# On 3 legs shall we stand: Combined innovation for treatment of ischemic cardiomyopathy



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***Feature Editor's Introduction***—*In the accompanying article, Kawabori and colleagues discuss new innovations in the treatment of ischemic cardiomyopathy. While surgeons are keenly aware of standard treatment options (guideline-directed medical therapy, revascularization, transplantation, and mechanical circulatory support), these authors explore the role of adjunctive therapies, including mitral valve surgery, ventricular restraint, and stem cell therapy in curbing the progression of this disease. They propose a future state where treatment for ischemic cardiomyopathy is more nuanced and tailored. This type of precision medicine would aim to treat patients earlier in their disease course with therapies that slow the progression to end-stage disease. Among the challenges we face is finding tools that achieve this goal. Given that revascularization and medical therapy are standard care for ischemic cardiomyopathy, the real question is do we have useful adjunctive therapies in 2021? To date, neither stem cell therapy nor ventricular restraint have shown efficacy in clinical trials. While the authors discuss how these concepts are being resurrected in new research, at this time, these particular therapies remain investigational.*

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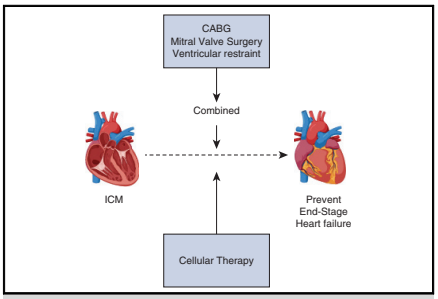


**Future treatment of early combined therapies for ischemic cardiomyopathy. Created using BioRender.com.**

**CENTRAL MESSAGE**

Patients at high risk for ischemic cardiomyopathy progression may benefit from a combination of early coronary artery bypass grafting, mitral valve surgery, and/or ventricular restraint therapy.

See Commentary on page 228.

In 1970, Burch and colleagues[1] first described the term ischemic cardiomyopathy (ICM) in the literature as the degenerative changes and subsequent heart failure resulting from chronic coronary artery disease (CAD) and myocardial ischemia. In 2002, this definition was expanded to describe ICM as heart failure in patients with a previous myocardial infarction or coronary revascularization (either coronary angioplasty or coronary artery bypass graft [CABG] surgery), 75% or greater left main or proximal left anterior descending artery disease, or 75% or greater stenosis in multivessel disease.[2] Today, ICM is often further refined when used in clinical trials to include ejection fraction. ICM can be considered a chronic condition with reduced myocardial function in which patients have epicardial CAD and an ejection fraction <35%, despite optimal medical therapy.[3,4] ICM continues to play a prominent role in the US health care landscape because those with CAD are at risk. CAD is the leading cause of cardiovascular death in the United States, and is estimated to account for 41.7% of deaths globally between 1990 and 2013.[5] Thus, finding effective treatments for ICM remains of critical importance.

The current gold standard treatment for end-stage ICM is heart transplantation (HTx) or the use of durable mechanical circulatory support (MCS), such as left ventricular (LV) assist devices, as destination therapy or as a bridge to transplant.[6] However, these therapies have limited applicability, particularly in patients with underlying medical conditions such as high pulmonary vascular resistance in HTx, severe right heart dysfunction, or the inability to tolerate anticoagulation in MCS.[6] Due to the limitations of HTx and MCS, there is increasing interest in treatments to alleviate disease burden for ICM patients before HTx and MCS become necessary.

The efficacy of CABG in treating ICM is well established in the literature. The Surgical Treatment for Ischemic Heart Failure/Surgical Treatment for Ischemic Heart Failure

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Extension Study trials demonstrated definitive benefits for ICM patients undergoing CABG compared with those treated with medical therapy alone in both the short- and long-term. ICM patients who underwent CABG had lower rates of death or hospitalization from cardiovascular causes at a median of 56 months of follow-up.[3] These benefits persisted even 10 years later. ICM patients who underwent CABG had fewer all-cause deaths, as well as better outcomes for all secondary outcomes recorded. A detailed subanalysis for death of any cause demonstrated a benefit from CABG for nearly all parameters measured.[7] Of course, when applying these results to clinical practice, it is important to take into account individual factors such as myocardial variability, ejection fraction, LV volume, and heart failure stage when determining the benefit of a CABG for any single patient with ICM.[8,9] For ICM patients with viable myocardium, Bax and colleagues[10] showed that early revascularization leads to lower mortality and significant functional improvement compared with those revascularized later. Non-viability limits the benefits of revascularization. Severely enlarged hearts with low ejection fraction may be nearing end-stage heart failure, and derive more benefit from end-stage heart failure surgeries, rather than revascularization. Risk stratifying individual patients based on likelihood of developing end-stage ICM, such as those with a strong family history of ICM, may lead to patient-specific preventative treatment. Higher-risk patients may benefit from frequent follow-up and early CABG to delay ICM progression.

