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Mitochondrial Transplantation's Effects on Cardiac Output

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ABSTRACT

The cardiovascular diseases (CVDs) are the most prevalent causes of death in the world with limited treatment of severe myocardial injury and end stage heart failure. According to the recent experimental and early clinical data, the transplantation of mitochondria, that is, the direct delivery of functioning mitochondria to the inflicted myocardium, may potentially restore bioenergetics, minimize oxidative stress and enhance cardiac functions. This systematic review, summarizes both preclinical and clinical evidence demonstrating the effectiveness, mechanism, and translational issues of mitochondrial transplantation in the heart. Based on the PRISMA-directed methodology the literature reviews are relevant, and were identified in PubMed, Embase, Scopus, Web of Science, and ClinicalTrials.gov where there was consistent improvement in the restoration of adenosine triphosphate (ATP), reduction in oxidative harm, increased left ventricular ejection fraction (LVEF), and structural recovery in both small and large animal models and in pediatric trials. Mitochondrial internalization through mitochondrial macropinocytosis, followed by fusion with native mitochondria, and mitophagy and biogenesis signaling are proposed to happen as suggested by mechanistic findings. Although the result is promising, there is still a challenge on methods of delivery, optimization of dosage, long term incorporation, and classification by the regulatory authorities. This paper concludes that mitochondrial transplantation is a new paradigm of subcellular regenerative therapy and it should be studied by standardized procedures and controlled clinical trials to prove the safety and efficacy

Keywords: *Mitochondrial Transplantation, Cardiovascular Disease, Cardiac Output, Myocardial Reperfusion, Myocardial Ischemia*

INTRODUCTION

Cardiovascular diseases (CVDs) are the most commonly encountered causes of morbidity and mortality in the world due to the approximate 17.9 million deaths each year (World Health Organization, 2021). The specific therapies to use on patients suffering severe myocardial injury or end-stage heart failure is limited despite the innovations in pharmacological therapy, interventional cardiology, and surgery. One of the obstacles to myocardial recovery is the irreversible damage of cardiomyocyte mitochondria, which prevents energy metabolism, augmented oxidative stress, and initiated apoptotic pathways (Ong et al., 2014). Though it is contradictory that mitochondrial transplantation has recently become an innovative treatment approach that directly delivers bioenergetics to ischemic or dysfunctional cardiac tissue by the transplantation of viable and functional mitochondria (Masuzawa et al., 2013; McCully et al., 2017).

This research encompasses the idea of cardiovascular medicine as a revolutionary form of therapeutic intervention through mitochondrial transplantation. Mitochondrial transplantation also treats the underlying cause of myocardial dysfunction, i.e., compromised mitochondrial integrity and bioenergetic collapse, contrary to conventional treatments which mainly relieve symptoms or do not worsen the situation (Emani & McCully, 2018). The initial studies and experimental results indicate that transplantation of autologic mitochondria can enhance the contractility of the myocardium, decrease the area of infarction, and provide cardiac function (Shanmughapriya et al., 2020). This paper analyzes the role of mitochondrial transplantation to improve the gap between experimental success and clinical practice in managing cardiovascular diseases by systematic analysis of clinical and preclinical evidence.

On the basis of literature reviews it is observed that mitochondrial transplantation as a treatment modality of cardiovascular disease with special attention to ischemia-reperfusion injury, myocardial infarction, and pediatric heart failure. This study includes the information on the animal models, human pilot studies and developing clinical trials from the past. In order to add depth, some literature reviews are analyzed, and this offers practical insights into the application of mitochondrial transplantation in real-life cardiac interventions.

Although the topic of the main interest will be cardiovascular pathology, some cross-disciplinary results of neurological and metabolic diseases will be briefly taken into account in this study
because this offers mechanistic insights on cardiac applications.

The overall issue that is aimed to be addressed in this paper is to assess the potential therapeutic application of mitochondrial transplantation in restoring failing hearts and reducing the cardiovascular disease burden.

This study investigates what intensity of effect is mitochondrial transplantation in the treatment of cardiovascular diseases? It is a compilation of results of various experimentation, clinical research, and literature reviews to provide a holistic summary of existing knowledge. Although there are a number of narrative and systematic reviews on the subject of mitochondrial therapy (e.g., Cowan et al., 2016; Kesner and Hoppel, 2021), this paper is a systematic review to evaluate the efficacy and applicability in practice.

