BPI

HEART FAILURE: ANXIETY, DEPRESSION AND MEMORY IMPAIRMENT

C. D'Ovidio

Section of Legal Medicine, Department of Medicine and Ageing Sciences, G. D'Annunzio University of Chieti/Pescara, Chieti, Italy

Correspondence to:
Christian D'Ovidio MD,
Section of Legal Medicine,
Department of Medicine and Ageing Sciences,
G. D'Annunzio University of Chieti/Pescara,
Via dei Vestini 21,
66100 Chieti, Italy
e-mail: cristian.dovidio@unich.it

INTRODUCTION

Blood vessels are essential for the regular functioning of cardiac and peripheral circulation, and occlusion can cause heart failure, heart attack and death of the heart muscle (1). Heart disease (failure and myocardial infarction) ranks first in the global fatal cause of all diseases. In addition, systolic heart disease can cause neurological problems with impaired cognition, memory loss, and depression (2). Thus, systolic dysfunction causes decreased cerebral blood flow and a pathological state of the brain with glial activation, oxidative stress, inflammation, and cell death (3).

There is evidence that patients with myocardial infarction have brain impairment; although the cardiac disease does not appear to affect cognitive impairment, anxiety, and depression directly, limited data is available in the literature to date (4). Myocardial infarction leads to heart failure with impaired contractility of the heart muscle, decreased blood flow, and cognitive brain dysfunction. Therefore, reducing cerebral blood flow (CBF) in myocardial infarction impairs cognitive function, including attention span (5).

The main mechanisms leading to neuroinflammation, such as cell death and oxidative stress, are reduced blood flow induced by systemic alteration and inflammation. For example, Angiotensin has two receptors, AT1 and AT2 (7). AT1 is a G protein-coupled receptor that activates phospholipase C and the phosphatidylinositol pathway (8). Its action leads to a general increase in blood pressure due to resistance and cardiac activity. Thus, AT1 receptor dysfunction may also be responsible for neuroinflammation. These effects involve a reduction of oxygen and cerebral nutrients and increasing substances such as reactive oxygen species (ROS) accompanied by synaptic and mitochondrial dysfunction and cell and brain death (9).

Myocardial infarction leads to heart failure with impaired contractility of the heart muscle, decreased blood flow, and cognitive brain dysfunction. These effects involve a reduction of oxygen and cerebral nutrients and increasing substances such as reactive oxygen species (ROS) accompanied by synaptic and mitochondrial dysfunction and cell and brain death (10). In these dynamics, inflammation occurs with the activation of the toll-like receptor4 (TLR4) and pro-inflammatory cytokines such as IL-1, TNF and IL-6. These cytokines are released by activated microglia, which in their

physiological state, protect the brain tissue against infections and infectious products (11). After myocardial infarction, microglia are activated and contribute to the cognitive disorder. In addition, by producing pro-inflammatory cytokines, heart failure causes dysregulation of membrane phospholipids by releasing phospholipase A2, which activates the arachidonic acid cascade via cyclooxygenases 1 and 2 (12).

These reactions lead to the formation of inflammatory prostaglandins. Moreover, the activation of arachidonic acid causes the release of lipoxygenase with the formation of leukotrienes LTC4, D4 and E4, which contribute to systemic
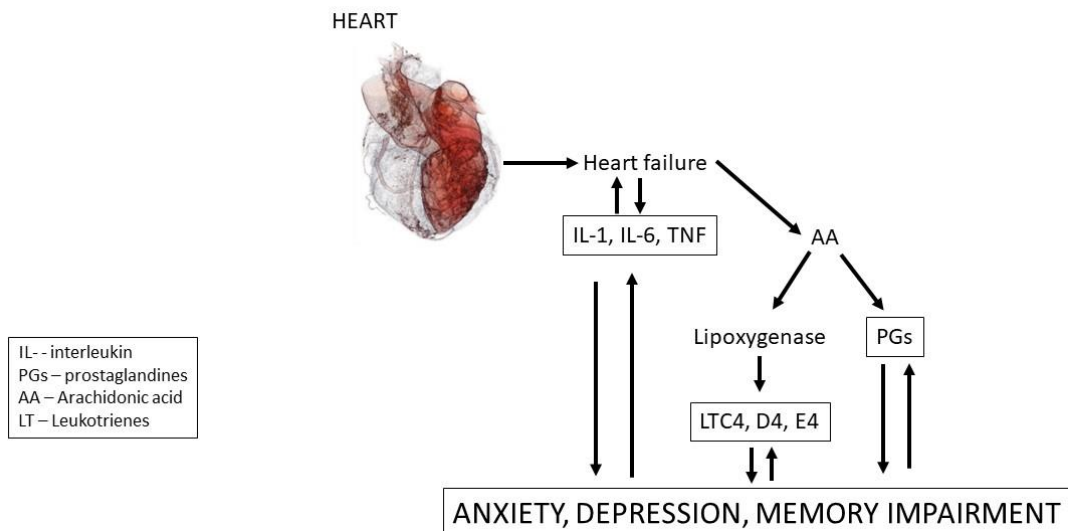

Fig. 1. *Heart failure generates inflammatory cytokines (IL-1, IL-6, and TNF) and activate arachidonic acid cascade with the production of pro-inflammatory leukotrienes and prostaglandins which all together lead to anxiety, depression and memory impairment. In addition, brain dysfunction (anxiety, depression and memory impairment) through microglia, can release inflammatory compounds which contribute to heart failure.*

low-grade inflammation and pain (13). Using non-steroidal anti-inflammatory drugs by blocking cyclooxygenase inhibits the formation of prostaglandins and can help against inflammation and pain. Corticosteroids also strongly inhibit the arachidonic acid cascade by inhibiting phospholipase A2 (14) (Fig. 1).