However, revascularization does not treat the full spectrum of complications associated with ICM. Ischemic mitral regurgitation (IMR) often occurs in ICM patients, and is associated with reduced survival, even after revascularization.[11] Mitral valve replacement (MVR) or repair (MVr) provides more benefit for patients in earlier phases of ICM who have relatively preserved myocardial function because these surgeries decrease IMR and pulmonary congestion. Studies have also suggested that MVR may be more effective than MVr. In the well-known Cardiothoracic Surgical Trials Network randomized clinical trial where patients were randomized to receive MVR or MVr for severe IMR, there was more recurrent severe MR in the repair group after 1 year, despite no difference in LV reverse remodeling or mortality ($P < .05$).[12] However, performing MVR or MVr in end-stage heart failure patients with significantly decreased ventricular function may further stress the LV by increasing afterload via decreased MV regurgitation. An overloaded LV with high diastolic filling pressure does not eliminate elevated left atrial pressures, thereby reducing diastolic coronary flow and further worsening myocardial ischemia. End-stage ICM patients may derive more benefit from HTx or MCS to obtain a more physiological, unloaded LV. In addition to MVR and MVr, percutaneous therapy such as the MitraClip (Abbott, Abbott Park, Ill) may also play a role in treating ICM in the near future. A review by Takagi and colleagues[13] suggests that MitraClip has similar survival outcomes to surgical mitral valve interventions. It is important to note that mitral valve interventions alone will not treat ICM. To further refine the indications for these procedures, individual investigations are required to determine how each aspect of ICM-stage, mitral valve anatomy, IMR severity, myocardial viability, predictions for progression of ICM, and the likelihood of developing end-stage heart failure, affect patient postoperative outcomes. Similar to revascularization, patients who are at high risk for developing end-stage ICM may benefit from early risk analysis and surgical procedures to slow disease progression.

Ventricular restraint therapy (VRT) emerged in the 1980s with Carpentier's invention of the cardiomyoplasty procedure as a way to supplement current surgical therapies for ICM by providing diastolic support and preventing ventricular remodeling, without needing to be in direct contact with the patient's blood.[14-16] VRT has shown enough promise that 2 ventricular restraint devices were approved by the National Institutes of Health for human clinical trials to prevent adverse remodeling: the CorCap (Acorn Cardiovascular, Inc, St Paul, Minn) and the HeartNet (Paracor Medical, Sunnyvale, Calif). Initial results for these trials were promising: in 2012, the 5-year results from the Assessment of a Cardiac Support Device in Patients with Heart Failure trial showed that the CorCap is safe, improves quality of life, and decreases remodeling.[4] Similarly, in 2008 early clinical data for the HeartNet showed that it is safe and improves quality of life.[17] Unfortunately, neither of these devices were ultimately used in clinical practice. The Food and Drug Administration felt there was not enough evidence to approve the CorCap, asit showed no survival benefit and there were some safety concerns, and the HeartNet clinical trial was halted, primarily due to a lack of evidence suggesting tangible benefit after 6 months and 1 year.[14] The Assessment of a Cardiac Support Device in Patients with Heart Failure trial found that patients with an intermediate indexed LV end diastolic diameter derived the most benefit from the device, suggesting that ventricular size may affect the utility of VRT.[18] The idea that ventricle size is important for determining outcomes after therapy has been previously hypothesized.[19] Ghanta and colleagues[20] began to investigate the idea that VRT must be carefully matched to patient ventricular parameters with their quantitative ventricular restraint device. In large animal testing, the quantitative ventricular restraint device showed superior efficacy over static pressure devices, suggesting that individualized VRT may be beneficial.[21]

Perhaps an additional modality of ICM therapy lies in building off of the relative success of historical VRT devices, as many newer VRT devices have been showing

promise in preclinical animal studies.[22-24] The EpicHeart device (CorInnova, Houston, Tex) is designed to be implanted minimally invasively to provide systolic support for heart failure patients. It improves hemodynamic parameters in an ovine acute heart failure model.[24] A soft robot sleeve device developed by Roche and colleagues[23] has also shown initial promise in small and large animal models as a way to support the heart by attempting to mimic native motion and biomechanical properties. The use of VRT technology does not preclude the inclusion of cellular or regenerative medicine in the quest for newer, less-invasive therapies for ICM. In fact, a 2010 small animal study showed increased efficacy of VRT when combined with cellular therapy.[25] The idea of combination therapy is being tested with Naveed and colleagues[22] multifunctional Active hydraulic ventricular Support Drug delivery system (ASD, X. Zhou), which has shown improved heart function in small animal studies when the ASD device was used in conjunction with a therapeutic agent. The ASD represents the next generation of VRT, as it combines physical support with real-time heart monitoring and the ability to deliver targeted pharmacologic therapy.[22] Thus, it has the potential to adapt to a patient's heart in real time. The mesh-like design of the ASD also allows for the possibility of using it for patients undergoing cardiac surgery, such as CABG. This device gives rise to the idea that VRT may be able to augment already existing therapies, such as improving outcomes for patients who have had prior CABG or MVR or MVr. Among the major questions that remains as VRT continues to develop is how these devices may be used in conjunction with surgical or pharmacologic therapy to meet each patients' unique support needs and prevent progression of ICM.

