ACUTE INFECTIONS AND ACUTE MYOCARDIAL INFARCTION

İSMAİL BIYIK,
OKTAY ERGENE*

From:
Department of Cardiology,
Uşak State Hospital,
*Department of Cardiology
Atatürk Educational Hospital,

Heart diseases, especially coronary artery disease and myocardial infarction (AMI), are among the leading reasons of morbidity and mortality in industrialised countries. During the past decades several clinical or life style risk factors such as hyperlipidemia, hypertension, diabetes mellitus, obesity, smoking and lack of physical exercise have been accused of AMI and other forms of coronary artery disease. However, there are growing interest in the role of acute infections in the etiology of acute myocardial infarction (AMI) and increasing evidence for a causal association between exposure to infective agents and increased risk for developing acute coronary events. Hence, in this review, we aimed to look over this interesting association between acute infections and AMI under the light of recent studies.

Key words: acute infection, acute myocardial infarction, vaccination

Acute myocardial infarction (AMI) is a life threatening event commonly arising from rupture of an atheromatous plaque with subsequent aggregation of platelets and the development of endoluminal occlusive thrombus. In the studies that were carried out during the last decade, different pathophysiological properties such as the presence of thin fibrous cup, the high lipid content, the accumulation of macrophages, the low content of smooth muscle fibers and sudden intense emotional stress have been accused of this rupture as predisposing factors (1, 2). There has been growing interest in the associations between infections and process of atherosclerosis. Although their importance is not as clear as that of previously well known conventional risk factors, infectious diseases have been suggested to be associated with the incidence and the pathogenesis of coronary artery disease (3, 4). Some infections especially those caused by Chlamydia pneumonia and Helicobacter pylori may play role in the pathogenesis and the progression of atherosclerosis and therefore behave as long term chronic risk factors for coronary artery disease and AMI (5, 6, 7)

Address for reprints:
İsmail BIYIK
İsmetpaşa caddesi 75/1 posta kodu: 64100 Uşak/ TÜRKİYE(TURKEY)
Tel.:+90 276 2234519 / 2279117
Mobile Phone:+90 542 4173209
e-mail:ismailbiyikmd@yahoo.com

CLINICAL AND EPIDEMIOLOGICAL ASSOCIATIONS

Previous epidemiological studies have suggested an association between infection, inflammation and the risk of cardiovascular diseases (8, 9, 10). Death arising from cardiovascular illnesses, especially AMI, is greater during winter than in summer (11, 12). Although many factors such as changes in temperature, hours of daylight and diet could contribute to this association, the growing number of respiratory tract infections in winter may be a possible risk factor. Acute infections might cause a transient additional increase of acute coronary events. Deaths from cardiovascular disease are higher during and after influenza epidemics both among weak elderly people and among healthy middle-aged subjects (13).

Table 1: Biphasic response of endothelium to inflammation(19)

A: Healthy endothelium produces anticlotting, antiaggregatory, antiadhesive and vasodilatator mediators (e.g., prostaglandin I2, nitric oxide)
B: In infective or inflammatory states de novo synthesis of inducible nitric oxide synthase and cyclooxygenase II occurs. Down regulation of physiological endothelial cell nitric oxide synthase and cyclooxygenase I have been reported. The result is excessive vasodilatation and increased prostanoid production.
C: After recovery of the acute effect, the endothelium may remain dysfunctional (stunned) for a long time before fully recovering its ability to contribute towards homeostatic functions. This loss may result in predisposition towards vasospasm and thrombosis.

Previous case-control studies have showed that approximately 4% of bacteraemic patients might suffer from AMI within a month after the onset of infection (14). Also, after abdominal surgery which is frequently accompanied by transient bacteraemia or release of bacterial endotoxin into the circulation and a systemic inflammatory response with cytokine production, the high frequency of AMI continues for several weeks (15, 16). The results from the study of Meier and colleaques, which include 9571 patients, suggest that an acute respiratory tract infection is a risk factor for AMI (17). According to this study, the risk of AMI is three times higher among patients having an acute respiratory tract infection in the previous 10 days than those not. However, the high risk of AMI reduced with elapsed time between the acute respiratory tract infection and the acute coronary event, and returned to basal levels after approximately two weeks. In this study, there was no increase in the incidence of AMI associated with urinary tract infections.

