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Review Article

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How to evaluate efficacy of stem cell therapy: The role of current imaging modalities

Abstract

Left ventricular dysfunction and adverse remodeling due to myocardial ischemia is one of the common manifestations in chronic coronary artery disease. Timely restoration of blood flow can reduce infarct size, but ischemic regions of myocardium remain in up to two-thirds of patients due to microvascular obstruction. Ischemic left ventricular dusfunction and remodeling with viable or partially viable myocardium may have better outcomes when receive appropriate therapy. One of the novel therapeutic strategies to reduce or probably prevent adverse remodeling is stem cell-based therapy. Ability to measure and visualize cardiac remodeling at cellular level may be extremely useful for clinicians and shifts paradigm of treating cardiovascular diseases. Due to the technical limitations of the "in vivo" visualization of transplanted stem cells, the therapeutic mechanisms and biosafety of stem cells are poorly defined, which limits the speed of clinical translation. We hypothesize that evaluation of viability might give insights into a state of myocardium at cellular or molecular level. Viability simply refers to a cell that is not irreversible damaged and may indicate a myocardial substrate that can improve in response to a range of interventions. The goal of viability testing as a surrogate is to identify amount of viable myocardium that would provide reverse remodeling , reflecting molecular processes in myocardium under stem cell therapy.

Keywords: Stem cell therapy, myocardial viability, cardiac remodeling

INTRODUCTION

Cardiovascular diseases are pointed out by the World Health Organization as the leading cause of death and represent a massive social and economic burden. From the pathophysiological point of view, the heart is very vulnerable to hypoxia and has a limited capacity to regenerate. Myocardial infarction is mainly caused by the rupture of an atherosclerotic plaque leading to a thrombus formation within the coronary artery, which blocks the blood flow to distal myocardium. Ischemic necrosis induces the death of millions of myocytes simultaneously, leading to an immune response and an influx of inflammatory cells into the infracted area. Neutrophils and macrophages cause the destruction of the extracellular collagen matrix and the expansion of the infracted area. After reaching the maximum inflammatory response, fibroblasts are directed to the infracted area and create a new collagen matrix and scar (1). All these processes lead to changes in the cardiac architecture and geometry, which is known as adverse ventricular remodeling. The size of the infarct zone and level of perfusion affect the progression of these events. There is a direct correlation between aggressive inflammatory responses associated with high concentration of leucocytes and adverse remodelling and poor prognosis. Cardiac remodeling is defined as a group of molecular, cellular and interstitial changes , which determine alteration in shape, size and function of the heart after cardiac injury (2).

One of the novel therapeutic strategies to reduce or probably prevent adverse remodeling is stem celltherapy. Cell-based therapy became popular in the 1990s and is promoted as a promising field in regenerative medicine for repairing of cardiac damage. Now, efforts are focused on cell-based therapy and the

question is how to mobilize and promote cardiomyocytes that have potential to proliferate in mammalian hearts. While endogenous cardiomyocytes can proliferate at a low frequence, methods that promote cardiomyocyte proliferation may be vital research field in the future. But, one of the prime challenges of stem cell therapy consists in the survival, retention and differentiation of stem cells delivered to the harsh microenvironment of hypoxic tissues. However, there is little evidence of long-term engraftment of transplanted stem cells,processes that contribute to adverse remodelling such as inflammation, oxidative stress, increased apoptosis, endothelial disfunction, fibrosis, suppressed vasculogenesis are targets of stem cell therapy. Stem cells secrete an array of growth factors, cytokines, chemokines, exosomes, metalloproteinases and others that directly counteract each of these mechanisms. These components act in an autocrine or paracrine manner (3). In support of paracrine hypothesis, studies have demonstrated protective effects of stem cells , including promotion of cell survival and proliferation, immunomodulation, cardiac remodelling, inhibition of apoptosis, neovascularization, activation of resident cells etc (4). Based on these hypotheses, stem cell therapy seems as a promising field for treatment of ischemic heart diseases, especially with concomitant revascularization.