Since the early 2000s, cellular regenerative medicine has exploded, with the aim of treating ICM by using stem cells to preserve cardiac function, prevent scar formation, and regenerate healthy myocardium.[26] Many aspects critical to the development of a successful cellular therapy remain under investigation, and it is unclear how the cells exert their effects on myocardium, if the stem cells effectively differentiate, or what the correct therapeutic dose should be.[26-28] Stem cells might exert their benefits through the release of signaling molecules to promote healing or revascularization and through differentiation to replace damaged myocytes.[27] Although preclinical studies show potential, current clinical trials of cell therapy have yet to show definitive benefits: a 2019 clinical trial using mesenchymal precursor cells to support patients with an LVAD found no difference in survival or in rates of LVAD weaning success between patients treated with mesenchymal precursor cells and those treated with a control solution.[26,29] Other studies, such as the 2017 Intracoronary ALLogenic heart STem cells to Achieve myocardial Regeneration trial, have also shown no therapeutic effect with cellular therapy on ventricular remodeling after myocardial infarction.[26] Similarly, cellular regenerative medicine has not yet shown applicable benefits to human patients. Although neonatal mice, rats, and piglets are all able to regenerate myocardium after injury within the first few days of life, the mechanism behind cardiac regeneration is still being elucidated and has not been studied in humans.[30-34] Although there are high expectations for the future of this field, more evidence from double-blind, controlled, randomized trials is necessary to establish clinical outcomes, as stated by the European Society of Cardiology's consensus statement.[35]

Although HTx or MCS therapy remains the mainstay of treatment for end-stage ICM, there is a substantial population of patient ineligible for these interventions. HTx opportunities are severely limited by donor availability and long waiting times.[36] MCS also presents its own limitations—namely the need for anticoagulation, an external driveline, and the effects on patient quality of life—that may exclude certain patient populations from being supported on MCS.[22] Although no prior clinical trials have evaluated the efficacy of early combination therapy (CABG, mitral valve surgery, and/or VRT), each intervention has individually shown benefits and potential, and may be effective in preventing remodeling and slowing the disease progression of ICM (Figure 1). However, because these therapies are invasive, early intervention may be of the most benefit for the highest-risk patients. Thus, risk stratification that predicts the progression of ICM can inform optimal timing for surgical procedures to maximize the benefits to patients. Much like how combination chemotherapy for cancer attacks oncologic disease at different pathophysiology points and increases therapeutic efficacy, so too might a similar approach be effective for ICM.

*Tonight, I am launching a new precision medicine initiative to bring us closer to curing diseases… and to give all of us access to personalized information to keep ourselves and our families healthier.*[37]

–Barak Obama

In the 2015 State of the Union Address, US President Barak Obama ushered in the era of precision medicine.[37] For the medical community, this meant sequencing individual genomes and utilizing trends in population genetic data to help tailor medicine and interventions to an individual's unique genetic profile.[38] During the past 5 years, precision medicine has evolved to include early genetic disease detection, risk stratification, and individual prevention. Multiple genetic risk factors have been identified for CAD, and polygenetic risk scores are being studied to assess risk for CAD and ICM.[39,40] With this information, it may be feasible to identify patients at risk for future ICM who may benefit from earlier surgical intervention. Perhaps then the future

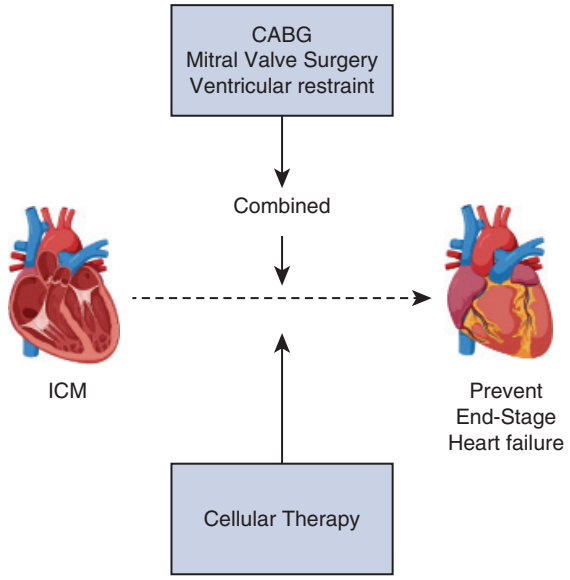


**FIGURE 1.** New treatments for ischemic cardiomyopathy (ICM) are still under investigation. A combination of early coronary artery bypass grafting (CABG), mitral valve surgery, and/or ventricular restraint therapy or cell therapy tailored to individual high-risk patients offers a potential avenue to slow the progression of ICM to end-stage heart failure. Created using BioRender.com.

of treating ICM is "Precision Surgery," or utilizing patient physiology, anatomy, and genetic risk score to intervene early in the disease process and prevent remodeling and end-stage heart failure with a unique combination of effective therapies. Only time will tell what role "Precision Surgery" will play in the treatment of ICM.

## Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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