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Perspective

Treatment of chronic heart failure in the 21st century: A new era of biomedical engineering has come

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Abstract

Chronic heart failure (CHF) is a challenging burden on public health. Therapeutic strategies for CHF have developed rapidly in the past decades from conventional medical therapy, which mainly includes administration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists, to biomedical engineering methods, which include interventional engineering, such as percutaneous balloon mitral valvotomy, percutaneous coronary intervention, catheter ablation, biventricular pacing or cardiac resynchronization therapy (CRT) and CRT-defibrillator use, and implantable cardioverter defibrillator use; mechanical engineering, such as left ventricular assistant device use, internal artery balloon counterpulsation, cardiac support device use, and total artificial heart implantation; surgical engineering, such as coronary artery bypass graft, valve replacement or repair of rheumatic or congenital heart diseases, and heart transplantation (HT); regenerate engineering, which includes gene therapy, stem cell transplantation, and tissue engineering; and rehabilitating engineering, which includes exercise training, low-salt diet, nursing, psychological interventions, health education, and external counterpulsation/enhanced external counterpulsation in the outpatient department. These biomedical engineering therapies have greatly improved the symptoms of CHF and life expectancy. To date, pharmacotherapy, which is based on evidence-based medicine, large-scale, multi-center, randomized controlled clinical trials, is still a major treatment option for CHF; the current interventional and mechanical device engineering treatment for advanced CHF is not enough owing to its individual status. In place of HT or the use of a total artificial heart, stem cell technology and gene therapy in regenerate engineering for CHF are very promising. However, each therapy has its advantages and disadvantages, and it is currently possible to select better therapeutic strategies for patients with CHF according to cost-efficacy analyses of these therapies. Taken together, we think that a new era of biomedical engineering for CHF has begun.

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Introduction

Chronic heart failure (CHF) impacts nearly 15 million individuals worldwide, and 550,000 new-onset cases are estimated to occur every year. CHF with high rates of early post-discharge re-hospitalization and mortality is a major burden to public health and a challenging problem in clinical settings. In the management of patients with CHF, the goal is to improve cardiac function and eliminate symptoms to improve patients' quality of life (QOL) and survival. The 21st century is the era of biomedical engineering. The treatment of CHF has developed from medical and surgical engineering to other strategies of biomedical engineering, which include interventional, mechanical, regenerate, and rehabilitating engineering. Herein, the treatment of CHF in the 21st century is reviewed, and it is believed that a new era of biomedical engineering for the management of CHF has commenced.

Medical engineering

Evidence-based, large-scale, multi-center clinical trials lay solid basis for pharmacotherapy of CHF (Table 1). The outcomes of patients with CHF are improved greatly owing to the further understanding of the mechanisms and continuous development of new drugs. A prospective European study found that guideline-recommended target dosages of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) and beta-blockers for CHF have a lower risk of mortality and/or hospitalization.[1] Moreover, the use of higher dosages of neurohormonal blockers (e.g., ACEI/ARBs and beta-blockers) and lower dosages of diuretics is associated with reduced morbidity and consequent mortality.[2] Recent studies found that the angiotensin receptor-neprilysin inhibitor LCZ696 is superior to enalapril in reducing the risks of mortality and hospitalization.[3] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a promising class of new drugs for CHF.[4] Other drugs, such as cardiac myosin activators[5] and antagomirs with the actions of miRNAs, also improved cardiac function. Traditional Chinese medicine Qili qiangxin capsules as a standard treatment could be used in combination with other therapies for CHF, as they reduce the levels of amino-terminal pro-B type natriuretic peptide.[6] However, there are currently no guidelines for recommendation.

Some believe that beta-blockers should not be used preferentially over other rate-control medications and not regarded as a standard therapy to improve the prognosis of patients with CHF and atrial fibrillation (AF).[7] Conversely, others believe that patients with CHF should receive beta-blockers, irrespective of age or sex, to reduce the risk of mortality and hospital admission.[8] Although nitrates can enhance activity tolerance in patients with CHF and promote a preserved ejection fraction (EF), patients who received isosorbide mononitrate have been reported to be less active and have not shown better QOL or submaximal exercise capacity than patients who received placebo.[9] Taken together, there is a declining risk of sudden cardiac death (SCD) in CHF with reduced EF with the use of evidence-based treatment employing medications.[10]

As diabetes mellitus type 2 (T2DM) is a major risk factor for CHF, controlling the development of T2DM may help prevent and decrease the incidence of CHF and other cardiovascular events (CVEs). Previous studies have found that some glucose-lowering drugs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, may worsen CHF. Thus, there is an arising need for developing new glucose-lowering drugs.[11] However, the EXAMINE trial showed that the DPP-4 inhibitor alogliptin did not increase the risk of CHF outcomes.[12] Moreover, data from large cohorts also showed that DPP-4 inhibitors and glucagon-like peptide 1 analogs were not associated with an increased risk of hospitalization for CHF when compared with combinations of other oral antidiabetic drugs.[13]

Both the EMPA-REG OUTCOME trial[14] and the CANDLE trial[15] confirmed the effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors empagliflozin (EMPA) and canagliflozin on improving cardiac function and their potential role in treating CHF and reducing CVEs in patients with T2DM.[16] The mechanisms of SGLT2 inhibitors for CHF[17,18] are linked to osmotic diuresis and natriuretic effects, systolic and

Table 1
Major pharmacotherapy of CHF and related clinical trials.

