and high grade of inflammation. The levels of the pyramid are occupied by adverse events, which start from the base and lead to the apex with this increasing degree of clinical complexity: systemic symptoms, heart disease, hyperinflammatory multisystemic syndromes (MIS). The timeline correlates with the degree of inflammation and both relate to the different severity of the clinical manifestations temporally associated with the first injection of COVID-19 mRNA vaccines.

Conversely, we believe that cytokines production alone is not sufficient to generate myo-pericarditis without the participation of an immune and non-immune cell population. At this level, pro-inflammatory cytokines and immune cells collaborate since

the former prepare the cellular infiltration of the myocardium by the latter. All this manifests itself clinically after about a month from the initial event.

Finally, MIS are characterized by a hyperinflammatory condition involving various organs and systems and begin clinically 4-6 weeks after the initial event (infection or vaccination). It would seem that with the passage of time the continuous immune stimulation due to the vaccine Spike protein, which remains circulating even in the exosomes, is able to evoke increasing degrees of inflammation which in hyperinflammatory syndromes do not seem to need a second hit; while the second shot seems to be decisive in the case of myo-pericarditis which begins essentially a few days after the second dose of the vaccine (about one month after the first dose).

Finally, we have attributed the cause to the systemic symptoms (pro-inflammatory cytokines), the cause to arrhythmias (pro-inflammatory cytokines), the presumed cause and concomitant causes to myo-pericarditis (pro-inflammatory cytokines and immune cells); while to the various forms of MIS we must attribute cause and contributing cause. All this growing clinical complexity takes time to complete its progression, as represented in our hypothesis of IP.

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Abbreviations

ACE	Angiotensin-Converting Enzyme
ACE2	Angiotensin-Converting Enzyme 2
AEs	Adverse Events
ANS	Autonomic Nervous System
AP	Action Potential
AT_1R axis	Angiotensin II/ AT_1R axis
AT_2R axis	Angiotensin II /AT_2R axis

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CECs	Cardiac Endothelial Cells
CD	Cluster of Differentiation Molecules
CFs	Cardiac Fibroblasts
CMR	Cardiac Magnetic Resonance
CMs	Cardiomyocytes
CoV-2-S1	S1 Subunit of CoV-2 Spike Protein
DCs	Dendritic Cells
ECM	Extracellular Matrix
ECs	Endothelial cells
EMB	Endomyocardial Biopsy
HPA axis	Hypothalamic–Pituitary–Adrenal axis
ICAM-1	Intercellular Adhesion Molecule 1
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IP	Inflammatory Pyramid
LGE	Late Gadolinium Enhancement
LNPs	Lipid Nanoparticles
LQT1	Long QT syndrome type 1
MIS-A	Multisystem-Inflammatory-Syndrome in adult
MIS-C	Multisystem-Inflammatory-Syndrome in children
MIS-V	Multisystem-Inflammatory-Syndrome following COVID-19 mRNA vaccines
MHC	Major Histocompatibility Complex
MSCs	Mesenchymal Stem Cells
NF-κB	Nuclear Factor- κB
RAAS	Renin – Angiotensin – Aldosterone System
SAM axis	Sympathetic-Adreno-Medullar axis
SRS	Stress Response System
TLR4	Toll-Like Receptor 4
TNF-α	Tumor Necrosis Factor-α
VCAM-1	Vascular Cell Adhesion Protein 1

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