Pharmacological and Cardioprotective Interventions

Potent Long-Term Cardioprotective Effects of Single Low-Dose Insulin-Like Growth Factor-1 Treatment Postmyocardial Infarction

Summary: Chronic heart failure after ST-segment–elevation myocardial infarction (MI) remains a public health burden despite current percutaneous interventional and pharmacological treatment. Strategies to reduce infarct size are needed but remain a therapeutic challenge. Insulin-like growth factor-1 (IGF-1) is a known central regulator of cardiac function with prosurvival, proliferative, and differentiation effects in the heart. However, clinical trials of IGF-1-related compounds in heart failure were abandoned >1 decade ago because of the side-effect profile of chronically administered drug and presumed therapeutic inefficacy. Importantly, IGF-1 has never been tested clinically for its acute prosurvival effects in the context of MI. The current study examined the potency of IGF-1 at a lower dose and as a single injection that would not be expected to cause the side-effects manifested in previous IGF-1-related studies. Moreover, the authors treated large MIs in pigs in the reperfusion phase to more closely model the scale, hemodynamic, and functional parameters seen in the clinical ST-segment elevation MI setting. They show here that a 1-time bolus of low-dose IGF-1 has potent acute cardioprotective effects on cardiomyocytes within the infarct zone associated with activation of classic prosurvival signaling pathways and that acute cell salvage translates into long-term preservation of cardiac structure and function without the significant side-effects seen in previous trials. These data suggest that low-dose IGF-1 may be a useful adjunctive therapy for acute MI. Further study is warranted to investigate whether low-dose IGF-1 is a safe and effective treatment, particularly in patients with large MIs at risk of developing long-term heart failure.

Conclusions: One-time LD-IGF-1 effects potent acute myocardial salvage in a preclinical model of left anterior descending artery occlusive MI, extending to long-term benefits in MI size, wall structure, and function and underscoring its potential as an adjunctive therapeutic agent.1

Impact of a Single Intracoronary Administration of Adiponectin on Myocardial Ischemia/Reperfusion Injury in a Pig Model

Summary: Acute myocardial infarction (AMI) is a major cause of death in industrial countries. Reperfusion therapy immediately after onset of AMI has been shown to limit infarct size and preserve cardiac function. However, successful reperfusion determined by coronary angiography is not always accompanied by adequate reperfusion at the heart tissue level and improvement of cardiac dysfunction. Therefore, it is reasonable to develop a promising adjunctive therapy in patients with AMI. Adiponectin plays a protective role in the development of obesity-linked disorders such as AMI. Here, the authors explored the effectiveness and feasibility of adiponectin treatment for AMI in a preclinical animal model that closely reproduces the current procedural management of AMI in humans. The left anterior descending coronary artery was occluded in pigs for 45 minutes and then reperfused for 24 hours. Recombinant adiponectin protein was given as a bolus intracoronary injection during ischemia. A 1-time administration of adiponectin reduced myocardial infarct size and improved cardiac function after ischemia-reperfusion in this preclinical pig model and was accompanied by suppression of inflammation, apoptosis, and oxidative stress. A single intracoronary injection of adiponectin during percutaneous coronary intervention could be a useful adjunctive therapy for AMI.

Conclusions: These data suggest that adiponectin protects against ischemia-reperfusion injury in a preclinical pig model through its ability to suppress inflammation, apoptosis, and oxidative stress. Administration of intracoronary adiponectin could be a useful adjunctive therapy for acute myocardial infarction.2

Erythropoietin in Patients With Acute ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: A Randomized, Double-Blind Trial

Summary: Experimental studies have demonstrated a protective role of erythropoietin during ischemic and reperfusion in the heart, with a reduction in infarct size and apoptosis. This randomized, double-blind, clinical trial investigated the effect of short-term erythropoietin in patients with acute myocardial infarction. One hundred thirty-eight patients received either erythropoietin or placebo intravenously during percutaneous coronary intervention, as well as 24 and 48 hours later. The primary end point, left ventricular ejection fraction after 6 months, measured by MRI, showed no differences between groups. Left ventricular ejection fraction, end-systolic end-diastolic volumes, and infarct size were also similar. Moreover, the cumulative 6-month rates of death, recurrent myocardial infarction, stroke, or target vessel revascularization in the 2 groups were not different. The present clinical study could not confirm any benefit of short-term erythropoietin treatment for patients with acute myocardial infarction.

