

Role of platelet-rich plasma in ischemic heart disease: An update on the latest evidence

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Abstract

Myocardial infarction is the most common cause of congestive heart failure. Novel strategies such as directly reprogramming cardiac fibroblasts into cardiomyocytes are an exciting area of investigation for repair of injured myocardial tissue. The ultimate goal is to rebuild functional myocardium by transplanting exogenous stem cells or by activating native stem cells to induce endogenous repair. Cell-based myocardial restoration, however, has not penetrated broad clinical practice yet. Platelet-rich plasma, an autologous fractionation of whole blood containing high concentrations of growth factors, has been shown to safely and effectively enhance healing and angiogenesis primarily by reparative cell signaling. In this review, we collected all recent advances in novel therapies as well as experimental evidence demonstrating the role of platelet-rich plasma in ischemic heart disease, focusing on aspects that might be important for future successful clinical application.

Key words: Platelet-rich plasma; Ischemic heart disease; Myocardial infarction; Myocardial regeneration; Cardiac repair

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Core tip: Tissue regeneration requires precise coordination among endothelial, epithelial and mesenchymal morphogenesis. Growth factor-induced angiogenesis plays a key role in recovery from ischemic disease and organ regeneration. Recent studies show that stem-cells and PRP together have opened new horizons in the myocardial infarction treatment.

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INTRODUCTION

Coronary infarction is the most frequent cause of death globally^[1]. The loss of cells during ischemia and resultant fibrosis are the main reasons for cardiac failure^[2].

As cardiac muscle has very little potential to create new cells, methods of heart regeneration have been studied further as repair modalities for failing myocardium after acute coronary infarction or chronic ischemia^[3].

In this article, we investigate current advances and demonstrate approaches such as the upcoming challenges of platelet-rich plasma (PRP) application as well as opportunities to develop its role.

We have gathered all experimental and clinical studies in which PRP was used as a therapy post-MI, and have focused on aspects that might be important for future successful clinical application. The PubMed database was searched for articles using the terms "platelet-rich plasma" and keywords "ischemic heart disease", or "myocardial infarction", or "coronary disease".

NOVEL REGENERATIVE THERAPIES

The majority of patients survive a myocardial infarction (MI). Their outcome, however, is negatively influenced by several events, such as loss of viable cardiomyocytes due to a post-MI inflammatory response, eventually resulting in heart failure and/or death. Regenerating the human heart is a challenge that has engaged researchers around the globe almost a century. Although the human cardiac muscle has not been regenerated yet, decades of experimental progress have guided us onto a promising path^[4].

Stem cell approach has become a promising tool for cardiac regeneration^[5]. The main target is to repair functional myocardial tissue by implanting exogenous or by activating native stem cells.

Cardiac stem progenitor cells (CS/PCs) are one kind of adult stem cell with the ability to differentiate into heart lineages. Induced pluripotent stem cells (iPSCs) may differentiate into the needed cells in order to repair injured myocardium. These two types of stem cells play a key role in cardiac regeneration. Two main delivery modes of stem cells (percutaneous intramyocardial or intracoronary) are used today for patients with recent acute MI or ischemic cardiomyopathy^[6]. Other delivery routes, such as intravenous *via* coronary sinus or

peripheral veins and surgical have also been used with less success^[6].

While further studies intent to increase the efficacy of current approaches, experimental protocols using new methods such as exploiting paracrine effect and tissue engineering could enhance repair of injured human heart.

Various chemical methods, including both microRNA and anti-microRNA approaches, proteins and modified peptides demonstrate serious potential^[7].

Takahashi *et al*^[8] investigated pluripotent stem cells (iPSCs) revealing in a new horizon of cellular reprogramming in organ regeneration. It has been shown that iPSCs can be differentiated efficiently into multiple cell types that may be used in the future for regenerative strategies^[9].

Finally, transmyocardial laser revascularization (TMR) is a controversial therapeutic technique that relieves angina but can't create a significant effect on heart function^[10]. It improves the clinical status without confronting the underlying atherosclerotic disease. Therefore, TMR offers palliation and not cure^[10].

ROLE OF PRP

What is PRP

Autologous PRP is an increased amount of platelets in a small portion of plasma^[11]. This is why the term PRP is preferred to plasma-rich growth factors (PRGFs), platelet concentrate or platelet-rich gel. PRP is a source of autologous growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epithelial growth factor and transforming growth factor beta 1 (TGF- β 1), that is secreted by platelets in order to trigger the healing cascade^[11,12]. Structurally similar to the natural fibrin clot, it can be used as scaffold for cells infiltration and assembly of vascular networks.

One of the most crucial questions regarding methodology, refers to the ideal mechanisms of intramyocardial delivery of PRP. Surgical (epicardial) application is performed into ischemic areas with a thin needle, allowing for multiple injections within and especially around the infarct area. The other less invasive interventional delivery route is the transendocardial catheter injection.

PRP and neovascularization

Neovascularization plays a significant role post-ischemia regeneration and organ repair.