No.	Types	Drugs	Clinical trials
1	ACEI	Captopril	SOLVD, CONSENSUS,
		Delapril	AIRE, SAVE and TRACE
		Enalapril	
		Lisinopril	
2	ARB	Valsartan	Val-HeFT
		Telmisartan	
		Irbesartan	
3	ARNI	LCZ696	
		Sacubitril/Valsartan	PARADIGM-HF
4	Beta-blockers	Carvedilol	US-Carvedilol, CIBIS-ll,
		Bisoprolol	MERIT-Hf COPERNICUS
5	MRA (aldosterone antagonists)	Spironolactone	TOPCAT
			ATHENA-HF
6	Other diuretics	Loop diuretics	ASCEND-HF
7	Nitrates	Isosorbide-5-mononitrate (IS5MN)	DRAMI
8	PCSK9 inhibitor	Alirocumab	Uncertain
		Bococizumab	
		Evolocumab	
9	SGLT2 inhibitors	Canagliflozin	CANDLE trial
		Dapagliflozin	
		Empagliflozin (EMPA)	EMPA-REG trial
10	TCM	Qili qiangxin capsules	
		Qishen yiqi dripping pill (QSYQ)	CACT-IHF
		Shencao tongmai granule (STG)	
		Shenfu injection	
		Shensong yangxin capsules	
11	Other drugs:		
	3,5-diiodothyropropionic acid		
	Cardiac myosin activator		
	Cytokine inhibitors (TNF antagonists)		
	Endothelin antagonists		
	Glycosides		
	Growth hormone		
	Neutral endopeptidase inhibitors		
	NT-proBNP (BNP, nesiritide)	NT-proBNP	PROTECT
	PDE5 inhibitors	Udenafil	ULTIMATE-SHF
	Statins		
	Thyroid hormone analogue		
	Vasopressin antagonism	Tolvaptan	EVEREST

CHF: chronic heart failure; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid-receptor antagonists; PDE5: phosphodiesterase type 5; TCM: Traditional Chinese Medicine; NT-proBNP: amino-terminal pro-B type natriuretic peptide; PCSK9: proprotein convertase subtilisin/kexin type 9; SGLT2: sodium/glucose cotransporter 2; TNF: tumor necrosis factor.

diastolic blood pressure reduction, left ventricular (LV) remodeling, reduced arterial stiffness and weight loss, and other cardiovascular and kidney benefits. The benefits of SGLT2 inhibitors in CHF may be mediated by the inhibition of sodium-hydrogen exchange rather than the effect on glucose reabsorption.[19] The prognostic improvement in CHF by SGLT2 inhibitors is mostly through their diuretic (hemodynamic) rather than metabolic (antiatherogenic) effect.[20] Animal experiments showed that EMPA lowered myocardial cytoplasmic Na^+ ($[Na^+]_c$) and Ca^{2+} ($[Ca^{2+}]_c$) and enhanced mitochondrial Ca^{2+} ($[Ca^{2+}]_m$) through impairment of the myocardial Na^+/H^+ exchanger flux, independent of the SGLT2 activity.[21] On the basis of the findings of the EMPA-REG trial, the SGLT2 inhibitor EMPA, as a new class of anti-diabetic agents,

has been recommended in the new guidelines for the prevention of CHF in high-risk patients (class IIa/B indication).[22] Previous clinical trials and evidence also support the rationale behind the use of SGLT2 inhibitors in patients with T2DM and CHF owing to their cardioprotective effects.[23–25]

Depression is frequently observed in patients with CHF and reduced left ventricular ejection fraction (LVEF) and is associated with adverse clinical outcomes. However, long-term treatment with selective serotonin reuptake inhibitors compared with placebo did not significantly reduce all-cause mortality or hospitalization in CHF; further, there was no significant improvement in depression.[26] It is indeed a puzzle of CHF treatment. This finding remains controversial in CHF treatment.

The five Ws (who, why, when, which drugs, and what targets), two Hs (how to and how much), one E (effect), and one S (safety) should be recommended for evaluating pharmacotherapy for CHF. The option and dosage of drugs should be individualized, and new fixed-dosage combinations, e.g., sacubitril/valsartan, are worthy of recommendations. Complex pharmacological therapies achieve success, but not in all patients. For example, the addition of aliskiren to enalapril for CHF led to more adverse events without an increase in benefit.[27] Therefore, non-pharmacological treatment of CHF is needed.