Conclusions: In patients with acute ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention,
Cardioprotective Effects of Ischemic Postconditioning in Patients Treated With Primary Percutaneous Coronary Intervention, Evaluated by Magnetic Resonance

Summary: Acute restoration of myocardial blood flow with primary percutaneous coronary intervention in itself jeopardizes the cardiomyocytes. In some cases, this phenomenon accounts for 50% of the final size of the myocardial infarction. Therefore, it is important to look for means to protect the myocardium during reperfusion. Ischemic postconditioning has been suggested as such a method. Few small studies have demonstrated a beneficial effect of ischemic postconditioning, but the effect on the final infarct size only has been assessed in 38 patients with perfusion defect index measured by scintigraphy as a surrogate measurement for the infarct size. Ischemic postconditioning is simple, cheap, not time consuming, and a safe adjuvant to primary percutaneous coronary intervention, and the method can be introduced in the catheterization laboratories almost overnight. However, the possible introduction of this modality in the authors’ view should be demonstrated in a substantial number of patients before taken into consideration. With the use of cardiac magnetic resonance to measure final infarct size in 86 patients, this article demonstrates a decrease in infarct size of 18% with ischemic postconditioning. Being the first to evaluate effect of ischemic postconditioning by cardiac magnetic resonance, the authors believe that this study makes an important contribution. Furthermore, it is the first, to the authors’ knowledge, to suggest an effect on functional status evaluated by New York Heart Association classification.

Conclusions: Mechanical postconditioning reduces infarct size in patients with ST-segment–elevation myocardial infarction treated with primary percutaneous coronary intervention. The impact of mechanical postconditioning seems to be independent of the size of myocardium at risk.

Stromal Cell-Derived Factor-1 Retention and Cardioprotection for Ischemic Myocardium

Summary: The current standard of care for myocardial infarction (MI) includes early reperfusion to limit cardiomyocyte death and subsequent use of β-blockers and other medications to prevent cardiac remodeling and reduce future events. Despite the success of current therapies, new treatments for MI are needed because many patients with MI still have development of heart failure. The authors explored the possibility that protease-resistant stromal cell-derived factor-1 (SDF-1) could represent a new treatment to prevent heart failure after MI. SDF-1 is a small protein that can attract endothelial progenitor cells and increase blood vessel formation. However, SDF-1 is rapidly cleaved and inactivated by proteases that are present in the inflammatory environment of infarcted myocardium. The results of this study showed that BM-MNC implantation was an independent predictor of prevention of major amputation and that hemodialysis and diabetes mellitus were independent predictors of major amputation. In the present study, the authors confirmed that BM-MNC implantation is safe and effective in patients with CLI during long follow-up periods. Patients with Buerger disease, but not PAD patients who have diabetes mellitus and are undergoing hemodialysis, are eligible for treatment with BM-MNC implantation. Future large-scale studies with a randomized, double-blinded, and placebo-controlled design are needed to confirm the effects of cell therapy on the clinical symptoms and cardiovascular outcomes in patients with CLI.

Conclusions: These findings suggest that BM-MNC implantation is safe and effective in patients with CLI, especially in patients with Buerger disease.

