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RECENT UPDATES ON THE TREATMENT OF HEART FAILURE: A REVIEW OF THE LITERATURE

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ABSTRACT: The goal of this review is to supply an overview of the ongoing pharmacological, surgical, and instrumental techniques that are being used to deal with heart failure. This study will also propose a new concept of "second body cavity" based on the ongoing development of new cardiac devices and therefore offers as reference for future studies and research. This article presents a complete overview of options for treating end-stage heart failure, the concept of "second body cavity," and the implantation and administration of surgical and instrumental devices. Therefore, we hope that this paper will provide some possibilities for future research studies and improvement of the different strategies such as ASD based on the concept of "second body cavity."

Keywords: Active hydraulic ventricular support drug delivery system, second body cavity, heart failure, pharmacological therapy, phytotherapy, device treatment.

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1.INTRODUCTION

Heart failure (HF) is a situation in which the muscle can't pump adequate blood to the body. The early signs of HF are dyspnea and fatigue after exercising or at rest. Dyspnea due to fluid that backs up into the lungs or when oxygen-rich blood isn't provided to the body.

Patients with end stage coronary heart failure fall into category III–IV of the New York Heart Association (NYHA) functional classification [1]. The development of HF syndrome occurs in stages, that are beginning with a cardiac arrest or long-term excessive blood stress that has a decreased ventricular performance and extended ventricular wall stress as outcome. Various pharmacological and non-pharmacological treatments have evolved, not only to improve underlying cardiac diseases but also to prevent hospitalization and death. Pharmacological remedy includes: β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), Calcium channel blockers (CCBs), and Diuretics. Evidence confirmed that these drug treatments are able decrease mortality and re-admissions [2]. Nevertheless, the prospect is nonetheless insufficient, and a great proportion of these patients progress to advanced HF. Further surgical interventions for chronic heart failure (CHF) include coronary revascularization, valve repair or replacement, and biventricular pacing as appropriate. Current interventions stay unsatisfactory for many patients as contemporary treatments often fail to control symptoms and restore quality of life [3]. Except for heart transplantation, for which the epidemiologic impact remains restrained by the donor pool. The quest for alternatives interventions exploring the roles of additional pathways that contribute to the development and progression of HF therapy has accelerated and alternative interventional therapies for the treatment of HF are demanded [4]. In this review, we will talk about ongoing drug, surgical and device treatment for coronary heart failure. We will also present the latest evidence from experimental studies on the development of an active hydraulic ventricular support device (ASD) based on the "second body cavity" concept proposed by the external intervention strategy, which has emerged in treating heart failure.

PHARMACOLOGICAL TREATMENT

Pharmacologic remedy of heart failure with reduced ejection fraction (HFrEF) pursuits to decrease the development of heart failure and lengthen survival, whereas therapy for patients with heart failure with preserved ejection fraction (HFpEF) focuses on monitoring quantity status, controlling the blood pressure, and managing the presence of one or more disorders.