Interventional engineering

Rapid development in interventional cardiology during the last decades owing to the invention of cardiac catheter technology provided a new option for non-pharmacotherapy of CHF (Table 2). Interventional engineering greatly decreases the total mortality in advanced CHF owing to significant symptomatic and hemodynamic improvements, as well as cardiac remodeling and circulation improvement.

Biventricular pacing, also called cardiac resynchronization therapy (CRT), presents as a new therapeutic approach in patients with CHF. Patients with AF, CHF, and QRS prolongation may respond better to CRT rather than to LV pacing. Therefore, the management of patients with reduced LV function, wide QRS, and symptomatic refractory CHF, despite optimal drug therapy, should include CRT as an option. Two prospective randomized multi-center trials (i.e., VIGOR and VENTAK CHF trials) confirmed the clinical effects of CRT on functional capacity, QOL, and hemodynamic status.[28]

SCD accounts for >40% of all mortality cases in patients with CHF. Thus, the prevention of life-threatening cardiac arrhythmia is a major goal in the management of CHF. In several randomized clinical trials, electrical therapy with the use of implantable cardioverter defibrillator (ICD) has been proven to be superior to medical antiarrhythmia therapy in both the secondary and primary prevention of SCD in patients with CHF. The updates and perspectives on current primary prevention trials of ICD therapy for CHF are encouraging. However, the presence of AF in patients who received ICD is associated with the progression of CHF. Approximately 10% of patients who received ICD had an indication for CRT at the time of implantation. Thus, implantation of a CRT-ICD system (CRT-D) should be considered in every patient with appropriate indications. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed that when the patients' EF is <35% or even <30%, ICD should be used; conversely, CRT-D should be considered if the EF is <30%.[29] Landmark trials, including COMPANION and CONTAK-CD, InSync ICD, MIRACLE, and MUltisite STimulation in cardiomyopathy (MUSTIC), showed that implantation of CRT-D is a new therapeutic approach for CHF and SCD.[30]

Early intervention using CRT-D was associated with a significant long-term survival benefit.[31] However, it does not reduce mortality or hospitalization and may even increase mortality in patients with CHF and a narrow QRS complex (QRS duration <130 ms).[32] Among patients undergoing CRT-D implantation, left bundle branch block (LBBB) with a QRS duration $\geq$150 ms, compared with LBBB and QRS duration <150 ms or no LBBB regardless of the QRS duration, was associated with a lower risk of all-cause mortality and readmission.[33]

Catheter ablation is another form of electrical therapy that can help the treatment of CHF. In patients with tachycardia-mediated cardiomyopathy due to drug-refractory AF with rapid ventricular response, catheter ablation of the atrioventricular node and pacemaker implantation can effectively restore a physiologic heart rate, often with dramatic regression of LV dysfunction.[34] Catheter ablation of ventricular tachycardia is also an effective adjunct therapy. Since CHF and AF often coexist, catheter ablation for AF in CHF was associated with better clinical outcomes than medical therapy.[35] New catheter ablation techniques and new atrial pacing

Table 2
Non-pharmacotherapy: other biomedical engineering strategies and clinical trials.

No.	Non-pharmacotherapy strategies	Types	Related clinical trials
1	Interventional engineering	Percutaneous balloon mitral valvotomy (PBMV)	
		Percutaneous coronary intervention (PCI)	
		Pacing	
		left ventricular pacing (LVP)	VIGOR CHF trials
		biventricular pacing (BiVP) or cardiac	VENTAK CHF trials
		resynchronization therapy (CRT)	COMPANION
		implantable cardioverter defibrillator (ICD)	REVERSE
		CRT-ICD (CRT-D)	SCD-HeFT
		Catheter ablation (AF, VT)	COMPANION, CONTAK-CD, InSync ICD
			MIRACLE
			MUSTIC
2	Mechanical engineering	Left ventricular assistant device (LVAD)	MOMENTUM 3
		VA-ECMO	US SUSTAIN
		Impella Recover 2.5 (IR2.5)	
		TandemHeart	
		Venoarterial Shunt (VAS)	DuraHeart
		Internal artery balloon counter-pulsation (IABP)	
		Cardiopulmonary support (CPS)	
		Cardiac support device (CSD)	
		Total artificial heart (TAH)	ACORN
		Pulmonary artery pressure sensor	
		Interatrial shunt device (IASD)	
3	Surgical engineering	Intravenous inotropic therapy	RESCUE study
		Coronary artery bypass graft (CABG)	STICH
		Valve surgery (VS)	
		Partial left ventriculectomy	
		Dynamic cardiomyoplasty	
		Myosplint implantation	
		Heart transplantation (HT)	
		Heterotopic HT (HHTx)	
		Orthotopic HT (OHTx)	
4	Regenerate engineering	Gene therapy (GT)	TAC-HFT
		Stem cell transplantation	CHART-1
		Cellular cardiomyoplasty	
		Myocardial tissue engineering	
5	Rehabilitating engineering	Cardiac rehabilitation (CR)	HF-ACTION
		External counter-pulsation (ECP)	
		Enhanced ECP (EECP)	
		Health education	
		Psychological interventions	
		Home-based hydrotherapeutic	
		Thermal program	
		Functional electrical stimulation	
		Nursing	
		Intravenous ferric carboxymaltose (FCM)	
		Diet: Flavanol-rich chocolate	
		Palliative care	