Cell Therapy

Autologous Bone Marrow Mononuclear Cell Implantation Reduces Long-Term Major Amputation Risk in Patients With Critical Limb Ischemia: A Comparison of Atherosclerotic Peripheral Arterial Disease and Buerger Disease

Summary: Preclinical studies and clinical trials have shown that cell therapy, including autologous bone marrow mononuclear cell (BM-MNC) implantation, improves clinical symptoms and increases collateral vessel formation in patients with peripheral arterial disease (PAD). Unfortunately, there have been few studies on the long-term follow-up of clinical symptoms and events such as major amputation and mortality, and there has been no information on predictors of major amputation with BM-MNC implantation. The authors found that autologous BM-MNC implantation decreased the rate of major amputation in patients with critical limb ischemia (CLI), both patients with atherosclerotic PAD and patients with Buerger disease, compared with that in control patients. After BM-MNC implantation, the amputation-free rate was markedly worse in patients with atherosclerotic PAD than in patients with Buerger disease. Overall, the survival rate was also markedly worse in patients with atherosclerotic PAD than in patients with Buerger disease.

Conclusions: These findings suggest that BM-MNC implantation is safe and effective in patients with CLI.
attractive approach to improve left ventricular function and remodeling in addition to interventional and medical therapy. The randomized, placebo-controlled, double-blind REPAIR-AMI trial has demonstrated a significant greater contractile recovery and improvement of microvascular function in the BMC treated patients compared with the placebo group after 4 months. The current analysis with extended 2-year follow-up confirms the excellent safety profile of intracoronary BMC administration compared with placebo, demonstrating a significant reduction in the cumulative end points of death, myocardial infarction, and revascularization as well as death, recurrence of acute myocardial infarction, and rehospitalization for heart failure. In parallel, there was no evidence of increased restenosis or atherosclerotic disease progression after BMC therapy nor any evidence of increased ventricular arrhythmias or neoplasms. In addition, in a subgroup of patients undergoing MRI imaging, regional left ventricular contractility of the infarcted segments was significantly better in the BMC group compared with the placebo group, suggesting that beneficial interference of BMC therapy with remodeling processes may contribute to improved clinical outcome. These findings make it intriguing to speculate that intracoronary application of BMC may be associated with improved regional contractility, leading to a better clinical outcome at 2-year follow-up. However, larger randomized, adequately powered outcome trials are urgently needed to assess the effects of progenitor cell therapy on prognosis in patients with acute myocardial infarction.

Conclusions: Intracoronary administration of BMC is associated with a significant reduction of the occurrence of major adverse cardiovascular events maintained for 2 years after acute myocardial infarction. Moreover, functional improvements after BMC therapy may persist for at least 2 years. Larger studies focusing on clinical event rates are warranted to confirm the effects of BMC administration on mortality and progression of heart failure in patients with acute myocardial infarction.

Regulation of Circulating Progenitor Cells in Left Ventricular Dysfunction

Summary: The development of left ventricular dysfunction has many important systemic manifestations. Neurohumoral activation is a key mediator of cardiac decompensation. This report describes a novel association between the development of left ventricular dysfunction and the regulation of circulating progenitor cells in the blood. The authors identified that circulating hematopoietic progenitor cells are decreased in a canine model of severe left ventricular dysfunction and that this decrease correlated with aldosterone levels. In additional models utilizing mineralocorticoid delivery, similar changes were seen. These decreases were associated with evidence of cellular senescence in these cells. Because these circulating progenitors may be important mediators of multipotent cardiovascular and hematologic regeneration, these findings are significant. The potential clinical importance of these findings is evident from pathophysiologic and therapeutic perspectives. As neurohumoral mediators of oxidative stress, the effects of mineralocorticoid activation on progenitor cells may define a mechanism for the decreased numbers of cells identified in clinical studies of heart failure. Additionally, one of the beneficial effects of aldosterone inhibition may be manifested through effects on progenitor cells. The findings presented in these large animal studies may provide new concepts by which to consider the development and treatment of left ventricular dysfunction.

Conclusions: This is the first study to demonstrate that mineralocorticoid excess, either endogenous or exogenous, results in reduction in hematopoietic precursor cells. These data suggest that mineralocorticoids may induce accelerated senescence of progenitor cells, leading to their reduced survival and decline in numbers.

