Literature Review

Mesenchymal Stem Cells Role in COVID-19 Myocardial Injury

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Abstract

Coronavirus Disease-19 (COVID-19) has become a global pandemic that affected the lives of billion individuals. The clinical spectrum of the disease varies from asymptomatic form to severe manifestation in term of acute respiratory distress syndrome (ARDS), shock and septic shock and multiple organ dysfunction syndrome (MODS). Clinical studies have also reported an association between COVID-19 and cardiovascular manifestation, such as myocardial injury, arrhythmias, acute coronary syndrome (ACS) and thromboembolism. Myocardial injury has been reported frequently and is associated with high mortality. The currently approved strategies for COVID-19 are supportive rather than curative treatment. Cell-based approaches, primarily using mesenchymal stem cell (MSC) has demonstrated safety and possible efficacy as an adjuvant therapy in COVID-19 patient. Mesenchymal stem cells have shown important role in the therapy of cardiovascular disease due to their prominent features including their ability to differentiate into cardiovascular cells, immunomodulatory properties, antifibrotic activity and ability to undergo neovasculogenic.

Keywords: COVID-19, mesenchymal stem cell, myocardial injury

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INTRODUCTION

COVID-19 pneumonia began with the start of pneumonia epidemic of unknown etiology in Wuhan city, China at the end of 2019. Epidemiological surveillance showed that the case was related to seafood market in Wuhan. In 7th January 2020, Chinese government announced that the epidemic was caused by a new strain of coronavirus, which was in the same family with the viruses causing severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), therefore named SARS-CoV-2. SARS-CoV-2 is more virulent and easier to spread, and status of pandemic was declared in 11th March 2020.[1]

SARS-CoV-2 infection will activate natural and cellular immune response. In COVID-19, excessive immune response called 'cytokine storm' may occur, causing severe to critical clinical manifestation. Cytokine storm will cause acute respiratory distress syndrome (ARDS) and multiorgan failure. After binding to ACE2 receptor, SARS-CoV-2 will invade respiratory tract epithelium. Dendritic cells and alveolar macrophages activated by SARS-CoV-2 entry will release interleukin-6 (IL-6) which is also secreted by epithelial cells in respiratory tract. Interleukin-6 (IL-6) will induce the release of some acute phase proteins such as CRP, D-dimer and ferritin, and other proinflammatory cytokines like IL-1B, IL-12, TNF-α. These cytokines will induce leukocyte to releasse other proinflammatory cytokines, which aggravate the ongoing inflammation process.[2]

MYOCARDIAL INJURY IN COVID-19

Myocardial injury is the most common cardiovascular manifestation found in COVID-19 pneumonia. Prevalence of myocardial injury in COVID-19 pneumonia reported by some studies was 5–20%, and higher in severe and critical degree of disease, reaching 44%.[3] Meta-analysis by Zou F et

al reported 24,4% prevalence of myocardial injury in admitted patients with increased mortality rate 5 times higher compared to those without myocardial injury.[3] Shao MJ et al reported 5,9 times increase of mortality rate in COVID-19 pneumonia patients with myocardial injury compared to those without myocardial injury.[4]

Myocardial injury is defined as an increase in cardiac Troponin I (cTnI) level in blood above 99th percentile from upper range of normal values. Myocardial injury can occur in acute or chronic duration.[4–8] Cardiac troponin I and troponin T are the component of contractile apparatus in cardiac muscle cells, secreted almost exclusively in myocardial muscle cells. Increase of troponin I was reported to not occur in injuries other than myocardial cells, however, troponin T was also reported to increase in skeletal muscle injury. Therefore, troponin I has high sensitivity and is a recommended routine evaluation.[8]

Cardiac troponin is located intracellular, with more than 90% found in sarcomeres, unbound in cytoplasm. Cardiac troponin can be released in the circulation in the situation of myocyte necrosis, apoptosis, form and release of bleb in membrane, increase of membrane permeability and release of degradation product of proteolytic troponin. Moreover, mechanism outside the heart may also induce troponin release without myocyte necrosis, some of which are mechanical stretch in overload condition inducing activation of intracellular protease related to intracellular troponin degradation, condition of tachyarrhythmia stimulating stress response in cardiomyocyte causing troponin release from viable cardiomyocyte cells and in diseases with proinflammatory and prothrombotic environment causing platelet aggregation to thromboembolism.[5]