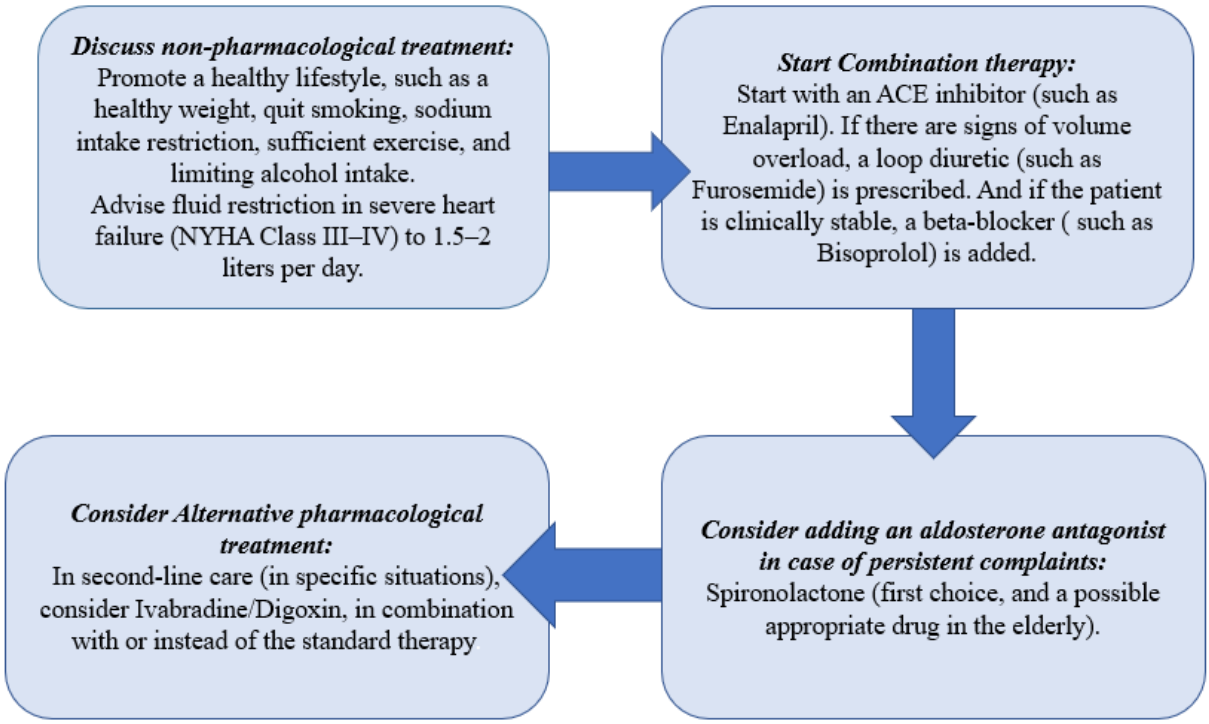


Table 1: A treatment plan according to the Dutch Society of General Practitioners (Nederlands Huisartsen Genootschap) in the treatment of heart failure according to the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2021

Angiotensin-Converting Enzyme Inhibitors (ACEi) and Angiotensin II-AT 1 Receptor Blockers (ARBs)

The renin-angiotensin gadget (RAS) performs a crucial function in the pathogenesis of heart cardiovascular diseases. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II is an effective vasoconstrictor and it stimulates aldosterone secretion, which consequences in accelerated sodium and water retention. ACEi inhibits angiotensin I to change to angiotensin II, whereas the angiotensin II-AT 1 receptor blockers (ARBs) block the angiotensin II type 1 receptor. It is shown that ACEi are the favored drug class due to the clinical benefits, whilst ARBs are prescribed to patients who are allergic to ACEi or go through undesirable adverse drug events.

Beta-(Adrenoreceptor) Blockers (β-blockers)

Beta blockers block the action of the hormone, epinephrine. Blocking the release of these hormones lowers stress on the coronary heart and reduces the pressure of the contractions of the coronary heart muscle. In turn, it also takes away the pressure from the blood vessels in the heart, the brain, and the rest of the body. Beta-blockers are often prescribed after a coronary heart attack, for heart cramps (angina pectoris), irregular heartbeat, and for excessive blood pressure, collectively together with ACE inhibitors, β-blockers are the fundament of clinical therapy for all tiers of coronary heart failure.

When using beta-blockers in chronic HF, caution is required due to the risk of an abrupt decline in left ventricular systolic performance, which could aggravate the clinical state [5].

Calcium Channel Blockers (CCBs)

CCBs are broadly used pharmacological agents in the treatment of heart failure. They exert their action through selectively blocking off the cell entry of calcium through calcium channels on the cell membranes. They have a range of therapeutic applications, which includes angina, excessive blood stress and supraventricular arrhythmias treatment. CCBs block the mobile entry of calcium through L-type calcium channels and, in doing so, limit the concentration of free intracellular calcium. Clinically, it will result in a reduction in afterload and extended coronary perfusion, anti-dysrhythmic activity, and decreased contractility. CCBs are a heterogeneous group of drugs that can be chemically categorized into the dihydropyridines (DHPs) and the non-DHPs [6].