IL-1 released by microglia after heart failure resulting in depression

IL-1 was cloned about 30 years ago, and after a few years, caspase-1 was identified, a molecule capable of transforming inactive pro-IL-1 into the biologically active form and activating protein complexes called inflammasomes. The inflammasome consists of a nucleotide oligomerisation domain (NOD)-like receptor (NLR), which consists of an intracellular sensor and adapter protein that recruits pro-caspase with caspase cleavage and activation (15). The NLR comprises 22 receptors, in which NLRP1 and P3 have been characterised; they form the inflammasomes that activate pro-caspase-1, which transitions into the mature form (16). The CNS is a cage where peripheral immune cells cannot enter due to the blood-brain barrier (BBB). This protection can be impaired by pathological brain conditions such as tumors and inflammation. Infiltrating immune cells into the brain generates pro-inflammatory cytokines and microglia activation, producing IL-1, IL-6, and TNF (17).

Since microglia are connected to neurons and cerebral vessels, inflammatory cytokines can influence the physiological state of the brain, causing anxiety, depression and memory impairment. Conversely, it is known that anxiety, depression and memory impairment can activate microglia to produce pro-inflammatory cytokines (18).

Brain inflammation may be related to depression after myocardial infarction with activation of the STAT3 pathway and IL-1 production. In fact, IL-1 and TNF increase in circulation both in depressed patients and in those with myocardial infarction (19).

Neuropeptides bound to their receptors mediate numerous biological effects on the CNS locally and peripherally. For example, some neuropeptides play important roles in regulating systemic blood pressure, memory and anxiety, effects that can be inhibited by specific antagonistic receptors that can have therapeutic effects in hypertension, heart failure, anxiety and depression (20).

In heart failure, brain inflammation caused by IL-1, IL-6, TNF and other pro-inflammatory molecules is responsible for anxiety, depression and memory impairment. Several cells, such as calcium-binding cells CD11b, are

increased in the CNS after myocardial infarction, with microglial overactivity, suggesting the close link between heart disease and the brain (21). IL-1, IL-6 and TNF mRNA levels are also upregulated in the CNS. CNS diseases, such as cognitive impairment due to myocardial infarction, often lead to neuron loss and brain cell death leading to cognitive impairment. In this heart disease, inflammatory genes may increase with the involvement of the amygdala and dysfunction of calcium-binding proteins with cell death. In addition, Bcl-2, a regulator of apoptosis, a mechanism involving caspase, may also be impaired (22).

IL-6

Cells of innate immunity produce IL-6, a cytokine essential for various physiological functions in host defence. IL-6 plays a vascular protective role in heart disease. This cytokine is mainly generated by macrophage cells, fibroblasts, and endothelial cells. IL-6 can be activated by IL-1 during the inflammatory process and, by binding to the IL-6R receptor, forms a complex that binds to the GP130 protein, activating cellular biological effects (23). By blocking IL-6 through inhibition of its IL-6R receptor or gp130, or transcription factors, a valid therapeutic approach can be obtained for inflammatory pathologies, including myocardial infarction. In addition, IL-1 inhibitors, such as IL-37 and IL-38, may also have a valuable therapeutic effect against IL-6-mediated pathologies.

IL-6 inhibition with monoclonal antibodies is still in an experimental phase, and therefore, further studies are needed to clarify their effects (24).

TNF

Inflammatory cytokines participate in the pathophysiology of heart failure. TNF is strongly implicated in the pathogenesis of coronary artery disease, influencing the contractile function of cardiac cells and contributing to the inflammatory process. TNF is an important inflammatory cytokine in heart disease, although there are no studies that blocking TNF does not help patients with heart failure. TNF, in myocardial infarction, can be induced by mechanical action but also by IL-1 and plays a key role in the pathogenesis of the heart muscle and can be generated by different types of cells, such as cardiomyocytes, macrophages, mast cells, vascular cells, fibroblasts, etc. The action of TNF in this pathology can contribute to the patient's death, aggravating the inflammatory network (25).

TNF is part of the inflammatory cascade in activating central and peripheral neuropathic pain, contributing to cell death with memory impairment and neurodegeneration. Therefore, its inhibition could be a viable therapeutic route in subjects with systemic inflammation and cases of neurodegenerative pathologies (26).

CONCLUSIONS

Myocardial infarction may activate microglia and astrocyte remodelling resulting in the production of inflammatory compounds, including cytokines IL-1, IL-6, TNF, prostaglandins, leukotrienes and ROS, demonstrating a close relationship between cardiac disease and brain functions such as anxiety, depression and memory impairment. However, many of these works have been done on rodents, and some authors report conflicting results; therefore, these data should be confirmed by further future studies (27).

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