This study places mitochondrial transplantation in the context of the overall cardiovascular therapeutics, thereby contributing to the development of the current discourse of regenerative medicine and can serve later to guide translational research, clinical trial design, and therapeutic design.

Literature Review

The product of the heart rate and stroke volume is still known as the cardiac output which is the most basic determinant of the systemic perfusion and delivery of oxygen to tissues. Depressed cardiac output, in other afflictions like ischemic heart disease, cardiac arrest and genetic cardiomyopathies, is the factor that causes morbidity and mortality in spite of new advances in reperfusion therapy, mechanical support and medications. The fact that cardiac contraction is an energy-demanding phenomenon gives much promise to the therapies that directly restore or enhance myocardial bioenergetics (Shin et al., 2019).

Mitochondrial transplantation, where viable exogenous mitochondria are transferred into injured myocardium has become a new method of restoring energy metabolism, oxidative stress, and apoptosis. The method, which was initially shown in large-animal ischemia-reperfusion and subsequently piloted in pediatric cardiac surgery (Emani et al., 2017), has been indicated in a variety of preclinical studies. The literature review is a synthesis of recent discoveries in mitochondrial transplantation and its effect on cardiac output which incorporates mechanistic understanding, delivery innovations, safety issues, and translational opportunities.

Mitochondrial Transplantation and Resuscitation of Cardiac Output.

It was Aoki et al. (2025) who demonstrated the first evidence of mitochondrial transplantation as a way of enhancing cardiac output in a model of rat cardiopulmonary resuscitation (CPR). There was severe depressive left ventricular ejection fraction (LVEF) in rats that were put into cardiac arrest and resuscitated. Isolated mitochondria intramyocardial delivery increased LVEF, decreased oxidative stress indicators, and survival in comparison with untreated controls.

Electron transmission microscopy showed that there was restoration of myofibril orientation and augmentation of the density of mitochondrial cristae, structural indicators of restored contractility.

There is a direct correlation between recovery of mitochondrial respiratory complexes, II and IV, and functional improvement. Both Aoki et al. (2025) and Shin et al. (2025) found that myocardial ATP content increased after transplantation, which is a mechanistic evidence of the recovery of the oxidative phosphorylation capacity by transplanted organelles. This vigorous resuscitation is vital since the failure of myocardium is characterized by ATP deficiency and disconnect between excitation and contraction.

Functional recovery is also supported by the use of biochemical endpoints. Aoki et al. (2025) showed a lower level of malondialdehyde and an increased level of superoxide dismutase (SOD) activity, which is an evidence of a decreased oxidative stress. Such alterations were accompanied by reduced cardiomyocyte apoptosis. All these data allow developing a causal link: transplantation can restore mitochondrial ultrastructure and bioenergetics, decrease oxidative damage, and preserve viable myocardium that can result in the improvement of cardiac output.

These findings are supported in other preclinical studies of ischemia-reperfusion and infarction. As an illustration, [Ref. Placeholder 1: McCully et al., large animal ischemia-reperfusion model] was able to show the increased stroke volume and the decreased size of the infarct when the hearts of pigs were receiving autologous mitochondria. Interspecies overlap of data enhance the level of translational confidence.

Uptake, Fusion and Quality Control mechanisms.

The success of the mitochondrial transplantation is based on the effective uptake and integration of cells. It was revealed that internalization takes place mainly through macropinocytosis and actin-dependent endocytosis (Pacak et al., 2015; Kami and Gojo, 2020). Mitochondria then go through internalization followed by traffic across endosomal-lysosomal compartments. Although a significant percentage do not undergo degradation and end up in the cytoplasm.

The study by Cowan et al. (2017) was able to support the idea that the transplanted mitochondria are capable of fusing with the endogenous ones, which restores the mitochondrial membrane potential, calcium buffering, and respiratory capacity. The continuity of bioenergetic functioning, as supported by such fusion, and transfer of intact mitochondrial DNA may be facilitated as a consequence of such fusion, and may be required to compensate faulty genomes in diseased cells.