Diuretics

Diuretics are one of the mainstays in the therapy of heart failure. They are the first-line treatment for patients with chronic heart failure, disregarding of aetiology, age, sex, and personal traits of the patient, since they supply symptomatic relief [7-9]. The loop diuretics exert their effects extra proximally and are the most desirable of all the diuretics. The diuretics specifically fluctuate in their duration of action (e.g., Furosemide 6-8 hours, Hydrochlorothiazide 6-12 hours, Metolazone 12-24 hours) and in their ability to cause sodium excretion (‘low ceiling’ diuretics like Hydrochlorothiazide or ‘high ceiling’ diuretics like furosemide). As HF progresses, an extend in absorption and failure to filter the drug in the tubular fluid may be the contributing elements to the need for increasing diuretic doses in some patients [10-12]. Loop diuretics are often used in patients with HF and volume overload.

Ivabradine/Digoxin

Ivabradine is a selective blocker that lowers heart rate without the functional impairments and blood pressure-lowering side effects seen with beta-blockers. Ivabradine lowers the risk of being admitted for worsening heart failure and mortality in patients with sinus rhythm who have an excessive resting heart rate (>75 BPM) despite being titrated to their maximally acceptable beta-blocker dose [13]. The reason for taking ivabradine in heart failure patients is that it slows down the heart rate, allowing more time for diastole. Digoxin is a glycoside that can be used to reduce the heart rate in people with a very rapid uncoordinated contractions of the atria resulting in a lack of synchronism between heartbeat and pulse, who have failed to respond to ivabradine. Digoxin enhances left ventricular filling by slowing conduction in the atrioventricular (av) node by increasing the parasympathetic tone. This results in a lower heart rate, longer diastole, and hence better left ventricular filling. Furthermore, digoxin alters the force or energy of muscular contractions and increases intracellular calcium levels by blocking the Na/K pump, thereby stimulating Na/Ca exchange.

PHYTOTHERAPY

Plant-derived medications

In the management of chronic heart failure, two groups of cardioactive phytopharmaceuticals are worthy of consideration in terms of pharmacodynamically appropriate components, pharmacological characteristics of action, and therapeutic efficacy.

These two groups are:

- extracts which contain cardiac glycosides (Fig. 1).
- extracts of Crataegus (hawthorn) leaves and flowers (Fig. 2).

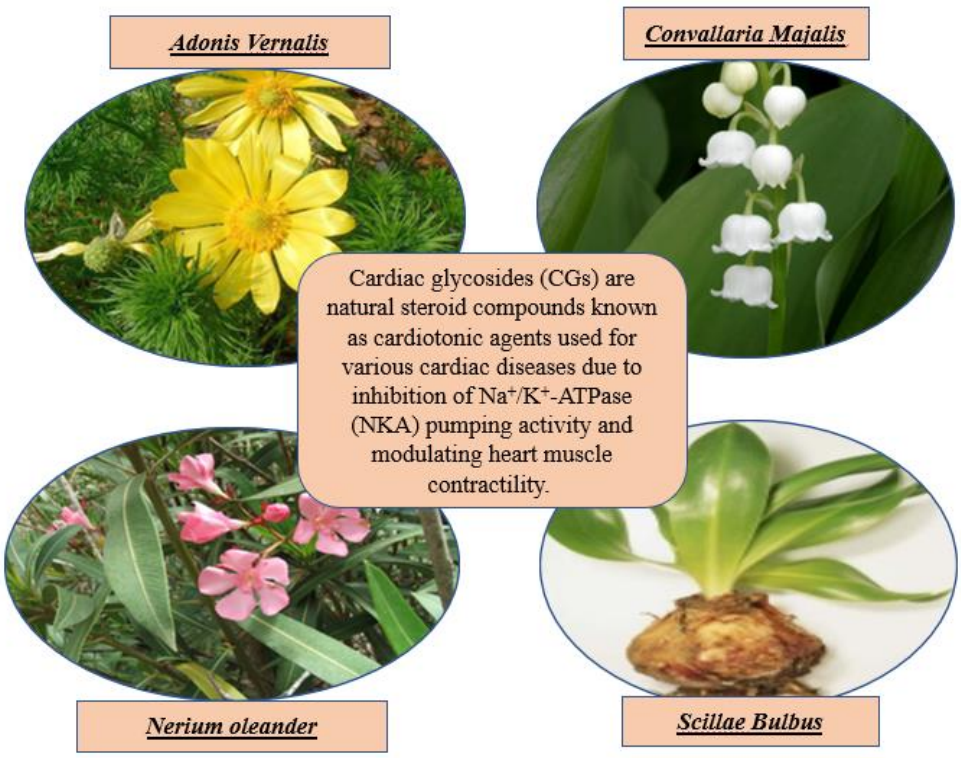


Figure 1: Plant extracts containing cardiac glycosides [14]