Intramyocardial Bone Marrow-Derived Mononuclear Cell Injection for Chronic Myocardial Ischemia: The Effect on Diastolic Function

Summary: Bone marrow cell therapy has emerged as a potential therapeutic option for patients with chronic ischemic heart disease. In patients with chronic myocardial ischemia, improvements in myocardial perfusion and left ventricular systolic function have been documented after intramyocardial bone marrow cell injection. However, only limited data are available on the effect of bone marrow cell injection on diastolic function. The current substudy of a randomized trial evaluated the effect of intramyocardial bone marrow cell injection on diastolic function in patients with chronic myocardial ischemia. In 50 patients (25 in the bone marrow cell group, 25 in the placebo group), diastolic function was evaluated using standard echocardiography, speckle tracking strain analysis, and MRI (in a subset of patients). At 3 months follow-up, modest improvements were observed in the parameters of myocardial relaxation and filling pressure in bone marrow cell-treated patients. In placebo-treated patients, no changes were detected in the parameters of diastolic function. These findings indicate that intramyocardial bone marrow cell injection is associated with a beneficial effect on diastolic function in patients with chronic myocardial ischemia. The results of this study extend previously reported observations that bone marrow cell injection improves myocardial perfusion, left ventricular systolic function, and anginal symptoms in patients with chronic myocardial ischemia.

Conclusions: The current study demonstrates that intramyocardial bone marrow cell injection is associated with a beneficial effect on myocardial relaxation and filling pressures in patients with chronic myocardial ischemia.

Left Ventricular Assist Devices

Central and Peripheral Blood Flow During Exercise With a Continuous-Flow Left Ventricular Assist Device: Constant Versus Increasing Pump Speed: A Pilot Study

Summary: The present study shows that patients with end-stage heart failure provided with an axial-flow left ventricular assist device have significant increases in cardiac output and leg blood flow even during strenuous cycling but that cerebral perfusion is compromised. In these patients, cerebral perfusion at rest is only 80% of what is seen in normal subjects. During exercise, cerebral perfusion decreases, whereas normal subjects show a substantial elevation in cerebral perfusion. In a randomized fashion, with patients being their own controls, the authors evaluated the effect of increasing left ventricular assist device pump speed in parallel with exercise and found that increased pump speed increased cardiac output during light exercise and improved cerebral perfusion. Although not achieving normalization of cerebral perfusion, the latter nonetheless increased during exercise as seen in normal subjects. In light of these pilot results, the authors think that it might be advantageous during exercise to increase the pump speed of continuous flow left ventricular assist devices.

Conclusions: With maximal exercise, the axial-flow left ventricular assist devices supports near-normal increments in cardiac output and leg perfusion, but cerebral perfusion is poor. Increased pump speed augments cerebral perfusion during exercise.

Left Ventricular Assist Device Therapy in Patients With Restrictive and Hypertrophic Cardiomyopathy

Summary: Patients with end-stage restrictive or hypertrophic cardiomyopathy have a dismal prognosis. The only option that may increase survival in these patients is heart transplantation. However, because of continued donor shortages, a long transplant waiting time, and development of irreversible pulmonary hypertension, many of these patients die of irreversible heart failure and incur high mortality.
Continuous-flow left ventricular assist devices (LVAD) have been recognized to improve outcomes in patients with advanced dilated or ischemic cardiomyopathy who are failing maximal medical treatment; however, patients with end-stage restrictive cardiomyopathy or hypertrophic cardiomyopathy were not represented in these LVAD trials. This is the first report to show the feasibility of continuous axial-flow pumps in patients with end-stage restrictive or hypertrophic cardiomyopathy. However, these patients can incur more right heart failure and central venous catheter-related infections. There are also numerous technical challenges with implantation of LVAD that are unique to these patients, including the need for myomectomy to enable inflow cannula implantation and the increased risk for suck-down events. This single-center experience lacks the statistical power to make conclusions regarding survival and these data cannot necessarily be extrapolated to other centers. This feasibility study should prompt prospective clinical trials or a national registry to assess whether LVAD therapy can be used routinely as destination therapy or bridge to transplantation in this challenging group of patients.