The recent research also brings out the effect of transplanted mitochondria on quality control. Liu et al. (2022) stated that exogenous mitochondria stimulate mitophagy, with a specific removal of injured resident organelles. Jia et al. (2022) also demonstrated that mitochondrial transfer enhances the process of mitochondrial biogenesis through the PGC-1a activation pathway, elevating the number of healthy organelles. These two effects of the organelle turnover guarantee that the transplanted mitochondria do not only carry out instant energy rescue but also extend the functional recovery.

The mechanistic connection to the cardiac output is direct: an increase in mitochondrial density, the increase of calcium cycling, and the recovery of oxidative phosphorylation all increase contractility, and this increases stroke volume and cardiac output.

New Sources and Bioengineered Mitochondria.

Autologous mitochondria (characteristically derived out of skeletal muscle) have proven to be safe and effective in preclinical and clinical applications (Emani et al., 2017). Nevertheless, they can be used only with respect to acute emergencies due to the time required to harvest and isolate them. In order to counter this, other sources and modified mitochondria are being explored.

It was shown by Kim et al. (2025) that the mitochondria formed by stem cells enhanced the contractile activity in the models of Barth syndrome, one of the genetic cardiomyopathies, affected by the failure in the cardiolipin-remodeling processes. These results indicate that intrinsic organelle dysfunction can be fixed by allogenic or engineered mitochondria. A different alternative source that was proposed by Baharvand et al. (2024) is a mitochondria which is derived from platlet and is abundant, has a robust resistance to stress, and can be isolated rapidly.

The goal of bioengineering methods is to increase therapeutic potency. According to Millay & Cowan (2022), one of the reviews covers advances like the modification of mitochondria to become resistant against oxidative stress or inflammation, which may increase their ability to survive ischemic tissue provided superior engraftment and functional integration of the murine models. These inventions are wider in their application and enhance translational viability.

Modalities of Delivery:
Translational Barriers.
One of the main challenges is delivery strategy. Local delivery is guaranteed by intramyocardial injection which is however invasive and not suited in an emergency setting. On the contrary, intracoronary infusion is minimally invasive and can be scaled clinically, yet tends to cause lesser myocardial retention (Kesner & Hsu, 2021). In the porcine models, comparative studies indicate a greater regional engraftment when intramyocardial route is used but a more widespread distribution with intracoronary routes ([Ref. Placeholder 3: Large animal delivery comparison study]).

These trade-offs are to be reconciled by the emerging technologies. Mitochondrial infused scaffolds can absorb and release the mitochondria (Millay and Cowan, 2022). Mitochondrial stability during circulation and targeted delivery is increased by the digestion of nanoparticles ([Ref. Placeholder 4: Wang et al., nanoparticle-facilitated delivery]). Microfluidic systems have been suggested in ex vivo conditioning of mitochondria before transplantation.

Another important parameter is dose optimization. In rodents, Shin et al. (2019) found effective doses at 108109 mitochondria, which were associated with the best improvement of LVEF. Human dose-finding studies have not been done yet which is a critical translational gap. It is also imperative to ensure that the mitochondrial integrity remains intact throughout the isolation, preservation, and delivery of the organelles; damaged organelles might not engraft or even make (2017) no evidence of immune or inflammatory problems in pediatric patients who got mitochondrial transplants during heart surgery. Similarly, Guariento et al. (2020) did not describe any arrhythmias, as well as no post-procedural hemodynamic instability.

Allogeneic transplantation on the other hand increases immunogenicity. Kesner and Hsu (2021) also noted that mitochondrial peptide that is displayed on MHC molecules has the potential to trigger immune responses, which is why immunoprofiling should be done comprehensively in future studies. This warn goes hand in hand with that of Ishikawa et al. who investigated immunological recognition of mitochondrial antigens.

Regulations on mitochondrial therapies are in a flow of change. With these, Millay and Cowan (2022) highlighted the ambiguity in categorizing mitochondria as biologics or cellular therapy, or tissue products. Certain standards concerning the method of isolation, potency tests, and sterile tests are in dire necessity. The harmonization of multi-institutional protocols will facilitate in developing protocols, not only in clinical studies, but also concerning safety and reproducibility.

Comparison to the Other Mitochondrial Treatments.
Mitochondrial transplantation is not to be considered as only the method that focuses on the mitochondrial dysfunction. Small molecule such as SS-31 (elamipretide) stabilizes cardiolipin and improves the mitochondrial activities, whereas antioxidants such as MitoQ inhibit reactive oxygen species ([Szeto et al., SS-31 cardioprotection]; [Smith et al., MitoQ in cardiac ischemia]).

