

Acute myocardial infarction induced by influenza virus

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Abstract: Influenza virus which belongs to the Orthomyxoviridae family, is responsible for spreading infection in specific weather conditions which can lead to serious health complications and fatality. Typically, it starts out with mild respiratory symptoms and escalates to deadly pulmonary and extrapulmonary complications. Individuals who are extremely young or very old and those who have a coexisting medical condition have usually been the patients who have related complications. Cardiovascular symptoms such as myocarditis and pericarditis, neurological consequences such as meningitis and encephalitis, renal failure, and others are examples of serious extra-pulmonary effects. One of most prevalent cardiovascular complication of influenza infection is Acute myocardial infarction (AMI), enhances the diseases severity and death rate. There was a strong link between population levels of influenza and Acute MI hospitalizations and deaths in both temperate and subtropical climates after adjusting for seasonality and environmental factors. In temperate regions, influenza epidemics occur each winter and are consistent with increased cardiovascular mortality. Although heart problems spurred on by influenza may be prevented by vaccination, it is crucial to verify that influenza can cause acute myocardial infarction. An improvement in approach which would increase the existing insufficient vaccination coverage within the individuals who are at increased risk for acute myocardial infarction could result from more proof that influenza causes heart related complications. The prothrombotic mechanisms that result in coronary artery obstruction, the production of inflammatory cytokines, and the bursting of atherosclerotic plaque constitute the basis for the pathophysiological explanation. Our review focuses primarily on the pathogenetic mechanisms underlying the link between influenza and AMI, as well as the preventative role of influenza vaccination.

Index Terms: Influenza, Myocardial infarction (MI), vaccination, cardiovascular diseases, atherosclerosis

I. INTRODUCTION

Influenza is a seasonal viral infection that causes severe morbidity and mortality. It usually begins with moderate respiratory symptoms and progresses to severe pulmonary and extra-pulmonary problems, as well as death [1]. Complications have always been limited to patients at the extremes of age (6 months or >65 years) and those with the concomitant medical disease. In the United States, influenza is projected to cause 36,000 deaths and more than 200,000 hospitalizations each year, the majority of which are due to secondary pulmonary and extrapulmonary complications [2] [3]. Cardiovascular symptoms such as myocarditis and pericarditis, neurological consequences such as meningitis and encephalitis, renal failure, and others are examples of serious extra-pulmonary effects. One of most prevalent cardiovascular complication of influenza infection is Acute myocardial infarction (AMI), enhances the diseases severity and death rate. The epidemiological link between acute myocardial infarction (AMI) and flu syndrome was discovered in 1930 when increased mortality from cardiovascular causes coincided with the epidemic influenza peak. To date, during influenza epidemics, there is an increased rate of hospitalization and death from cardio- and cerebrovascular diseases, especially for AMI [4]. There was a strong link between population levels of influenza and Acute MI hospitalizations and deaths in both temperate and subtropical climates after adjusting for seasonality and environmental factors. In temperate regions, influenza epidemics occur each winter and are consistent with increased cardiovascular mortality. There is corresponding ecological evidence that cardiovascular mortality is associated with the circulation of the influenza virus; these associations were reproducible and biologically plausible in studies of different designs. Furthermore, the incidence of AMI decreases linearly with the development of respiratory infections [5]. Although heart problems spurred on by influenza may be prevented by vaccination, it is crucial to verify that influenza can cause acute myocardial infarction. An improvement in approach which would increase the existing insufficient vaccination coverage within the individuals who are at increased risk for acute myocardial infarction could result from more proof that influenza causes heart related complications. Peretz et al. identified a link between influenza infection and acute myocardial infarction (AMI). During the 7 days following laboratory confirmation of influenza infection, the rate of hospitalisation due to AMI was six times higher than during the control interval (10-fold in influenza B, 5-fold in influenza A, 3.5-fold in respiratory syncytial virus, and 2.7-fold for all other viruses) [6]. The prothrombotic mechanisms that result in coronary artery obstruction, the production of inflammatory cytokines, and the bursting of atherosclerotic plaque constitute the basis for the pathophysiological explanation. Our review focuses primarily on the pathogenetic mechanisms underlying the link between influenza and AMI, as well as the preventative role of influenza vaccination.

