Pathogenesis of depression after myocardial infarction: rationale, state of the art and perspectives

Roriz Dias M.*, Koike MK.

Universidade Cidade de São Paulo – UNICID, Brazil

ABSTRACT

Relation between depression and myocardial infarction is known, but the mechanism that explains depression occurrence after myocardial infarction (AMI) is still unclear. The objective of this study was to review the literature to better understand the pathogenesis of post-myocardial infarction depression. Using a strategy similar to systematic review, we found experimental and clinical evidences. The post-myocardial infarction depression (PMID) has multiple causes such as psychological, biological dysfunctions or a combination of both. The inflammation of central nervous system and neurons destruction in specific regions of the brain resulted of AMI could be responsible to PMID, and it seems to be the main mechanism.
Key words: depression, myocardial infarction, etiology, rats, mood disorders

***Corresponding author:**
Maurílio Roriz Dias
Address: Rua Itacolomi nº523 apt 11A São Paulo – SP
Brasil – CEP 01239-020
Tel: 55 11 9 8742-7695
e-mail: mrorizdias@gmail.com

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INTRODUCTION

The depression is characterized by increased dissatisfaction with its performance and recurrent depressive episodes [1, 2], and it is considered an independent risk factor to cardiovascular disease, such as stroke [2] and coronary artery disease [3]. In patients with coronary artery disease, depression occurs in 10% to 40% of cases, and could be a predictor of mortality after acute myocardial infarction (AMI) [4, 5].

AMI is already recognized as a risk factor for major depression. One in each five hospitalized patients after AMI presents symptoms of major depression [5]. In addition, it was observed that mortality after AMI increases in patients who developed subsequent depression, called post-myocardial infarction depression (PMID) [6]. PMID goes often unrecognized as only 10% of these patients are diagnosed as such. This underestimation of depression is attributed to its atypical profile, tendency of physicians to interpret depressive symptoms as a transient and 'natural' reaction to a life-threatening event, and the scarce knowledge of risk factors associated with development of PMID [7].

Thus, the fact of depression frequently is associated to AMI is well known; however the pathogenesis that explain PMID occurrence is controversial. This study presents the literature reviewed to better understand the pathogenesis of post-myocardial infarction.

METHODS

Based on similar strategy of systematic review, we reviewed the literature using a combination of Medical Subject Headings descriptors. We used two, three or four words to perform the searching: myocardial infarction, depression, mood disorders, depressive Symptoms and rats. Full text articles were obtained in indexed databases of Academic Search Elite, MEDLINE, Library Information Science & Technology Abstracts and EBSCO. The inclusion criteria were the studies that had information about the pathogenesis of PMID – clinical or experimental, independently by year of publication. Other articles were excluded. Initially, 71 studies were found; then, 26 full text studies were selected and used to this review.

RESULTS

The psychosocial factors that predict the occurrence of PMID has been well studied. In a cohort study, 785 patients were observed to establish the possible predictors of depression 12 months after hospitalization due to cardiac causes and the natural history of depression. The authors identified characteristics associated with moderate to severe depression: depression during hospitalization, history of emotional health problems [self-reported depression, anxiety or stress) and current smoking [8]. Complication during hospitalization can be not just a biological risk factor, but a psychological risk factor if we consider it like a stressful life event [7].

Negative mood states, a mental state characterized by exhaustion, unusual fatigue, feeling of being defeated and increased irritability [9-11] and, have a type D personality, characterized by the tendency to suppress emotional distress [12], often occurred concomitantly in the presence of depression or preceding it [13].

Some studies showed the importance of psychological risk factors for poor outcome after acute myocardial infarction, such as: living alone [14], social isolation [15], patients exposed to a highly stressful life [15] and lack of emotional support [16].

Thus, patients without close friends were more susceptible to develop PMID [5] and symptom of exhaustion had the strongest relationship with PMID development compared to other risk factors [17]. Curiously, patients who have serious events in their private life in the two years preceding the AMI had more severe levels of depression [17]. It is unclear, if these factors are direct risk factors for poor prognosis after AMI or if they are risk factors for the development of PMID and than lead to a worse prognosis [7].

After AMI, patients take multiple trajectories of anxiety and depression according to gender. A study interviewed 226 women after AMI or undergoing coronary artery bypass surgery [18] at 4 times in a 12 month period. It was found that a small group started with different levels of anxiety and/or depression which worsened over time, being commonly found reports of extreme loneliness and not have English as their first language.

Therefore, how the patients coping to AMI event could influence their prognosis of PMID. Repetitively and/or passively thinking related to negative feelings and aspects and exacerbated terror experience are related to more intense depressive symptoms. Give a positive meaning to the event in terms of personal growth, thinking about joyful and pleasant issues instead of thinking about the negative experience and creating new meaningful goals in substitution of the last goals – impeded because of the disease – were associated with lower depressive symptoms [17, 19].

Biological aspects that predict PMID occurrence has been studied to understand the pathogenesis.