Conclusions: These preliminary data show that patients with end-stage heart failure caused by restrictive cardiomyopathy or hypertrophic cardiomyopathy may benefit from continuous-flow LVAD therapy. This small study suggests that mortality is comparable with those patients who have dilated or ischemic cardiomyopathy, but right heart failure, prolonged inotropic use, and central venous catheter infections are more common in patients with restrictive cardiomyopathy and hypertrophic cardiomyopathy who were treated with LVAD. Because of the small numbers the differences should be interpreted cautiously, and prospective clinical trials would be required to recommend this therapy for these patients as bridge to transplantation or destination treatment.12

Patient-Reported Outcomes in Left Ventricular Assist Device Therapy: A Systematic Review and Recommendations for Clinical Research and Practice

Summary: Evidence suggests that patients receiving left ventricular assist device (LVAD) therapy experience an improvement in health status over time, independent of device type and setting. However, although their physical disability becomes less prominent after implantation, many patients experience difficulties with psychological adjustment, especially early after implantation, which is associated with worrying about LVAD malfunction, complications, waiting for a donor heart, and being away from family. Furthermore, overall functioning of LVAD patients is still more impaired compared with transplant recipients on physical, social, and emotional functioning. Extensive information on patient-reported outcomes in LVAD patients is limited, with many of the existing studies having methodological shortcomings. To advance the field of LVAD research and to optimize the care of an increasingly growing population of LVAD patients, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on patient-reported outcomes.

Conclusions: There is a paucity of studies on the patient perspective of LVAD therapy. To advance the field of LVAD research and to optimize the care of an increasingly growing population of LVAD patients, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on patient-reported outcomes.13

The Development of Aortic Insufficiency in Left Ventricular Assist Device-Supported Patients

Summary: Severe aortic insufficiency (AI) after left ventricular assist device (LVAD) implantation can lead to ineffective cardiac output and heart failure symptomatology. In this analysis, echocardiograms (n=315) from 78 subjects supported with a HeartMate-XVE (n=25) or HeartMate-II (n=53) LVAD were reviewed, and AI severity was quantified at baseline and postoperatively. AI was noted to progress with the duration of LVAD support. Correlates of worsening AI post-LVAD were female sex, smaller body surface area, and HeartMate-II model. AI also was worse in subjects with increasing aortic sinus diameters postoperatively or an aortic valve that did not fully open on systole. Further studies are needed to determine whether progressive AI has a clinical impact on long-term LVAD support and whether interventions may be undertaken to retard its development.

Conclusions: AI progresses over time in LVAD-supported patients. As we move toward an era of long-term cardiac support, more studies are needed to determine the clinical significance of these findings.14

Incomplete Recovery of Myocyte Contractile Function Despite Improvement of Myocardial Architecture With Left Ventricular Assist Device Support

Summary: Sustained recovery of the failing left ventricle (LV) during pressure-volume unloading with an LV assist device (LVAD) is rare and may be related to incomplete recovery of sarcomeric contractility. In this study, the authors evaluated contractility and biochemistry at the most fundamental contractile level of the heart: the sarcomere. Force development in muscle is the result of actin and myosin interactions and cross-bridge cycling, processes regulated by modifications of the sarcomeric contractile proteins. Sarcomeric contractility was assessed by measuring isometric forces on skinned LV myocytes from patients with nonischemic cardiomyopathy before and after LVAD placement. The authors found that contractile dysfunction at the level of the sarcomere was present in failing hearts and paralleled organ-level contractile dysfunction as assessed by ejection fraction. Furthermore, there were improvements in LV and myocyte size with partial recovery of sarcomeric force after LVAD placement, but LVAD-supported myocyte forces were still half of that seen in nonfailing hearts. The persistence of sarcomeric contractile dysfunction may be one of the reasons most LVADs cannot be explanted in clinical practice. In assessing for biochemical alterations of sarcomeric proteins after LVAD implantation, there were changes in troponin-I phosphorylation that may account for some of the improvement in sarcomeric force, but the other sarcomeric contractile proteins revealed minimal biochemical changes, suggesting that other interventions (in addition to mechanical unloading with an LVAD) may be needed to optimize troponin-I phosphorylation, modify other sarcomeric protein biochemistry, or both to further enhance sarcomeric and organ-level recovery.