II. PATHOPHYSIOLOGY

The physio pathologic characteristics of MI vary widely. Type 1 myocardial infarction results from thrombosis brought on by plaque rupture or ulceration. On the other hand, type 2 myocardial infarction occurs due to myocardial necrosis brought on by an imbalance between oxygen supply and demand [7]. Influenza, by direct or indirect effects on atherosclerotic plaques, may be linked to both forms of MI.

Viral attachment to host cells triggers a cascade of innate immune responses, including the production of type I and type III IFNs, as well as pro-inflammatory cytokines (IL-1, IL-6, and TNF) and chemokines (CCL2, CCL4, and CCL5). This systemic inflammatory response appears to have a direct inflammatory effect on atherosclerotic plaque and coronary arteries. A study by Mehran et al. revealed the presence of influenza virus antigens in the aorta using PCR and immunohistochemistry [8].

The influenza illness can encourage the onset of a prothrombotic state by promoting platelet aggregation and vascular dysfunction as a consequence of the release of cytokine production. Increased expression of adhesion molecules promotes leukocyte binding in vascular endothelial dysfunction. Influenza virus infection has been demonstrated to enhance the expression of chemokines CCL2, CCL5, and IL-8, as well as the adhesion molecules ICAM1, VCAM-1, and E-selectin in human coronary endothelial cells (HCEC), and CXCL10 and CXCL9 in HUVEC cells [8] [9]. A study showed that viral particles, like live viruses, upregulate the production of chemokine genes [10]. These findings imply that both the whole virus and viral particles boost antiviral and inflammatory mediators, potentially worsening atherosclerosis.

The accumulation of oxidised LDL (OX-LDL) in the subendothelial region, which is a key factor in the development of atherosclerosis, was found to be synergistically amplified in influenza. This promotes the expression of pro-inflammatory, adhesion, and chemokine molecules. Macrophages boost scavenger receptor expression, ingest ox-LDL, and transform into foam cells [11] [12] [13]. Foam cells eventually die or become necrotic, which causes cell debris to build up and the intima to develop a necrotic core. The fibrous cap that surrounds the necrotic core is then created by smooth muscle cells by means of the synthesis of collagen and elastin. If the fibrous cap is weak, it could rupture and result in MI and other forms of coronary artery disease.

The virus's induction of systemic inflammatory mediators and cell trafficking is expected to have an indirect influence on atherosclerosis. Infection with the influenza virus produces interferons and a number of inflammatory cytokines both systemically and locally [14] [15]. According to research, type I IFNs increase atherosclerotic plaques by activating chemotactic factors, which result in macrophage accumulation and smooth muscle cell proliferation [16]. IFN- γ stimulates MMP synthesis in macrophages and vascular smooth muscle cells, promoting plaque rupture [17].

In addition to interferons, influenza virus infection causes the release of several inflammatory cytokines and chemokines. Pro-inflammatory cytokines (IL-1, IL-6, and TNF) have been demonstrated to increase vascular endothelial adhesion and chemokine production, hence promoting atherosclerosis [18].

Endothelial dysfunction in atherosclerosis increases adhesion molecules, causing monocytes to move into the sub-endothelial compartment and develop into macrophages. Furthermore, macrophages enhance the expression of scavenger receptors and engulf ox-LDL to form foam cells. IFN- γ and LPS promote macrophage differentiation into M1 macrophages, which promotes the advancement of atherosclerotic lesions [19].

T cells are also important in the progression of atherosclerosis. T cells differentiate into inflammatory effector T (Teff) cells or anti-inflammatory regulatory T (Treg) cells in response to antigen-specific responses. One study found influenza-specific proliferative responses in T cells isolated from atherosclerotic plaques in patients having endarterectomies, implying that influenza viral antigens may promote T cell activation and eventual atherosclerosis exacerbation.