But how we can assess effects of stem cell therapy on myocardial function? Ability to measure and visualize cardiac remodeling at cellular level may be extremely useful for clinicians and shifts paradigm of treating cardiovascular diseases. Current clinical cardiac imaging modalities assess anatomy, perfusion, function of the myocardium, yet do not offer any insight into the specific molecular pathways involved in the repair process. Molecular imaging is a relatively new and exciting approach which aims to visualize pathological processes at a molecular and cellular level, which could aid clinical management. This approach is safe and non-invasive technique to visualized biological processes in vivo, therefore, attractive alternative to other invasive methods such as biopsy (5). There is a large body of literature on preclinical evaluation of imaging targets for detection of key molecules involved in angiogenesis and vascular remodeling, as vascular endothelial growth factor (VEGF) receptors, αvβ3 integrin. Angiogenesis is a part of myocardial healing after ischemic injury. VEGF is a potent angiogenic agent ,its receptors are potentially good targets for imaging of angiogenesis. 64 CU-DOTA-VEGF121 is explored as a positron emission tomography (PET) tracer, targeting VEGF receptors in a rat model of myocardial infarction. In this study, tracer levels peaked 3 days post-MI and decreased over time until it reached baseline levels on day 24 (6).There are many tracers, mainly radiolabelled PET and SPECT tracers that have been evaluated in animal models to visualize not only angiogenesis, but also apoptosis, inflammation for the purpose of post myocardial infarction remodeling. Most of these studies have been conducted on animals and authors have described the differences between behavior of the tracers on mice, pigs and humans, especially in patients with co-morbidities and more complex cellular mechanisms (7). Yet, large multi-center clinical trials will be required to ensure they can successfully image their targets, provide prognostic information to patients and offer evidence to clinicians . This is an exciting field , but large scope of future work must be done in this area before its introduction into clinical practice.

So, one of the most challenging problems of cell-based therapies is assessing of effects. Due to the technical limitations of the in vivo visualization of transplanted stem cells, the therapeutic mechanisms and biosafety of stem cells in vivo are poorly defined, which limits the speed of clinical translation. While patient-centered outcomes (a direct measure of how an individual feels, functions, or how long they are survive) are health outcomes that are important to patients themselves, clinical trials may have measured the impact of the intervention on other endpoints. When used for this purpose, biomarkers and intermediate outcomes potentially become surrogate endpoints. Surrogate endpoints can be defined as successful biomarkers or intermediate outcomes that are used as substitutes for clinical outcomes of interest, often to expedite research or decision-making. Surrogate endpoints are not necessarily important to patients, but reflect changes in an outcome and predict health benefit or harm, therefore, they are frequently used in medical research and clinical trials when the patient-centered outcomes may be impractical, time-consuming, costly, or ethically challenging (8).

It is important to note that surrogate marker not directly involved in the pathogenic pathway, could potentially be as effective as a molecular mediatorand its detection and imaging. Rapid application of stem cells to clinical trials has outrun our understanding of their modes of action, making it unclear which surrogate endpoints to examine in order to make meaningful claims about efficacy. For all cardiovascular diseases a tremendous work of research has been done to find the most optimal quantitative parameter for diagnosis, treatment response prediction and patient monitoring. The ability to quantify molecular biomarkers in organs not rutinelly amenable to biopsy could open new clinical opportunities.

LVEF has been considered to be an important functional surrogate endpoint for trials in patients with heart failure. Some trials have reported profound improvements in LVEF, which may reflect the improvement in cardiomyocyte function as a result of cellular therapy (9). For years LVEF has been commonly used surrogate for diagnosis and management of patients with heart failure, however, LVEF is highly dependent on preload and afterload, and could misestimate LVEF contractile status because of the various methods used to acquire the data. In the STICHES trial no significant contractile recovery of dysfunctional myocardium was demonstrated in the surgical qroup (revascularization arm), but on extended follow-up a survival became apparent – a finding that suggests any residual myocardium in the absence of transmural scar may benefit from revascularization or other addressed therapy (10). Alike, the most commonly assessed endpoint is left ventricular remodeling. Remodeling is measured by viability, LVESV and LVEDV,infarct size and chamber dimensions (11). Stem cells are thought to reverse the remodeling

process by increasing perfusion to the stressed myocardium, maybe due to neoangiogenesis, stimulating new cardiomyocyte formation and improving existing cell survival and by reducing fibrosis. In our original study we choose myocardial viability as a surrogate endpoint to evaluate stem cell therapy effects, being assessed pre- and postprocedural (after implantation of stem cells). We hypothesize that evaluation of viability might give insights into a state of myocardium at cellular or molecular level and could predict effects of cell therapy on ischemic cardiomyopathy and help to make meaningful statements about efficacy. In conventional clinical practice the role of viability testing is identifying patients with ischemic cardiomyopathy who might benefit from surgical revascularization. However, viability may indicate a myocardial substrate that can improve in response to a range of interventions , not just revascularization. At the molecular level (myocyte level) viability refers to a cell that is not irreversible damaged. These cells still possess intact membrane integrity, cellular metabolism, and the potential contractile reverse. Viability is usually applied to areas of myocardium which show contractile disfunction at rest and in which contractility is expected to improve after appropriate therapy. Dysfunctional myocardium should not be distinguished as a binary state, viable or nonviable with no appreciation of varying degree of partially viable myocardium because it is a continuum, ranging from early stages of hibernation with no fibrosis to a terminaly, primarily a fibrotic phase, that might lead to findings that can not be explained (as in a STICH trial). Protection of the residual viable myocardium from acute coronary events and prevention of further deterioration are probably major contributors to improve outcomes (12). However, the ability to distinguish viable (or partially viable) myocardium from non-viable myocardium that might recover followed by revascularization or any other therapy presents challenge in clinical practice.