The focus of gene therapies is to enhance transcription factors such as TFAM or it is meant to replace mutations in the mitDNA ([Gammage et al., mtDNA repair in cardiomyopathy]).

In comparison to these approaches, transplantation has the ability to provide intact mitochondria of tomato seedlings that can produce ATP instantly and fulfill the same function. It is however intrusive and challenging technically. Mitochondrial transplantation used in synergy with drugs such as SS-31 or stem cell therapy might be beneficial ([Combination therapy review]).

Despite positive outcomes, multiple issues are yet to be tackled before mitochondrial transplantation becomes a widespread clinical application. To establish the long-term cardiac function, exercise capacity and survivability, large randomized trials are required. Extensive monitoring of immune responses at early-phase should be incorporated in early-phase studies, particularly in allogeneic transplantations.

To recognize the potential mechanics of transplanted mitochondria survival and functioning months or years into the future, long-term research by mechanical means is required.

Noninvasive tracking could be made with advanced imaging methods, such as mitochondrial-targeted PET tracers ([Noninvasive mitochondrial imaging study]).

Translational side the biggest requirement is high speed off-the-shelf mitochondrial products that can be used in acute conditions such as myocardial infarction or cardiac arrest. It will be necessary to develop cryopreservation protocols which preserve the activities of the mitochondria ([Cryopreserved mitochondria viability study]).

Lastly, one has to take into account the moral and social questions. With the relative disappearance of boundaries between tissues, cells, and drugs through organelle-based therapies, questions on patient consent, resources, and just access will emerge ([Bioethics commentary on mitochondrial therapies]).

Transplantation of mitochondrion is a disruptively novel treatment modality of cardiac disease in that it directly compensates underlying bioenergetic defects leading to myocardial injury. There is overwhelming preclinical and early clinical data of improvement in left ventricular ejection fraction, mitochondrial structure and oxidative stress indicators all leading to an increase in cardiac output.

Methodology

Research Design

This paper uses a systematic review, with an embedded study analysis to discuss the therapeutic promise of mitochondrial transplantation in cardiovascular disease. The systematic review allows the whole spectrum of preclinical and clinical evidence to be covered, and the literature review analysis allows the in-depth coverage of individual reports giving contextual details.

This is an efficient method because mitochondrial transplantation is an emergent treatment in which evidence exists at only the animal models, pilot and case series. The combination of the general evidence synthesis and specific real-life applications allow determining not only what is familiar, but also how results have been created, and substantiated.

Literature Search

Searched databases are PubMed, Embase, Scopus, Web of Science, and ClinicalTrials.gov, search key words were “mitochondrial transplantation" OR "mitochondrial transfer" OR "organelle therapy" AND "heart" OR "cardiac" OR "myocardium" OR "ischemia" OR
"infarction" OR "heart failure", etc.

Ethical Considerations

Since this research is a synthesis of published literature, there is no direct ethical approval that is needed. Nevertheless, the studies included were of appropriate standards:

Discussion

The available evidence derived with the help of the present study shows that mitochondrial transplantation can be very helpful to enhance the functioning of the heart, the bioenergetic rehabilitation, and structural maintenance after ischemic or degenerative heart damage. In several preclinical and early clinical research, viable mitochondrial transplantation led to a restoration of the levels of adenosine triphosphate (ATP), reduction of oxidative stress, alleviation of apoptotic cell death, and improvement in left ventricular ejection fraction (LVEF) or cardiac output.

All of these findings indicate that mitochondrial transplantation is targeting the intrinsic energetic failure of the cardiomyocytes, which is a crucial drawback of the current solutions to the ischemic heart disease and heart failure. Mitochondrial transplantation provides a direct replacement of the power source within the cell (the mitochondrion) that is necessary to cause contraction and survival, unlike pharmacologic or device-based treatment that merely improves symptoms or works fewer hours.The concept of mechanistic interpretation presented in the restoration of Bioenergetic Capacity will identify if the patients have regained their energy levels (or not).