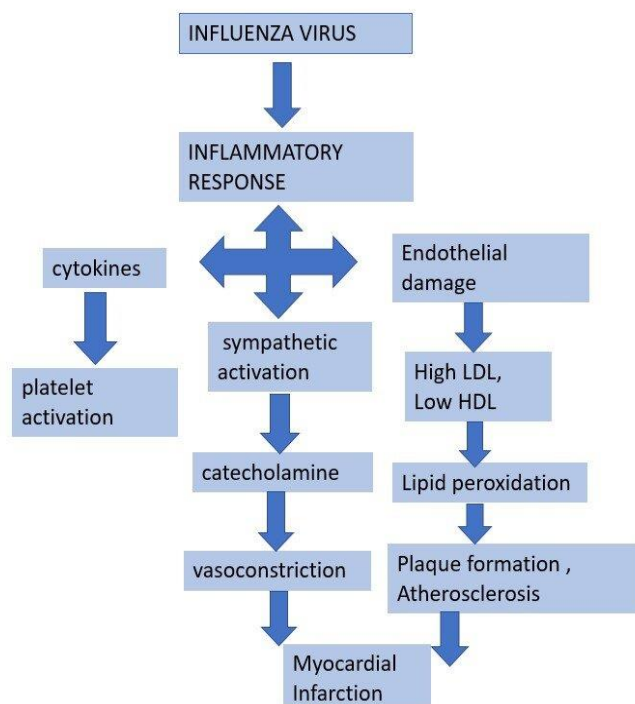


Figure 1 - Inflammatory response triggered by influenza virus leading to myocardial infarction.

III. ROLE OF INFLUENZA VACCINE

Influenza vaccination can prevent the potential threat of MI induced by the influenza infection, At the molecular level vaccine-induced antibodies interacts with human bradykinin receptors, this interaction could lead to increased levels of nitric oxide, which increases the efficiency of myocardial oxygen use, as well as leading to increased blood flow through vasodilation and possible angiogenesis [20], Using the informational spectrum method (ISM), a virtual spectroscopy method for analysis of protein-protein interactions, the bradykinin 2 receptor (BKB2R) was identified as a principal host protein which could mediate the mechanisms via which influenza vaccinations exhibit cardioprotective effects [21]. A study found that influenza vaccination within 72 hours of admission for acute myocardial infarction MI resulted in reduced rates of cardio-vascular mortality and a composite of all-cause mortality [22].

In contrast, some studies reported that the patients who have administered influenza vaccination trigger the cardiovascular events as the body shows inflammatory response against influenza vaccine which can articulate the incidence of releasing of certain amount of fever causing cytokines which can cause endothelial damage in vessels, cause increased amount of Low density lipoprotein (LDL) and decreased amount of High density lipoprotein (HDL), plaque and finally leading to atherosclerosis which can enable myocardial infarction.

Though Influenza vaccines should be considered as an integral part of preventing and managing the cardiovascular complications caused by influenza infection but it still does pose a slight risk of initiating the MI by the vaccination itself [23].

IV. CONCLUSION

Influenza is seasonal viral infection which can lead to serious cardiac complications like myocardial infarction. Inflammatory response triggered by the influenza virus can cause lipid peroxidation leading to plaque formation and atherosclerosis where rupturing of the atherosclerotic plaque and activation of prothrombotic processes lead to coronary artery blockage which eventually results in myocardial infarction. Role of influenza vaccination can play a major role in preventing and managing myocardial infarction induced by influenza virus as the vaccine induced antibodies of influenza vaccine interacts with human bradykinin receptors which results in increased level of nitric oxides leading to vasodilation and angiogenesis which enhances the efficiency of myocardial oxygen use, However, in some rare cases influenza vaccinations are also found to cause the myocardial infarction in the similar pathway which initiates with the inflammatory response.

Conflicts of Interest

AUTHORS HAVE NO CONFLICT OF INTEREST.

List of abbreviations

Abbreviation	Full form
AMI	acute myocardial infarction
LDL	low density lipoprotein
HDL	high density lipoproteins
IFN	interferon
LPS	lipopolysaccharides
ISM	information spectrum method
BKB2R	bradykinin 2 receptor
IL	interleukin
CCL	chemokines
TNF	tumor necrosis factor
ICAM	intercellular adhesion molecule
VCAM	vascular cell adhesion molecule
HCEC	human coronary endothelial cells
HUVEC	human umbilical vein endothelial cells

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