It has been reported that the mixture of angiogenic factors in an certain percentage is crucial for the creation of functional blood vessels^[13,14]. Angiogenesis-induced vessels, not only deliver nutrients and oxygen but also provide instructive regulatory signals to surrounding tissue affecting organ regeneration^[15,16].

Neovascularization involves multiple complex events such as the maturation and enlargement of size of the preexisting small vessels through vascular remodeling

(arteriogenesis), sprouting of pre-existing resident endothelial cells (angiogenesis) and the recruitment of bone marrow derived endothelial progenitor cells (vasculogenesis)^[17].

Angiogenesis involves both microvascular and macrovascular mechanisms. At the microvascular level, neovascularization is the genesis of capillaries, which, however, regress after pause of basic fibroblast growth factor (bFGF) triggering if pericytes are not gathered efficiently. Therefore, the stabilization of newly formed capillary networks by pericytes, known to be recruited by PDGF-BB, is crucial for therapeutic angiogenesis^[18]. The enhancement of blood vessel maturation is one of the main modalities implemented to treat such patients.

According to the above-mentioned issues, a limited portion of plasma enriched in platelets, is an attracting attention as a safe and cost-effective source of various growth factors^[19]. PRP, by containing these various cytokines, plays an important role in repairing damaged tissue^[20]. As we have already discussed, little is known about the mechanism of PRP-related regeneration of damaged tissue. Successful reperfusion of ischemic tissue depends not only on stimulation of angiogenesis but also on arteriogenic activity. Different growth factors in PRP have different roles in angiogenesis and restoration of blood flow following ischemia^[21]. It has also been shown that PRP effectively restores blood flow by significant increase of the number of capillaries (angiogenesis) as well as mature vessels (arteriogenesis) in the murine hind limb ischemia, which was confirmed by double staining with endothelial marker and pericytes marker respectively^[22].

The VEGF, TGF- β and PDGF-BB, have a significant effect as pro-angiogenic stimulators. Evidence shows that PDGF-BB has a potential as arteriogenic factor, promoting differentiation of endothelial cells^[17,23]. VEGF is known to trigger post-ischemia neovascularization^[24], and TGF- β enhances cell mitosis^[25]. Other reports, however, demonstrated that many growth factors, such as TGF- β and PDGF-BB, inhibit the angiogenic ability of bFGF^[26]. These studies evaluated the angiogenic impact using combined solutions of growth factors. Within growth factors, PDGF-BB is the one that allows blood vessels to grow functionally^[27,28]. According to this fact, multiple releases of prostaglandin F₂ alpha metabolite and bFGF will improve the maturation of blood vessels. It is also demonstrated that the mixed release of VEGF and PDGF promoted the maturation of newly created blood vessels against VEGF release alone^[29].

VEGF is the principle stimulatory factor of angiogenesis after ischemia^[30]. However, VEGF enhances the creation of unstable capillaries^[31]. It promotes mural cell accumulation, presumably through the release of PDGF-BB. It also causes endothelial cell proliferation and migration, resulting in capillary sprouting or angiogenesis. Lastly, it recruits hematopoietic stem cells to ischemic site from bone marrow *via* circulation.

Basic FGF and PDGF are chemoattractants to smooth

muscle cells. Those are also causes of growth of smooth muscle cell as well as enlargement of vessel (formation of mature vessels or arteriogenesis). These stem cells produce a capillary plexus and eventually form mature vessels. All of these together cause formation of new vessels for vascular supply in ischemic limbs. So, combined administration of different growth factors may lead to potentially therapeutic angiogenesis^[31,32]. PDGFR-beta are needed for vascular stabilization by gathering of mesenchymal progenitors. Absence of PDGF leads to fragile neovasculature^[33], indicating that PDGF-BB has potent arteriogenic effect after ischemia.

Insulin-like growth factor-1 (IGF-1) triggers angiogenesis and myogenesis, the pro-angiogenic impact, however, seems to be less efficient than that of other angiogenic factors^[34]. Finally stromal cell-derived factor 1 (SDF-1) has direct or indirect (*via* certain secondary cytokines) effects on endogenous angiogenesis^[35]. There is also cross talk between VEGF and bFGF; bFGF and PDGF-BB to induce post-ischemia angiogenesis^[36]. Finally, inhibition of Ang1-Tie2 signaling suppresses angiogenic ability of the PRP *in vivo* and PRP-induced angiogenesis *in vitro*.

Experimental evidence

Inspite of a large amount of evidence on PRP's usefulness, limited work has been conducted using PRP in myocardium.

Gallo *et al.*^[37] evaluated histological and morphological impact of the injection of PRP in ischemic sheep myocardium. Noteworthy was the formation of new blood vessels in hematoxylin-eosin-stained sections and factor VIII in PRGF-treated myocardia. According to this report, implantation of platelet growth factors in previously infarcted sheep hearts promoted neovascularization.

Hargrave *et al.*^[38] utilized the technique of nanosecond pulsed electric fields (nsPEF) in order to determine the efficiency of a protocol involving the *in vivo* treatment of the ischemic and reperfused myocardial cells in culture with PRP in rabbits. The left ventricle had faster contraction/relaxation rate and the size of the infarct was diminished in PRP-treated hearts compared to saline-treated. Mitochondrial depolarization and reactive oxygen species (ROS) production were reduced in PRP-treated cells. These facts show that PRP contributes in cardiac protection by stabilizing the mitochondria and reducing ROS generation of the ischemic-reperfused heart.