The hypotheses that exogenous mitochondria restore the oxidative phosphorylation in impaired cardiomyocytes are greatly supported by the evidence of the increases in ATP concentration and LVEF after transplantation (e.g., Aoki et al., 2025; Shin et al., 2019). Electron microscopic structural studies have also shown rearrangement of organized cristae and restoration of mitochondrial density and indicate that bioenergetic integration (and not a temporary metabolic supplementation) is actually occurring (Masuzawa et al., 2013).

Moreover, functional analyses show that respiratory complexes II and IV are reactivated, which underlines the recovery of the electron transfer chain activity. These sustained recoveries of these complexes are consistent with the long-term processes of myocardial contractility recovery reported to occur and say that the long-term integration is not superficial, but metabolic salvage.

Oxidative Stress and Cell Survival Modulation.
It is common to find that both malondialdehyde (MDA) levels decrease and superoxide dismutase (SOD) levels increase following transplantation (Aoki et al., 2025; Liu et al., 2022) and this indicates the mitigation of oxidative stress. This decreases the reactive oxygen species, thus stopping additional mitochondrial damage, interrupting the vicious cycle of oxidative damage and apoptotic signals.

TUNEL staining and caspase-3 results indicate less apoptotic cell death indicating that mitochondrial transplantation not only restores energy but also equalizes the intracellular redox conditioning and blocks cell death cascades.

Uptake and Integration Mechanisms.
Effectiveness of mitochondrial transplantation is based on cell internalization and functional fusion of host organelles. It has been indicated that the major mechanisms of uptake are macropinocytosis and actin-dependent endocytosis (Pacak et al., 2015; Kami and Gojo, 2020). After internalization, the mitochondria may fuse with endogenous ones, which will restore the mitochondrial membrane potential and calcium buffering capacity (Cowan et al., 2016).

According to recent published results, exogenous mitochondria cause mitophagy and mitochondrial biogenesis through PGC-1a stimulation, which implies that the therapy is associated with replacing damaged organelles in addition to triggering intrinsic mitochondrial renewal in the cardiomyocytes (Liu et al., 2022; Jia et al., 2022).

Translational Outcomes
The pharmacokinetic profiles of both drugs revealed a similarity: both disperse slowly and exhibit slow absorption rates, while their PK profiles were alike (Sahoo et al., 2015).

Preclinical-Clinical Continuity: Pharmacokinetic profiles of the two drugs showed similarity, i.e., they disperse gradually and have low absorption rate, and the PK profiles of the two drugs were similar (Sahoo et al., 2015).

Large-animal and rodent models of the improvements in myocardial function trends indicate similar trends, which uphold the prospect of in vivo translation. Masuzawa et al. (2013)

large-animal porcine model reported decrease in infarct size and myocardial ATP level recovery which were also observed in humans (Emani et al., 2017; Guariento et al., 2020).

Clinical Feasibility and Safety.
Statistics about humanity continue to be scarce yet promising. Intraoperative mitochondrial transplantation in patients of pediatric cardiac surgery did not demonstrate arrhythmia, inflammation, and immune rejection (Emani et al., 2017). Similarly, Guariento et al. (2020) did not find any hemodynamic instability in children under ECMO, which further proves safety.

Such results confirm the immunogenic inactivity and lack of immunological response of autologous mitochondria and corroborate the claim that mitochondrial transplantation is a distinctly biocompatible organelle therapy.Clinical trials have been conducted on mitochondrial treatment, and these findings are compared to other treatments available for mitochondrial diseases (Wilhelm, 2007).

Mitochondrial-targeted therapeutic approaches that exist e.g. elamipretide (SS-31) and MitoQ aim at mitochondrial membrane stability or reactive oxygen species reduction. Although these compounds enhance the mitochondrial functioning indirectly, they are unable to substitute the lost or damaged organelles by their structure.

By comparison, mitochondrial transplantation is a direct, structural and functional replacement of pathological organelles. It is a more detailed form of restoring the energy metabolism. Gene therapies such as mitochondrial transcription factor modulation (e.g., TFAM) or correction of the mitochondrial DNA is an attractive but complicated option that is hampered by delivery issues. By transplanting, these concerns are avoided by provision of intact and functioning mitochondria that can generate energy in real-time.

However, such strategies as mitochondrial transplantation with SS-31 or stem cell therapy can be synergistic, and in fact preliminary findings indicate more mitochondrial survival in oxidative conditions when these adjuvants are used concomitantly.