Table 1. Cause of Troponin Increase

Ischemic Myocardial Injury	Myocardial Ischemic Injury due to Imbalance of Oxygen Supply and Demand	Other Causes
Atherosclerotic plaque rupture or thrombosis	Decreased myocardial perfusion caused by: Coronary artery spasm, microvascular disfunction 1. Coronary embolism 2. Coronary artery dissection 3. Persistent bradyarrhythmia 4. Hypotension or shock 5. Respiratory failure 6. Severe anemia	Cardiac diseases: 1. Heart failure 2. Myocarditis 3. Cardiomyopathy 4. Coronary revascularization procedure 5. Catheter ablation 6. Defibrillation shock 7. Heart contusion
	Increase of myocardial oxygen demand, caused by: 1. Persistent tachyarrhythmia 2. Severe hypertension with or without left ventricle hypertrophy	Systemic problems: 1. Sepsis, infectious disease 2. Chronic kidney disease 3. Stroke 4. Lung embolism, pulmonary hypertension

Myocardial injury is a precondition for myocardial infarct diagnosis, but can also be its own entity due to etiologies other than ischemic process. Myocardial infarct is defined pathologically as death of myocardial muscle cells due to long term ischemic process. In the beginning of ischemic onset, structural changes that happen are damage of cellular glycogen, relaxing myofibrils, damage of sarcolemma structure and abnormality of mitochondria, while the death of myocardial muscle cells need a few hours. Myocardial injury can correlate to ischemic or non-ischemic process with various underlying condition (Table 1).[9]

Another biomarker that may be released by the myocardium during insult is N-terminal pro-brain natriuretic (NT proBNP). Some studies have investigated its role in myocardial manifestation in COVID-19. Troponin I and NT proBNP are important prognostic factors in COVID-19 patients. NT proBNP is a molecule secreted by myocardial muscle cells as a response towards mechanical stretch due to volume overload or ventricular volume overload. NT

proBNP is a quantitative biological marker of hemodynamic stress and heart failure that often increases in patients with inflammatory disease and/or severe breathing. In the condition of acute heart ischemia, BNP level increase in proportion to the degree of left ventricle dysfunction. In the event of acute myocardial infarcts, NT proBNP level may increase along with other myocardial injury markers such as troponin T, CKMB and myoglobulin. Gao L et al reported high NT proBNP level as death predictor in hospital stay for COVID-19 pneumonia patients.[10] Meta-analysis by Pranata R et al. reported that high NT proBNP level increases risk of death with 1.37 hazard ratio.[11]

PATHOGENESIS OF MYOCARDIAL INJURY IN COVID-19

ACE2 receptors as the entry point of SARS-COV-2 are also expressed a lot in the heart and vessels. ACE2 is a part of renin-angiotensin-aldosterone system (RAAS) involved in the development of hypertension, heart failure and diabetes. ACE converts angiotensin I into angiotensin II. Angiotensin II is the main effector molecule in RAAS. ACE2 will convert angiotensin II into angiotensin 1-7. Angiotensin II level increases in various pathological conditions, hence ACE2's protective properties in cardiovascular system. In SARS-COV-2 infection, it is thought that decreasing ACE2 level intermediate the process of disorder in the cardiovascular system.[6]

Cardiovascular manifestations in COVID-19 generally include myocardial injury, arrhythmia, acute coronary syndrome (ACS), thromboembolism, to heart failure and cardiac arrest. Mechanism of myocardial injury in COVID-19 pneumonia has not been fully understood. Some possible mechanisms include:[12,13]

1. Directly causing myocardial injury

   The binding of SARS-COV-2 with ACE2 in the heart will cause changes in heart signaling pathway, causing acute injury of heart muscles, lung muscles, as well as microvascular and macrovascular dysfunction.

2. Systemic inflammation

   In COVID-19 with severe to critical symptoms, excessive systemic inflammatory response occurs (cytokine storm). Cytokine storm causes multiorgan injury or even multiorgan failure, including in cardiovascular system. Furthermore, T cell and activated macrophages are thought to be able to infiltrate myocardium, causing fulminant myocarditis to severe heart damage. Severe systemic inflammation also causes increasing cardiometabolic demand due to hypoxia. This will change demand and supply ratio that further will cause myocardial injury.

3. Plaque rupture and coronary thrombosis

   Systemic inflammation also causes an increase in coronary blood flow along with hypercoagulable intravascular environment, resulting in unstable and easily ruptured atherosclerotic plaque, causing acute myocardial infarct.

4. Adverse effect of therapy

   Several antiviral medicines, quinine pills, corticosteroid and other medicines for COVID-19 management may cause adverse effects that affect cardiovascular system.