A new large scale study of Smeeth and collagues provides support for the concept that acute infections are associated with a transient increase in the risk of vascular events like myocardial infarction and stroke. In this study, 20,486 patients having a first myocardial infarction and 19,063 patients having a first stroke have been selected for the analysis. According to this very large scale analysis, the incidence of both events were substantially higher after a systemic respiratory tract infection and were highest during the first three days and then decreased gradually during the following weeks and did not return completely to the normal level within three months after infection (18). The risks for both events were also increased significantly but to a lesser degree after an urinary tract infection. The results for recurrent myocardial infarctions and stroke revealed similar findings to those for first

events. In this study, however, vaccinations for influenza, tetanus, and pneumococcal infections did not cause a detectable increase in the risk of acute vascular events like AMI. These observations reveal that acute infections or acute systemic inflammations might temporarily increase the risk of acute coronary event.

PATHOPHYSIOLOGIC MECHANISMS

Possible pathophysiological mechanisms by which acute infections or acute inflammations might trigger an acute vascular event such as AMI have been extensively discussed in the literature(18,19,20). In the study of Smeeth and colleagues, the finding that two different infectious events in separate organ systems are associated with transient increase in the risk of cardiovascular events like AMI provides strong support to the idea that systemic infection or inflammation itself changes the likelihood of the occurrence of a cardiovascular event such as AMI (18). High levels of inflammatory markers, especially C-reactive protein, reveal an increased risk of coronary heart disease (21, 22, 23). Systemic inflammation related to acute infection elevates levels of C-reactive protein which have been shown to be predictor for AMI, and may alter endothelial function, and may cause atheroma instability and subsequent plaque rupture (20, 24). Pre-existing atherosclerotic plaques may become more able to facilitate thrombosis and vasospasm. This instability may not always be limited to one plaque but may exist at many points in different vascular systems, which also suggests that the underlying mechanisms might be systemic rather than local in origin (19). Thus, the change from stable to unstable coronary artery disease appears to be related to a systemic inflammatory response (25). Acute infections might be considered triggering an atheromatous coronary plaque rupture and contributing to the initiation of an acute coronary event (12). Acute inflammation markers such as C-reactive protein and cytokines shows increased cardiovascular risk (26, 27).

What are the mechanisms? Acute infection or inflammatory response changes and impairs normal endothelial function. After the acute vasodilatator period of the disease, the remaining inability of the endothelium to produce vasodilatator mediators such as nitric oxide and prostanoids could change the balance between vasodilatator and vasoconstrictor mediators released in favor of vasospasm and thrombosis, and this result may be of importance in the pathogenesis of AMI in this clinical setting (19). Infection of endothelial cells or exposure to certain proinflammatory cytokines causes to the release of tissue factor, cell-surface adhesion molecules and activation of procoagulant activity (26, 28). Continuously released nitric oxide produces a basal vasodilatator effect in the vascular beds, prevents adhesion and aggregation of platelets and adhesion of white cells to the vascular wall (29).

Bacterial endotoxin and some proinflammatory cytokines such as tumor necrosis factor-· may also prevent agonist-stimulated production of nitric oxide and some vasodilatator and antiaggregatory prostanoids by endothelial cells(30,31) Even in healthy subjects, a brief exposure to endotoxin or certain cytokines impairs endothelium-dependent vasodilatation for many days, and this impairment may be much higher than that generated by other chronic risk factors. This event has been named ''endothelial stunning'' (32). Coronary vasoconstriction is considered as an important factor in the pathogenesis of acute coronary event; cysteinyl leukotrienes (LTs) and thromboxane

(TX) A2, generated by leukocyte and platelet cooperation in acute infections and inflammations , are powerful vasoactive substances that are able to change coronary vascular tone. Indeed, these mediators may cause coronary vasoconstriction; which may be temporary and end rapidly in normal subjects but may last long enough to cause acute coronary event or AMI in atherosclerotic subjects (33). These data together provide support for the opinion that endothelial dysfunction developing rapidly after acute infection or inflammation might be a temporary risk factor for acute coronary events, and might trigger abnormal vascular behavior, coronary vasospasm and AMI. Furthermore, activation and aggregation of platelets may develop with high incidence in patients suffering from streptococcal infection(34). Acute infections also make changes in circulating clotting factors such as fibrinogen, which may cause an increased clotting tendency and therefore to an increased risk of coronary thrombosis and occlusion (11).

CONCLUSION

These effects related to acute infections could probably trigger an acute coronary event and also promote AMI in the setting of acute infections with other facilitating factors. Acute respiratory and urinary tract infections which are common in community are associated with an increased risk of AMI for a period of about two weeks even in people without a history of clinical risk factors for AMI (13, 17, 18). There is no increased risk of AMI after vaccinations against common pathogens such as influenza and pneomococcus (18). Thus, vaccinations against common pathogens like influenza may become important in the future to decrease the number of acute coronary events and AMI and to provide reduction of hospitalizations for cardiac diseases, especially among frail elderly people(35).

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