CHF: chronic heart failure; AF: atrial fibrillation; VT: ventricular tachycardia; VA-ECMO: veno-arterial extracorporeal membrane oxygenation.

algorithms can significantly reduce the AF burden in patients with CHF who are particularly susceptible to decompensation owing to the development of AF.

The current guidelines recommend CRT in patients with low EF, wide QRS, LBBB, and mild to severe heart failure (New York Heart Association class II to IV),[36,37] which includes a novel class I/A indication for QRS durations >150 ms and LBBB, class I/B indication for QRS durations >130 ms and LBBB, and high-grade atrioventricular block with pacemaker indications.[22] Clinical trials confirm a benefit of ICD therapy in patients with coronary artery disease and reduced LV systolic function or heart failure and extend the indications for ICD therapy from patients with ventricular tachyarrhythmias, sudden mortality, and LV-based pacing to those without coronary artery disease. To date, no data are available to support percutaneous balloon mitral valvotomy recommendation for CHF.

Mechanical engineering

Mechanical device therapy is a feasible, safe strategy for the management of CHF, considering that the landmark ICD trials reported successful outcomes. Mechanical devices are currently available for cardiac support, and they can generally be categorized as pulsatile or continuous blood flow, internal (implantable) or external (extracorporeal), pneumatically or electrically powered, and for short-term or long-term support. The details are shown in Table 2.

LV assistant device (LVAD) and right ventricular assistant device (VAD; RVAD)

LVADs have revolutionized the treatment of patients with CHF as they yield a high QOL. Compared with optimal medical management, LVAD implantation significantly improved the survival and QOL of terminally ill patients. Outpatient treatment after LVAD implantation is feasible, and severe complications are uncommon. However, significant myocardial recovery after LVAD therapy in patients with end-stage congestive CHF occurs in a small percentage of patients. Most of these patients have dilated cardiomyopathy (DCM).[38] Continuous-flow VAD, a miniature centrifugal pump and fourth-generation VAD, which is fully suspended by magnetic bearings, is being developed for implantation in humans. Further, a small intrapericardial, centrifugal-flow LVAD was found to be non-inferior to an axial-flow LVAD for patients with advanced CHF, who were ineligible for heart transplantation (HT).[39] Moreover, implantation of a fully magnetically levitated centrifugal-flow pump was associated with better outcomes at 6 months than implantation of an axial-flow pump for advanced CHF.[40]

While the indications for LVADs are well established, the criteria for RVADs are much less defined. The current knowledge on the implantation of RVADs in clinical settings of isolated right CHF, biventricular failure, postcardiotomy failure, and right CHF post-LVAD implantation is controversial. Right-sided circulatory failure (RSCF), a common complication after LVAD implantation, results in a decreased systemic output due to diminished blood flow across the pulmonary vasculature. A venoarterial shunt may serve as the first-line, short-term therapy for LVAD recipients who develop perioperative RSCF. There is a novel surgical strategy comprising simultaneous implantation of a permanent LVAD and percutaneous TandemHeart® plus ProtekDuo®, which can provide temporary RVAD support and preempt right ventricular failure (RVF) in patients with impaired right ventricular function.[41]

Percutaneous veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides emergency circulatory support for patients with cardiogenic shock or acute cardiac failure and is used as a temporary LVAD or a bridge to an LVAD, since it reestablishes normal oxygen delivery and perfusion. Cardiopulmonary bypass machine use can be safely omitted when a long-term LVAD is implanted on VA-ECMO support.[42] However, QOL and survival after discharge were not significantly different compared with those of patients who were not bridged with ECMO.[43] Moreover, VA-ECMO can be limited by insufficient ventricular unloading, resulting in thrombus formation and pulmonary edema. The use of the Impella Recover 2.5 is a safe means to unload the LV while on peripheral VA ECMO to prevent LV thrombus formation and pulmonary edema worsening in patients transitioning to a HeartMate II LVAD.[44] Cardiac surgery or durable LVAD implantation for refractory cardiogenic shock significantly influenced survival to hospital discharge. However, the mortality is still high even with TandemHeart® support.[45]