Conclusions: There is significant improvement in LV and myocyte size with LVAD, but there is only partial recovery of ejection fraction and myocyte contractility. LVAD support was associated only with biochemical changes in troponin I, suggesting that alternate mechanisms might contribute to contractile changes after LVAD and that additional interventions may be needed to alter biochemical remodeling of the sarcomere to further enhance myofilament and organ-level recovery.15

Acquired Von Willebrand Syndrome in Patients With an Axial-Flow Left Ventricular Assist Device

Summary: Rotary blood pumps replaced pulsatile displacement pumps in long-term left ventricular support. Their mechanical stability combined with miniaturization of the pump was favorable compared with the first-generation pulsatile devices. However, with prolongation of support times, bleeding episodes became a limitation of this therapy. In addition to epistaxis, gastrointestinal bleeding from the small bowel was seen in these patients at an incidence not known in patients with pulsatile devices. The finding of acquired von Willebrand syndrome (vWS) in all of the authors’ patients being supported with the HeartMate-II axial-flow device may contribute to the pathophysiologic understanding of this clinical problem. In addition to intended anticoagulation and platelet inhibition, primary hemostasis is impaired by acquired vWS. Although there is no consensus yet on how to treat patients with bleeding episodes, it is helpful to know that in the case of gastrointestinal bleeding the source is likely to be found in the small intestine and that treatment of acquired vWS may be required. Recommendations for anticoagulation for patients with the HeartMate-II device were revised several times.
in the past to lower international normalized ratio levels to prevent bleeding. Patients should be advised that epistaxis and potential gastrointestinal bleeding are associated with long-term ventricular support. Physicians are encouraged to check for vWS also in patients with implanted rotary blood pumps other than the HeartMate II.

Conclusions: A diagnosis of vWS type 2 was established in all patients after LVAD implantation, and bleeding events confirmed this finding. Reversibility of this condition was found after removal of the device.16

Echocardiographic Variables After Left Ventricular Assist Device Implantation Associated With Adverse Outcome

Summary: A successful acute outcome after left ventricular assist device (LVAD) implantation depends on patient selection and the technical difficulty of surgery. However, how we treat our patients and LVAD settings may affect the patient outcome beyond the post-surgical period. In the present study, the authors retrospectively analyzed various variables in echocardiographic examinations performed 30 days after LVAD implant for their association with a compound end point (90-day mortality, readmission for heart failure, or New York Heart Association class III or higher at the end of the 90-day period). We found that mortality and persistent heart failure after LVAD surgery are predominantly associated with echocardiographic variables assessing the efficiency of unloading of the left ventricle and atrium, and those assessing right-ventricular function. The only right-ventricular variable significantly associated with adverse outcome was a decreased tissue Doppler velocity of the lateral tricuspid annulus. The variables assessing LV unloading, associated with adverse outcome were a high estimated left atrial pressure (>15 mm Hg) and a short mitral inflow deceleration time divided by the E wave velocity (<2 ms/[cm/s]). An interventricular septum deviated to the left was associated with worse outcome as well. In conclusion, echocardiographic variables suggestive of efficient but not excessive LV unloading are associated with favorable mid- and long-term outcome after LVAD surgery.

Conclusions: Mortality and heart failure after LVAD surgery appear to be predominantly determined by echocardiographic evidence of inefficient unloading of the left ventricle and persistence of right-ventricular dysfunction. Increased estimated LA pressure and short mitral deceleration index are associated with worse mid-term outcome. Leftward deviation of the septum is associated with worse outcome as well.11

References
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