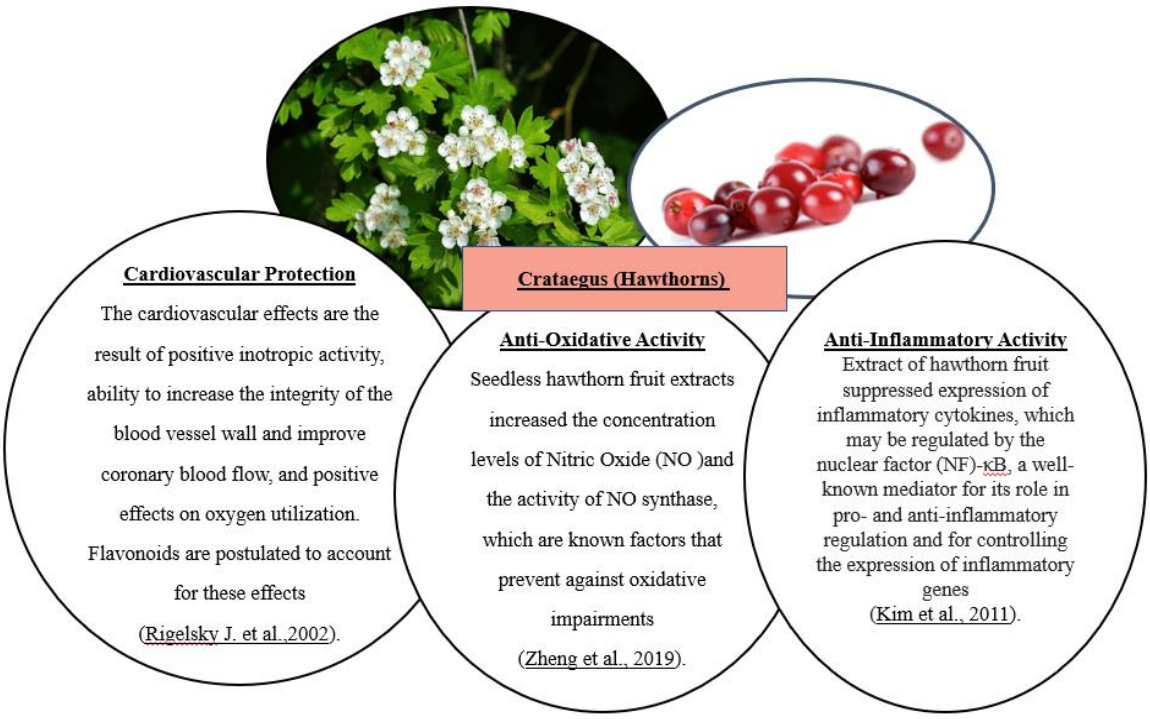


Figure 2: Mechanisms of the Extracts of Crataegus leaves and flowers [15]

Surgical Treatment

Even though pharmacological therapy has made significant progress in the last years and is now the standard care for heart failure (HF), there is still a significant unmet demand since morbidity and death rates keep on increasing. To treat these various medically refractory patients with heart failure, several novel surgical methods have emerged, with the goal of improving ejection fraction, quality of life, and eventually survival.

Coronary Artery Bypass Grafting (CABG)

Patients with ischemic left ventricular dysfunction could benefit from coronary artery bypass grafting (CABG) [16]. A coronary artery bypass graft is a procedure that includes attaching a blood vessel from another part of the body (typically the chest, leg, or arm) to the coronary artery above and below the narrowed area or blockage. A graft is the term for a new blood vessel. The number of grafts required is determined by the severity of the coronary heart disease and the number of blocked coronary blood vessels. The Veterans Affairs Cooperative Study of Surgery [17] demonstrated a substantially higher survival rate in a subset of patients with reduced left ventricular ejection fraction (EFs) (50%) after coronary bypass operation versus those who were randomized to a therapeutic strategy. Elefteriades and colleagues [18] demonstrated that coronary artery bypass operation in patients with EF 30% had a survival rate of 80% at 4.5 years.