Intra-aortic balloon counterpulsation (IABP)

IABP, also a kind of VAD, is performed using the same principles that were described in its first experimental use in 1962.[46] Experimental studies have shown significant increases in related indexes. High-risk patients not eligible for coronary artery bypass graft (CABG) may be

considered for percutaneous coronary intervention by IABP or cardiopulmonary support (CPS). Despite a higher risk profile, CPS allowed longer balloon inflation durations and higher percutaneous transluminal coronary angioplasty (PTCA) success rates than IABP. However, the incidence of peripheral vascular complications was higher in the CPS-treated patients, while that of major cardiac events was similar between the CPS- and IABP-treated patients. IABP combined with thrombolytic therapy(TT), PTCA, CABG, percutaneous cardiopulmonary support(PCPS), and VAD can also be used before or after cardiac transplantation.

Cardiac support device (CSD)

The use of CSD may be likened to the "Batista operation," in which the myocardium is surgically resected; this consequently acutely reduces LV volume in patients with advanced CHF, which remains controversial. In experiments on dogs with advanced CHF (LVEF <30%), acute LV reduction using the Acorn CSD prevented progressive global LV dilatation and ameliorated functional mitral regurgitation. The first CSD clinical trial *in vivo* was conducted in 1999. In the short and intermediate terms, CSD implantation seems to ameliorate symptoms and improve cardiac and functional performances in patients with CHF.[47] The Acorn CSD therapy can prevent LV dilation and stretch well. Rather than cardiac transplantation, CSD use is a good option when there are no donors available.

Total artificial heart (TAH) implantation

The first animal experiment on TAH implantation was conducted in a calf, which survived for 145 days.[48] The first experience on the use of a TAH in humans took place at the University of Utah, and the patient was a 61-year-old man with congestive CHF due to primary cardiomyopathy, who also had chronic obstructive pulmonary disease.[49] Mortality occurred on the 112th day, preceded by progressive renal failure and refractory hypotension, despite maintenance of cardiac output. Thereafter, a new smaller TAH design has been developed. The function of the two membrane pumps for orthotopic implantation was also studied in calf experiments.[50] The calf survived up to 180 days without problems. For bridging to transplantation, a new small Viennese TAH was implanted into a 45-year-old patient (height, 160 cm; weight, 75 kg) with end-stage coronary heart disease. In November 1989, a 50-year-old deteriorating transplant candidate with idiopathic cardiomyopathy underwent bridging for 6 days. Thereafter, a compact, efficient, durable, and bio-compatible TAH was developed in 1995. Rechargeable batteries, such as NiCd or NiMH, with 1-AH capacity can run the TAH for 30−45 min. An intrathoracic pulsatile artificial heart pump was then developed by Canadian scientists.[51] This was a remotely controlled and powered artificial heart pump via transcutaneous energy transfer and biotelemetry systems, with no percutaneous connections required. The electrohydraulic system can be used either as a VAD or with modifications as a TAH. The CardioWest is the only device available allowing total heart support.[52] Its use is justified in particular when other assistant devices yield unsuccessful outcomes.

Mechanical circulatory support has been also used to treat graft failure caused by rejection after HT; however, the prognosis remains bleak. Other device therapies include implantation of pulmonary artery pressure sensors[53] and interatrial shunt devices.[54] Taken together, mechanical engineering strategies for CHF, especially in the end stage, have yielded successful outcomes. The main problems in the application of mechanical engineering are its higher cost and lack of reliable resource.

Surgical engineering

Surgical engineering is necessary in patients with end-stage CHF for reconstructing or improving cardiac function. The currently available surgical approaches for patients with refractory CHF include intravenous inotropic therapy, CABG and valve surgery (VS), partial left ventriculectomy, dynamic cardiomyoplasty, myosplint implantation, and HT (Table 2).

CABG and VS improved QOL and increased long-term survival. Partial left ventriculectomy may be performed with results similar to those obtained in HT; however, long-term results are not yet available. Dynamic cardiomyoplasty and myosplint implantation have not yielded successful outcomes; however, they must be considered if passive cardiomyoplasty leads to better results. Aortomyoplasty (AMP), a procedure in which the latissimus dorsi muscle is wrapped around the aorta and stimulated during diastole, is a potential method of chronic counterpulsation.[55] Data demonstrate that AMP provides successful diastolic counterpulsation after CHF, which is equivalent to IABP.

With the introduction of cyclosporine immunotherapy in 1981, success was more the rule than the exception, and HT became an acceptable and effective

therapy, but it is strictly limited to approximately 2500 patients per year owing to donor shortage; the number of candidates exceeds 50,000. The 1-year survival after HT is currently approximately 80%–85%; 5-year survival, 66%; and 10-year survival, 60%. Rejection and infection are the most common causes of post-transplantation mortality. The "attenuation" of the immune response to prevent graft loss is achieved by administration of drugs, such as cyclosporine A, azathioprine, steroids, and antilymphocytic globulins. Novel methods of cardiac preservation are being designed to evaluate and utilize "extended criteria" donors safely.