ECG FINDINGS IN COVID-19

Until recently, there is no specific changes of ECG finding in patients with COVID-19 pneumonia, therefore it is thought that the damage in myocardial cells is minimal and doesn't cause specific ECG changes in most patients, although ST-elevation finding in myocarditis patient has been reported. Therefore, ECG diagnostic criteria in COVID-19 pneumonia is no different with any other heart diseases. One publication on 138 COVID-19 patients reported 16.7% arrhythmia cases and 44.4% in 16 ICU admitted patients, but the association between COVID-19 and arrhythmia had not been clearly known.[13]

ECHOCARDIOGRAPHY FINDINGS IN COVID-19

Echocardiography is not an established practice for COVID-19 patients. Skezely et al. evaluated 100 COVID-19 patients and found no abnormalities of basic examination in 32% patients. The most common abnormalities were dilatation and dysfunction of right ventricle (39%), diastolic dysfunction of left ventricle (16%), and systolic dysfunction of left ventricle (10%). Increase of troponin level is reported to be linked with decreasing right ventricle function and deteriorating clinical symptoms.[14]

CARDIOVASCULAR COMORBIDITIES IN COVID-19

Cardiovascular disease is a comorbidity often found in SARS and MERS (with 10% and 30% prevalence), as well as in COVID-19 pneumonia. The most common cardiovascular comorbidities in COVID-19 pneumonia are hypertension and diabetes mellitus. Some studies in China reported different prevalence of cardiovascular comorbidities in COVID-19 pneumonia, ranging from 2.5% to 15%. Meanwhile, report in America showed 11–14% prevalence, and 21% in Italy. The number of prevalence is reported higher in patients with severe and critical disease. China CDC reported overall mortality rate of 2.3% in China, but mortality rate for COVID-19 with cardiovascular comorbidity increased up to 10.5%.[6]

MESENCHYMAL STEM CELLS THERAPY IN COVID-19

Mesenchymal stem cell is introduced as one of adjuvant managements in COVID-19 pneumonia that is currently investigated abroad. In the last 20 years, studies about mesenchymal stem cell reported its safety for use and good tolerability. Leng et al reported that mesenchymal stem cell administration in COVID-19 patients improved patient's outcome with no report of serious adverse effects.[15] Zhang et al reported increase of CD3+, CD4+ and CD8+ cells and decrease of IL-6, CRP and TNF-α levels after administration of mesenchymal stem cell therapy.[16] Liang et al reported that mesenchymal stem cell administration is well tolerated and shows improvement of clinical condition and biological markers.[17]

Mesenchymal stem cell is a multipotent mature non hematopoietic stem cell with characteristic ability to self-renew and differentiate in mesodermal pathway (osteocyte, adipocyte and chondrocyte), ectodermal (neurocyte) and endodermal (hepatocyte). Mesenchymal stem cell is currently able to be isolated from various structures, such as adipose tissue, amniotic fluid and membrane, teeth tissue, peripheral blood cells, placenta and fetal membrane, salivary gland, skin, sub amniotic umbilical membrane and synovial fluid.[18] Mesenchymal stem cell offers multiple advantages, such as being easily obtained and cultured, multipotent, ability to be stored for repetitive administration of therapy, no reported serious adverse effects, and available report of efficacy from multiple prior clinical research.[19]

Mesenchymal stem cell has the potential as immunomodulator, proangiogenic, anti-apoptosis and having a role in tissue repair. Its role as an immunomodulator is crucial in reducing inflammatory response leading to ARDS in COVID-19. Mesenchymal stem cell can increase polarization of monocyte or M2 phenotype macrophage which serves as antiinflammation and inhibits proliferation and differentiation of T cells, thus suppressing inflammation process. Anti-inflammatory monocyte will secrete large amount of IL-10 mediated by IL-6 and *hepatocyte growth factor* (HGF). IL-10 will inhibit differentiation of monocyte into dendritic cells and induce monocytes into anti-inflammatory monocyte. Mesenchymal stem cell will also release prostaglandin E2 (PGE2) that induces macrophage to release anti-inflammatory cytokines and activate regulatory cell (T reg) thus inhibiting proliferation and activation of effector T cell, resulting in decrease of endothelium and alveolar epithelium permeability.[20–24]

On the other hand, mesenchymal stem cell will express class II MHC, CD45R dan CD11b that will suppress the activity of T cells. Monocyte will induce formation of T reg cells, mediated by CCL-18 and

transforming growth factor-β1 (TGF-β1). CCL-18 will inhibit CD4+CD25- effector T cell proliferation. Effector T cell proliferation is also inhibited by mesenchymal stem cell mediated by TGF-β1, IDO and galectin. Mesenchymal stem cell is also responsible for intra-alveolar fluid clearance when ARDS occurs by ventoral transport in alveolar epithelial cells done by fibroblast growth factor-7 (FGF-7). [20–24]