Myocardial Viability

Left ventricular (LV) dysfunction and adverse remodeling due to myocardial ischemia is one of the common manifestations in chronic coronary artery disease (CAD). Left ventricular dysfunction may be permanent, due to the formation of myocardial scar, or it may be reversible under several conditions. Timely restoration of blood flow can reduce infarct size, but ischemic regions of myocardium remain in up to two-thirds of patients due to microvascular obstruction. Ischemic left ventricular dusfunction and remodeling with viable or partially viable myocardium may have better outcomes when receive appropriate therapy. Reversible LV dysfunction occurs when the myocardium is viable but dysfunctional. There are two types of dysfunctional but viable myocardium: stunned myocardium and hibernating myocardium. Stunned myocardium is characterized by reduced contractile function in the presence of normal (or near normal) resting perfusion. This is caused by short periods of ischemia followed by restoration of perfusion (after an episode of unstable angina or after ischemia induced by exercise testing). The myocardium may be dysfunctional for several days, but after perfusion returns to normal, function is eventually restored (13).

Prolonged or repetitive reductions in perfusion may lead to a state of chronically dysfunctional but viable myocardium also known as hibernating myocardium. Hibernating myocardium is characterized by reduced contractile function but maintained cell viability (intact cell membrane and cell metabolism) in areas with reduced perfusion. In contrast to stunned myocardium, hibernating one does not recover function spontaneously. However ,it may shows improvement of function after restoration of normal blood flow (14).

Current myocardial viability imaging techniques interrogate structural and functional integrity of the cardiac myocytes and its intracellular processes: ischemic myocardial metabolic properties (cellular glucose uptake) by PET and late gadolinium hyper-enhancement and T1 mapping (myocardial fibrosis/ replacement scar) by CMR.

PET and CMR

PET is a functional imaging modality that uses several radiopharmaceutical tracers to assess the perfusion, metabolism and inflammation in various cardiac conditions. These PET tracers are labeled with short-lived positron emmiters produced by a cyclotron or generator. PET is applicable in almost all patients due to fewer side effects and minimal radiation exposure. The radiotracer F-fluorodeoxyglucose (18F-FDG) is a glucose analogue and most frequently used tracer for the assessment of cardiac viability.18F-FDG PET identifies glucose metabolism in the heart and thus myocardial viability. A region with preserved 18F-FDG uptake indicates the presence of viable myocardium (15). Depending on the applied tracer, PET is ideally suited for visualizing molecular and cellular events that occurs in the course of treatment (16).

Cardiac magnetic resonance (CMR) is accepted as the gold standard for cardiac morphological evaluation and volume quantification. CMR is an non-invasive imaging modality , where patients are placed in a large magnetic field. Hydrogen atoms inside the patient align with the magnetic field and are perturbed by short radiofrequency pulses to generate an MR signals . After perturbation hydrogen atoms emit a signal that can be measured with reconstruction of MR signals. Gadolinium , the contrast agent widely used in CMR, displays the characteristic late gadolinium enhancement (LGE) in myocardial fibrosis. The use of contrast agents improves the detection and evaluation of injured areas (17). Under the guidance of CMR and PET imaging, myocardium can be distinguished viable from partially viable with subendocardial scar and predominantly transmural scar. Else, diagnostic accuracy of these imaging modalities in estimating the viable status of the myocardium is comparable. Stem cell therapy with coronary vascularization of partially viable or viable myocardial territory may improve clinical outcomes by preventing future ischemic, infarct events and further worsening of left ventricular remodeling and function and could be measured by these modalities.

CONCLUSION

Cardiac imaging techniques have great potential to improve diagnosis and risk assessment, guide patient management and to be used as endpoint markers in clinical trials. However, there are differences in the diagnostic accuracy between recent imaging modalities. Assessment of in vivo remodeling models has relied on histological end points, which imply the sacrifice of the animal. Molecular imaging has emerged as a powerful tool for in vivo evaluation of molecular events non-invasively, but few if any molecular imaging methods have been validated as versatile methods. Interventional trials that evaluate treatment effects using surrogate endpoints have become increasingly common. Current surrogate endpoints are used in trials as a substitute of the treatment effects of an intervention on the target outcomes. The goal of viability testing as a surrogate is to identify amount of viable myocardium that would provide reverse remodeling , reflecting molecular processes in myocardium under stem cell therapy. We suppose that evaluation of viability could predict effects of cell therapy on ischemic cardiomyopathy and help to make meaningful statements about efficacy. Even so, there are some gaps in assessment of results that must be fill in. We need new level of knowledge aiming to understand the strengths and weaknesses of all these modalities, while issues could initiate more research in this field.

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