Xenotransplantation is under intense investigation as another alternative. The major obstacle for the widespread use of clinical xenotransplantation remains to include graft rejection, and fundamental research is ongoing to address hyperacute and delayed xenograft rejections. The heterotopic HT (HHTx) survival rate is comparable to the orthotopic HT rate.[56] Because of the scarcity of donors, the use of an undersized or marginal graft is a valid option to increase the number of transplanted patients. The major disadvantages of HHTx are the need for anticoagulant therapy, difficult hemodynamic and immunologic follow-up, and presence of the diseased native heart.

The surgical reconstructive therapies for CHF are invasive; therefore, there is a need to prepare patients carefully, and good perioperative management and perfect surgical skills are important to improve the symptoms of patients with CHF.

Regenerate engineering

Most cardiac myocytes lose their ability to proliferate and differentiate into new myocytes. Therefore, myocyte regeneration and replacement in adult myocardia were thought to be impossible by the medical community. However, gene therapy (GT), stem cell transplantation, and tissue engineering could have supportive effects on myocyte regeneration and myocardial revascularization in the damaged heart. Many experimental efforts focus on GT, cellular cardiomyoplasty, and myocardial tissue engineering. Myocardial regeneration is an alternative approach to TAH implantation and HT as a new option for patients with end-stage HF (Table 2).

GT

When conventional therapies are not effective or there is a higher cost in patients with severe CHF, GT is expected to become a viable alternative. GT for cardiovascular diseases has developed from preliminary animal experiments to clinical trials. In fact, GT modulating calcium homeostasis, manipulating beta-adrenergic receptor signaling, and augmenting cardiomyocyte resistance to apoptosis had been performed successfully in animal experiments; thus, it can be expected to be a useful therapeutic modality for CHF in clinical settings.[57,58] GT provides a therapeutic benefit in CHF by improving cardiac function and presents as a promising option by retarding the progression of, preventing, and perhaps reversing CHF.

Preclinical studies have previously shown benefits of increased adenylyl cyclase 6 (AC6) in cardiac myocytes and the heart. A randomized, placebo-controlled, phase 2 clinical trial found that intracoronary *AC6* gene transfer in CHF safely improved LV function beyond that observed in the standard heart failure therapy.[59] Other candidates for GT of CHF include those with *SERCA2a* and *SiPR1* genes.

Vectors and target genes used in GT are mainly focused on viral and nonviral vectors and single target genes or monogenes. Each vector system has a series of advantages and limitations. Chimeric vectors combine the advantages of viral and nonviral vectors; chimeric target genes combine two or more target genes. Novel gene delivery modes are still being developed. The gene delivery modes used in cardiovascular GT include non-chimeric vectors combined with non-chimeric target genes, chimeric vectors combined with non-chimeric target genes, and non-chimeric vectors combined with chimeric target genes. Obviously, chimeric vectors combined with chimeric target genes can be used to obtain more efficient results because most cardiovascular diseases are multi-gene diseases.[60] Studies have shown that chimeric vectors and chimeric genes are promising and thus have received considerable attention. They might open new perspectives for human GT. However, we should pay more attention to safety, efficacy, and stability in conducting clinical trials. At the same time, randomized, placebo-controlled studies on clinical trials of GT for CHF should be initiated for the final assessment. With the rapid development of biomedical technology, gene editing or base editing will make a great breakthrough in the treatment of CHF.

Cell therapy

Stem cells are now used instead of therapeutic agents. Since 1988, scientists had studied the transplantation of

myogenic stem cells from the skeletal muscle into the injured myocardium; these cells multiplied and differentiated, thereby improving the function of the failing heart. Data from animal studies suggested that it is possible to treat CHF by inserting genetic materials or myogenic cells into the injured myocardium.[61]

Cardiomyocyte transplantation into the infarct regions arising from coronary artery ligation yielded successful outcomes. However, only 33% of cardiomyocyte-injection sites demonstrated viable cardiomyocytes. Some clinical trials have been initiated using crude bone marrow-derived stromal cells. Autologous bone marrow transplantation was preliminarily successful for DCM and CHF;[62] we performed such successfully in two cases of unrelated cord blood transplant for complicated heart diseases. A clinical trial demonstrated the relative safety of intramyocardial injections of bone marrow-derived stem cells in humans with severe CHF and the potential for improving myocardial blood flow with associated enhancement of regional and global LV functions.[63] However, mobilization of bone marrow stem cells by granulocyte-colony-stimulating factor is considered to be an alternative to invasive transplantation of autologous myoblasts or stem cells directly into injured cardiac tissues. Intracoronary injection of autologous bone marrow-derived mononuclear cells has been performed; the findings suggested that cell therapy is a potentially safe and effective procedure in patients with CHF. It improves recovery of LVEF in patients with post-infarction CHF.[64] The transendocardial delivery of ixmyelocel-T for CHF due to ischemic DCM can significantly reduce clinical cardiac events.[65] A new study found that extracellular vesicles from human induced pluripotent stem cell-derived cardiovascular progenitors, as substitutes for cell transplantation, are effective in the treatment of CHF.[66]