Mishra *et al.*^[39] used permanent ligation, in order to find out whether PRP, enhances cardiac function in an ischemia-reperfusion model as measured by left ventricular ejection fraction (LVEF).

Compared with phosphate-buffered saline (PBS) controls, PRP-treated animals had a higher LVEF after ischemia, while PRP-treated animals who underwent ischemia-reperfusion had higher LVEF after ischemia. Histology revealed increased granulation in the control group vs the PRP group. In the same time, magnetic resonance imaging (MRI) revealed a positive impact

Table 1 Summary of the effects of platelet-rich plasma in ischemic heart disease

Ref.	Type of study	Animal model	Delivery method	Effect
Gallo <i>et al</i> ^[37]	Experimental	Sheep	Implantation	Increased formation of new vessels
Hargrave <i>et al</i> ^[38]	Experimental	Rabbit	Intramyocardial injection	Reduced reactive oxygen species generation Stabilized the mitochondria of the ischemic/reperfused heart
Mishra <i>et al</i> ^[39]	Experimental	Murine (Mouse)	Intramyocardial injection	Higher left ventricular ejection fraction after ischemia
Vu <i>et al</i> ^[40]	Experimental	Porcine	Intramyocardial injection	Attenuated adverse cardiac remodeling
Yu <i>et al</i> ^[41]	Experimental	Murine (Rat)	Intramyocardial injection	Decreased infarct size Increased ventricular wall thickness Improved cardiac function and reperfusion
Li <i>et al</i> ^[42]	Experimental	Murine (Rat)	Intramyocardial injection	Limitation of ventricular expansion, Attenuated myocardial hypertrophy in the noninfarct region Facilitated angiogenesis and arteriogenesis in the infarct.
Sun <i>et al</i> ^[43]	Experimental	Murine (Rat)	Intramyocardial injection	Improved LV performance
Wehberg <i>et al</i> ^[10]	Clinical	-	Intramyocardial injection	More efficacious at relieving angina Improved myocardial function

of PRP on left ventricular function in both ligation and ischemia/reperfusion murine model.

Vu *et al*^[40] attempted a translational, large-scale restorative but minimally invasive approach in a porcine model, aiming at both structurally stabilizing the LV wall and improving function following ischemic injury.

In this study, a combination of PRP, anti-oxidant and anti-inflammatory factors with intramyocardial injection of hydrogel had the potential to structurally and functionally enhance the injured heart muscle while attenuating adverse cardiac remodeling after acute myocardial infarction.

Yu *et al*^[41] conducted a study in order to investigate the impact of direct myocardial injection of PRP on cardiac function, ventricular remodeling and myocardial perfusion in rats. EF was significantly higher and myocardial perfusion significantly improved in the PRP group. Histological examination also confirmed that PRP treatment can decrease infarct size, increase ventricular wall thickness and improve cardiac function.

Li *et al*^[42] demonstrated that a platelet-mediated paracrine effect may accelerate the healing process after myocardial infarction in rats. According to this experimental protocol, implantation of thrombin-activated PRP into the ischemic myocardium lead in enhancement of ventricular remodeling and accelerated repair, as shown through the limitation of ventricular expansion, facilitation of neovascularization, arteriogenesis in the infarct and attenuation of myocardial hypertrophy in the noninfarct part.

Sun *et al*^[43] reported that adipose-derived mesenchymal stem cells (ADMSC) in a platelet-rich fibrin (PRF) scaffold were superior to direct ADMSC injection in enhancing LV function and diminishing LV remodeling in a post-MI animal model.

PRP and TMR

TMR induces a reconfiguration of the microcirculation, with blood shunted from epicardial to endocardial areas. Current literatures propose a synergistic effect among TMR and exogenously delivered growth factors.

Wehberg *et al*^[10] assessed the impact of PRP intramyocardial injection combined with TMR. Angina relief was similar in both groups (TMR-alone and TMR + PRP); the TMR + PRP group, however, had a decreased average angina score and more were angina free compared to the TMR-alone group. EF improved significantly in the TMR + PRP group compared to the TMR-alone group. This study suggested that intramyocardial injection of PRP and TMR may be more effective at treating angina and enhancing heart function than TMR alone.

All above-mentioned studies are summarized in Table 1.

CONCLUSION

While stem-cell therapies and cellular reprogramming hold promise, the use of PRP emerges as an additional modality for repairing cardiac muscle.

Development of tissues is based on accurate coordination among epithelial, mesenchymal and endothelial morphogenesis. Furthermore, growth factor-induced angiogenesis is significant in organ regeneration after ischemia. Recent tissue engineering researches suggest that cells and PRP-derived growth factors together into biomaterials have opened new horizons in the myocardial infarction treatment.

PRP should be investigated for its potential regenerative properties and its use as a therapeutic modality for ischemic myocardium.

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