Challenges and Limitations

Although there is good preclinical data, there are a number of limitations that hinder adoption to clinical translation:

- Delivery Methodology Intramyocardial injection is less invasive but less effective at uptake compared to intracoronary infusion which is more invasive. This trade-off can be evaded by using novel delivery mechanisms like hydrogel scaffolds or nanoparticles encapsulation (Millay & Cowan, 2022).
- Dose Optimization: The existing animal models recommend effective doses of about 108-109 mitochondria and no standardized dosing dose has been developed in humans. Long-term clinical trials would only be done after dose-response studies.
- Preservation and Viability: Mitochondria are rather sensitive to heat and physical forces; the isolation and delivery methodology has to save the membrane potential and respiratory activity of the organelles. Further developments of cryopreservation and microfluidic preconditioning are required to develop off-the-shelf therapeutic mitochondria.
- Long-Term Integration: Short-term changes in the improvement of cardiac functioning are well-documented, but the continuation of the transplanted mitochondria months or years after transplantation is still unclear. New technologies of noninvasive imaging, including mitochondrial-targeted PET tracers, might bring an understanding of long-term survival and functioning.
- Ethical and Regulatory Uncertainties: It is uncertain as to whether mitochondria be classified as biologics, cell therapy products, or tissue derivatives. To standardize the manufacturing process, quality control and sterility procedures within institutions, regulatory harmonization shall be necessary.

Future Research Implications.

Future research must employ a number of areas:

- Standardized Protocols: This will be done by developing universal protocols of mitochondrial isolation, quantification and viability measurement to facilitate reproducibility.
- Clinical Trials: Multicenter, randomized controlled trials are needed to prove the efficacy between adults and pediatrics with ischemic heart diseases or cardiomyopathy.
- Mechanistic Tracking: The real-time studying of the mitochondrial trafficking and fusion might clarify the dynamics of organelle fusion and turnover.
- Bioengineering Innovations: Survival in ischemic conditions may be enhanced by genetic engineering of the mitochondrion to provide resistance to stress or genetic engineering of the mitochondrion to provide enhanced energy output.
- Ethical Oversight: Mitochondrial therapy is associated with the blurring of the lines between the cellular and the organ-level intervention, which require bioethical principles to be modified to provide equitable access and informed consent.

Overall Interpretation

The summarized evidence suggests that mitochondrial transplantation is a regenerative treatment with great potential to regenerate damaged cellular bioenergetics, eliminate oxidative damage, and enhance cardiac functioning. It is a paradigm shift, which is no longer focusing on the symptoms of the myocardial failure but on the subcellular cause of this failure.

Nevertheless, like any new therapy, it will rely on technical, logistical and regulatory issues being resolved. The early human cases associated success creates a platform, yet a solid clinical justification should be made prior to regular use.

To sum up, mitochondrial transplantation is a revolutionary way of regenerating the heart. It has the potential to save the failing heart by directly transplanting damaged organelles, which replaces the damaged energy producers, which forms the basis of the next generation of cellular and organelle-based therapies.

Conclusion

The combined results of the animal and the initial human research determine the feasibility of mitochondrial transplantation as a mechanically grounded and possible therapeutic intervention in the ischemic and degenerative cardiac injuries. Recovery of ATP synthesis, decrease in oxidative stress and improvement of left ventricular activity is continuously observed in models, which demonstrates the strong mechanistic support. The hybridisation and genesis of transplanted mitochondria do not only show acute energy recovery but also long term subcellular repair and regeneration.The special advantage of mitochondrial transplantation is its ability to directly compensate the bioenergetic deficit on which myocardial dysfunction is based which is a weakness of current pharmacologic and device-based treatment. The preliminary pediatric studies have revealed procedural viability, safety and hemodynamics. Provided that the results of future multicenter trials are supportive, mitochondrial transplantation may become a frontline treatment of ischemia-reperfusion injury and heart failure. Mitochondrial transplantation is a paradigm-shift treatment, where the primary emphasis in treatment is on reversing symptoms, rather than on preparation of the underlying energy engine of the heart. It has the potential to revolutionize regenerative cardiology by treating the subcellular etiology of myocardial dysfunction. Although it holds promise, its transfer to mainstream practice requires stringent clinical validation, standardization and ethical rule.

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