Further knowledge on stem cells is needed to establish a standard protocol for cellular therapy. Cell-based therapies may have a potential application in neovascularization and regeneration of ischemic and infarcted myocardia and blood vessel reconstruction.[67] Stem cell therapy may be combined with pharmacological, surgical, and interventional therapies to improve the outcomes of CHF.

Tissue engineering

Tissue engineering strategies include endothelial cell seeding of vascular grafts, tissue-engineered vascular conduit use, heart valve leaflet generation, cardiomyoplasty, genetic manipulation, and *in vitro* condition stimulation for optimizing tissue-engineered cardiovascular constructs.[68]

Tissue-cell-gene combined therapy

If specific genes are transferred to stem cells, more efficient results may be obtained. In fact, it has been reported that mesenchymal stem cells genetically enhanced with the *Akt1* gene can repair more effectively infarcted myocardia, prevent remodeling, and nearly normalize cardiac performance.[69] Transfection of the gene for human hepatocyte growth factor combined with cellular cardiomyoplasty might regenerate the impaired myocardium possibly by stimulating angiogenesis,[70] restoring the impaired extracellular matrix, and promoting the integration of the dissociated grafted myocytes. The combined effects might improve cardiac performance. The potential use of stem cells as GT delivery cells is currently being studied. Thus, cell therapy combined with GT may be a promising strategy for the treatment of CHF. However, scientific and ethical issues also arise with the use of human stem cells.

Rehabilitating engineering

Cardiac rehabilitation (CR), as a nonpharmacologic therapy, is also very important in the management of CHF. Enhanced external counterpulsation (EECP) is a non-invasive outpatient treatment for cardiovascular diseases refractory to medical and/or surgical therapy. It is suitable for the treatment of a variety of cardiac conditions, including CHF. Augmented diastolic pressure and retrograde flow improve myocardial perfusion, while systolic unloading reduces cardiac workload and oxygen requirements. As a result of this treatment, most patients experience increased time to onset of ischemia, increased exercise tolerance, reduced number and severity of anginal episodes, and improved QOL. EECP plays as an emerging non-invasive outpatient therapy in CHF management. Based on the findings of a multicenter feasibility study, EECP is possibly the most potentially useful treatment in patients with CHF.[71]

Health education, including the complete explanation of various topics and disease management programs, can reduce hospitalizations. Psychological interventions in patients with CHF are necessary for their recovery.[72] Sports, as a therapy, should be considered as an additional or alternative strategy as compared with established pharmacological or

interventional options. In a recent meta-analysis, exercise therapy reduced the relative risk of CHF mortality by 35% and CHF-related hospitalizations by 28%.[73] Further, it increased exercise tolerance and perceived physical function. A randomized controlled trial found that a sustained improvement in QOL in CHF with moderate exercise training was associated with reduction in major CVEs, including hospitalizations and cardiac mortality.[74] It may improve the high-density lipoprotein-mediated vascular effects in CHF.[75]

At the same time, CR programs in patients with CHF are useful for improving their work capacity and psychosocial status. A specialized in-hospital CR program including education, patient self-management, and training has a sustained positive effect on cardiopulmonary parameters and physical well-being of patients with CHF. In addition, home-based hydrotherapeutic thermal programs and functional electrical stimulation also improve QOL and symptoms of patients with mild CHF.[76,77] Nursing focuses on education and self-management, spiritual support, and setting up good relationships. Intravenous administration of ferric carboxymaltose significantly improved the QOL of patients with anemia, iron-deficiency, and CHF.[78] Flavanol-rich chocolate acutely improved the vascular function of patients with CHF.[79]

A new therapy called palliative care for CHF is conducted worldwide owing to rapid aging.[80] It focuses on communication, shared decision making, and advance care planning; provides relief from pain and other distressing symptoms; integrates psychological and spiritual aspects of care; and offers a support system to help families cope during the course of CHF. This person-centered care approach shortens hospital stay and maintains functional performance in patients hospitalized for worsening CHF,[81] without increasing the risk for readmission.

Risk stratification in CHF is crucial for clinical and therapeutic management, as well as decision-making for CR, and a multiparametric score approach is a better method in stratifying patients' prognosis (Table 3).[82–85] For example, a BNP level at discharge of $\geq$250 pg/ml and a plasma creatinine level of >1.5 mg/dl are strong adverse outcome predictors,[86] and renal dysfunction is also crucial in the risk stratification of CHF.