The etiological risk factors identified are:

a) Complications during hospitalization, such as arrhythmia event in a short period of hospitalization, recurrent infarction, dyspnea, and persistent angina pectoris preceding AMI [17];
b) Smoking and hypertension [20- 22];
c) Use of benzodiazepine [13, 22], warfarin [5];
d) Gender – be female [23].

The limbic system controls both mood and cardiovascular system and it can explain higher risk of heart attacks and worse prognosis in PMID patients [6]. On the other hand, myocardial necrosis and inflammation after AMI promote intense production of C-reactive protein by hepatocytes via pro-inflammatory cytokines. C-reactive protein is a well-known marker for risk of coronary events and in depression for this protein can predict the occurrence of coronary event in individuals initially considered normal [24].

In a prospective study with 176 patients with a definitive diagnosis of myocardial infarction, left ventricular dysfunction was associated with increased risk of PMID [25].

Experimental studies had shown that there is an increased vascular permeability in the prefrontal cortex and, more severely, in the anterior cingulate cortex after AMI. The similar response was observed after intravenous injections of tumor necrosis factor alpha (TNF-alpha) in the tail vein of rats. These findings indicate that depression after AMI evolves selective dysfunction of the prefrontal cortex and the anterior cingulate cortex in response to excessive inflammatory mediators releasing. Neuroimaging in patients with mood disorders has confirmed this hypothesis [26].

The hypothalamus shows a high level of aldosterone synthase. After AMI, the increased levels of aldosterone in the hypothalamus and hippocampus lead to increase in TNF-alpha releasing and, consequently, promote local inflammation. The rising in plasmatic TNF-alpha can be prevented by aldosterone antagonism, and its can improve the prognosis [27].

The *dentate gyrus*, *hippocampus* and the medial amygdale, specifically, have an important increase of TNF-alpha and caspase-8 after AMI in rats. TNF-alpha is a cytokine that activates the extrinsic pathway of apoptosis, via caspase-8. Kaloustian et al. [28], following inhibition of TNF-alpha observed attenuation of caspase-8 activity in the *dentate gyrus* and *hippocampus*. Thus, TNF-alpha is a possible causative factor of the apoptotic processes.

The experimental model of myocardial infarction has been nominated as one possible experimental model of major depression. The presence of depressive behavior in infarcted rats was associated with an increase of Bax and Bcl-2 expression, proteins used as an index of vulnerability for apoptosis within prefrontal cortex and hypothalamus compared to control animals [29]. In addition, serum dosage of S100B protein, a marker of cerebral damage as well as a marker of neuronal impairment, after AMI is related to appearance of depression symptoms [30].

DISCUSSION

It is known that stressful events act as psychic etiologies for major depressive disorder [3]. In our study, we found that many psychological factors are associated with AMI and could lead to PMID.

The patient psychological reaction after AMI could determine the development of PMID [19]. The patient with repetitive thinking about negative aspects of the AMI experience has worst prognosis than the ones with positive meaning about the event and joyful/pleasant thinking. In association, there are other risk factors contributing to a worst prognosis: living alone [13], social isolation [15], exposition to a highly stressful life [15], lack of emotional support [16], reports of extreme loneliness [18]. These factors seem to turn bigger the stressful impact of the AMI. Patients who have serious events in their private life in the two years preceding the AMI had more severe levels of depression [17]. History of emotional health problems [self-reported depression, anxiety or stress) and depression during hospitalization [8] can be evidences that past psychological disorders can lead to a worst prognosis too. Avoid all these risk factors can be positive to a better prognosis.

It is known that neuronal damage leads do depressive symptoms and, as it was showed, in AMI it was found that S100B protein, a marker of cerebral damage, gets higher after the AMI which suggest that the AMI leads to a cerebral damage [30].

The release of inflammatory cytokines as TNF-alpha can be determinant to PMID. TNF-alpha seems to increase vascular permeability in the prefrontal cortex and, more severely, in the anterior *cingulate* cortex after AMI [26]. The inflammation can bring damages to the neuronal tissue, by activation of the extrinsic pathway of apoptosis. The inhibition of TNF-alpha leads to an attenuation apoptosis in, specially, the *dentate gyrus* and hippocampus [28]. The presence of depressive behavior in myocardial infarcted rats was associated with an increase of apoptosis proteins indicating vulnerability for neuronal death within prefrontal cortex and hypothalamus.

Complications during hospitalization, such as arrhythmia event in a short period of hospitalization, recurrent infarction, dyspnea, persistent angina pectoris preceding AMI [17], smoking and hypertension [20-22] were some factors that were associated with the development of PMID. They are all factors that can act intensifying

the inflammation and consequently the cerebral damage.

CONCLUSIONS

There is an important relationship between myocardial infarction and major depression. After AMI, psychotherapeutic support is an important aspect to patients to better prognosis. The inflammation and its products are most important biological component to the occurrence of PMID, mainly due injury in hypothalamus, limbic system, hippocampus and prefrontal cortex.

Conflicts of interest
The authors declare no conflict of interests.

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