Mesenchymal stem cell is administered through injection or inhalation. Mesenchymal stem cell administered with injection will be contained in lung capillaries. Then, it will improve the microenvironment in lung tissues, protect alveolar epithelial cells, decrease pulmonary fibrosis and lessen lung disfunction. In studies with lab animals, mesenchymal stem cell will be phagocytosed by monocyte or macrophage. Phagocytosis will cause changes of monocyte or macrophage properties into monocyte with type 2 phenotype, which is immunosuppressive. Accumulated immunosuppressive monocyte or macrophages will be distributed to neighboring tissue and undergo its role to suppress inflammatory response. Recommended dosage of mesenchymal stem cell administration is 0.5×10^6 to 1×10^7 cells/kgBW.[18,19,24]

ROLE OF UMBILICAL CORD MESENCHYMAL STEM CELLS IN MYOCARDIAL INJURY

Mesenchymal stem cell has an important role in cardiovascular disease. Mesenchymal stem cell has the ability to differentiate into cardiovascular cells, as an immunomodulator, antifibrotic and increase neovasculogenesis. Extracellular vesicle of mesenchymal stem cell is also able to mediate some cellular functions, such as increasing cardiomyocyte autophagic ability through HIF-1α/Jagged-1 pathway, decreasing cell apoptosis and activating pathway for cell survival through multiple microRNA (miRs). Currently, approaches have been implemented to increase therapeutic ability of mesenchymal stem cell, including genetic modification and combination with other biological agents.[25]

After implantation, mesenchymal stem cell will be distributed in myocardial tissue zone that is similar with cardiomyocyte cells. Increase of specific markers for myocardium such as troponin T, will affect mesenchymal stem cell differentiation into cardiomyocyte cells. Administration of *basic fibroblast growth factor* (bFGF) through coronary vein is able to increase differentiation of mesenchymal stem cell phenotypes into cardiomyocyte, maintain heart function and prevent poor remodeling. Moreover, mesenchymal stem cell can genetically induce itself into *cardiomyocyte-like cell*.[25]

When myocardial injury occurs, monocyte migrate to location of the injury and differentiate into macrophages in the tissue. Macrophage will then secrete cytokines, chemokines and growth factor that facilitates in suppressing process of injury or ongoing myocardial infarct. Macrophage will further differentiate into M1 and M2. M1 macrophage will release interferon, *tumor necrosis factor* (TNF) and IL-23 which has proinflammatory properties, while M2 macrophage has anti-inflammatory role by increasing cell proliferation and angiogenesis that regulate ongoing inflammatory process.[25]

Through study on experimental animals, Miteva et al. reported that mesenchymal stem cell administration will decrease the severity of myocarditis and the number of proinflammatory monocyte, while increase of Ly6C levels secreted by anti-inflammatory monocytes also occurs in the blood, heart, and spleen of experimental animals.[26] Chiossone et al reported that mesenchymal stem cell could increase polarization of macrophage differentiation into M2 through a pathway that requires prostaglandin and inhibit T cell proliferation. Mesenchymal stem cell interaction with macrophage will increase expression of CD206 and IL-10 in vitro that serves as anti-inflammatory cytokines.[27]

Myocardial fibrosis occurs following myocardial injury. Myocardial fibrosis is marked by excessive collagen deposit in heart muscle. This causes stiffening of heart muscle, therefore decreasing systolic and diastolic function, and scar may form on heart muscle. Heart muscle cells undergoing necrosis in the infarcted area will be replaced by

fibroblast tissue that may cause ventricle remodeling, arrhythmia, and even death. Mesenchymal stem cell is able to regulate matrix metalloproteinase which inhibits fibroblast activation and decreases extracellular matrix deposit.[25]

Clinical study of mesenchymal stem cell in cardiovascular disease was first conducted by Hare J at United Kingdom in 2005. This study included myocardial infarct patients and reported good safety profile and mesenchymal stem cell efficacy.[28] Another study with similar result was reported by Ankara university in 2015 by administering umbilical cord mesenchymal stem cell in chronic ischemic cardiomyopathy patients.[29]

CONCLUSION

Myocardial injury is the most common cardiovascular manifestation in COVID-19 pneumonia patients. Mortality rate of COVID-19 pneumonia patients with myocardial injury increases by 5.9 times compared to no myocardial injury. Myocardial injury in COVID-19 may occur in some possible mechanisms; directly causing myocardial injury, systemic inflammation, plaque rupture and coronary thrombosis and adverse effect of therapy. Mesenchymal stem cell has the potential as immunomodulator, proangiogenic, anti-apoptosis and plays a role in tissue repair. Its role as immunomodulator can be a promising alternative therapy to resolve myocardial injury. Nevertheless, further research is needed to understand cellular and molecular function that take part in interactions between mesenchymal stem cell, cardiomyocyte and occurring immune response. Clinical trial with large sample is needed to obtain characteristic risk-benefit profile of mesenchymal stem cell use, in order to make appropriately targeted selection of adjuvant therapy in COVID-19.

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