Table 3
Clinical variables for risk stratification of patients with CHF and rehabilitation.

Types of variables	Content
1. Clinical determinants	History of ischemic heart disease
	History of cardiovascular disease
	History of acute and chronic heart failure
	Insulin-dependent diabetes mellitus
	Chronic renal failure (i.e. serum creatinine >2 mg/dl)
2. Clinical markers	Age
	Female
	Blood pressure
	BMI
	Waist circumference
	Mid-upper arm circumference
	Frailty
	Nutritional Risk Index
	Renal function
3. Plasma biomarkers	Sodium concentration
	Admission and discharge NT-proBNP[83]
	Circulating adiponectin concentrations (HDL-C/triacylglycerols)
	Plasma BNP + Duke Activity Status Index (DASI)
	cTnI, hsCRP, and NT-proBNP (simultaneous measurement)
	eCrCl (BSA)
	Growth differentiation factor-15
4. Clinical scores	Metabolic Exercise test data combined with Cardiac and Kidney Indexes[84] (MECKI score)
	HF Survival Score
	Seattle HF Model
	NT-proBNP risk score[85]
5. Exercise capacity	Cardiopulmonary exercise testing
	Resistance exercise training
	Ventilatory gas exchange variables
	Ventilatory response to exercise
	A simple sarcopenia screening test
	Skeletal muscle phenotypes (muscle mass, fiber morphology, histochemistry)
6. Others	Guideline adherence

CHF: chronic heart failure; BMI: body mass index; NT-proBNP: amino-terminal pro-B type natriuretic peptide; HDL-C: high-density lipoprotein cholesterol; BNP: B type natriuretic peptide; cTnI: cardiac troponin I; hsCRP: high sensitivity C-reactive protein; BSA: body surface area; HF: heart failure.

Summary

Patients with end-stage CHF unresponsive to medical management have had no other viable alternatives in the past decades. However, with the development of biomedical engineering in the new era, there are six strategies for CHF, which we have summarized and mentioned above; they can be selected according to the patients' status, such as nutritional, economic, and QOL issues. As a standardized, comprehensive program for CHF (Table 4), the iRT-ABCDEF may be suitably conducted in different countries worldwide. Mass prevention is always the best therapy for chronic

Table 4
iRT-ABCDEF as a standardized comprehensive program for CHF.

iRT-ABCDEF	Tips
F	Follow-up registered subjects or patients, especially populations with CVD family history, IGT or diabetes, and unhealthy lifestyle for primary and secondary prevention. It's very important to population-based study.
E	Examination for early diagnosis, treatment, and prevention, which includes regular comprehensive or targeted physical examination, such as biomarkers (BNP-based screening), FBG, PBG or OGTT, echocardiography, and others.
D	Disease and risk factor control, which includes hypertension, dyslipidemia, coronary heart disease, arrhythmia, IGT, diabetes, heavy drinking or smoking, obesity, chronic infection, and chronic kidney disease, and other CVD).
C	Change unhealthy lifestyle by SEEDi$^{1.0-3.0}$ technologies, such as don't stay up later, physical activity, smoking cessation, don't drink, and cut genetic pathways by gene knockout or gene-editing technologies.
B	Biohazard control, which includes abnormal symptoms and signs, abnormal physiological indexes, biomarker BNP level, CVD family history, major CVEs, intensive weight management for obesity, and control of diabetes.
A	Antagonistic treatment, which includes control of hypertension, lipid level, arrhythmia, and other CVD by pharmacotherapy or non-phamacotherapy, such as ACEI/ARB, beta-blockers, diuretics and statin-based treatment as well as other biomedical engineering technologies. Traditional Chinese medicine (TCM) is also a good selection.
iRT	intervention with above strategies as routine, right, and reversible treatment.

CHF: chronic heart failure; CVD: cardiovascular disease; IGT: impaired glucose tolerance; BNP: B type natriuretic peptide; FBG: fast blood glucose; PBG: postprandial blood glucose; OGTT: oral glucosetolerance test; CVEs: cardiovascular events; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; SEEDi$^{1.0-2.0}$ strategies were developed on the basis of five core healthy elements, i.e., internal and external environments, sleep, emotion, exercise, and diet. When combined with the iRT-ABCDEF and Grade 210 prevention, it becomes the 3.0 version of the SEEDi (SEEDi$^{3.0}$).

diseases.[87,88] To date, with the epidemic of diabetes mellitus,[89] it is important to pay more attention to its prevention and related cardiovascular risk stratification for avoiding CHF.[90] With the success of transcatheter aortic valve implantation in animals using a new balloon-expanding valve stent,[91] it is highly possible that one of these new therapeutic strategies or a combination of them will have a significant impact on the future management of CHF.[92,93]

Conflict of interest

The authors declare that there are no competing interest.

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