Implantable Cardioverter Defibrillators (ICDs)

The ICD's main goal is to safeguard patients from death due to ventricular tachyarrhythmia (VTA) by providing a cardioverting or defibrillating shock and/or antitachycardia pacing (ATP). The role of ICD in patients with persistent ventricular arrhythmias has been confirmed in some clinical trials,

and the indications have broadened to comprise patients with coronary artery disease, left ventricular dysfunction, non-sustained ventricular tachycardia, and inducible ventricular tachycardia. Beside it benefits, it also has it risks. In a study of 446 individuals, the total risk of any early problem after ICD implantation was found to be 6.7 percent, with 4.9 percent requiring intensive treatment. Late procedure problems were reported in 3.1 percent of the cases [19].

Valvular surgery

When valves are damaged or diseased and do not work the way, they should need to be repaired or replaced. Valve stenosis (stiffness) and valve regurgitation (leaky valve) can be the causes of heart valve dysfunction. Valvular surgery is a surgical procedure performed for the management of these heart valve dysfunctions. It includes repairing or replacing dysfunctional or damaged heart valves.

Surgical Ventricular Restoration (SVR)

Surgical ventricular restoration is a surgical method that was created to try to counteract the unfavorable remodeling that happens after a heart attack. Ventricular restoration focuses on excluding more subtle regions of akinetic myocardium. The Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical shape to the LV (RESTORE) group reported in 2004 that there was an increase in ejection fraction (EF) from 29.6% to 39.5%, a decrease in end-systolic volume index, after ventricular restoration, and considerable improvement in NYHA function class [20].

Cardiac Resynchronization Therapy (CRT)

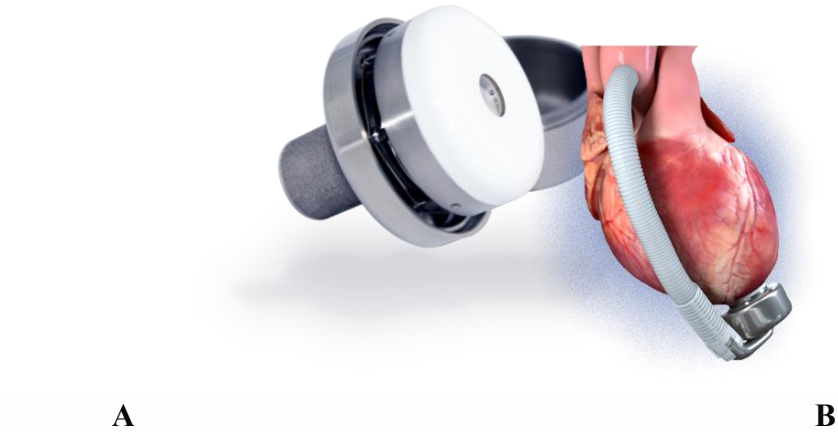
Cardiac resynchronization therapy (CRT) was first established in the 1990s and has been the improved treatment for many individuals with systolic heart failure [21]. CRT aims to reestablish mechanical coherence by electrically stimulating the heart in a synchronized approach.CRT works by pulsing an electrode in an epicardial coronary vein to increase cardiac performance. A catheter is inserted into the coronary sinus and then slid into a draining coronary vein to install the epicardial left ventricular electrode. CRT together with adequate medical therapy improves HF symptoms, left ventricular ejection fraction (LVEF), and quality of life (QOL), thereby reducing heart failure admissions and longevity [21]. Nonetheless, this procedure has the same risks as any other pacemaker procedure, including infection, lead removal, perforation, and so on.

Instrumental Treatment

Heart failure with preserved ejection fraction (HFpEF) is a syndrome with an unfavorable prognosis, and the number of the patients continues to grow. Because no successful therapy, including pharmacological treatments, has been established as a standard, a drive to develop and evaluate device-based therapies is an important emerging area in the treatment of heart failure. Many instruments have set their target to reduce the left atrial pressure or pulmonary capillary wedge pressure such as: (1) interatrial shunt devices, (2) left ventricular assist devices, and (3) mechanical circulatory support devices.

Corwave Left Ventricular Assist Device

CorWave LVAD is a unique implantable novel heart pump (*Fig. 3A*) that gives new hope to end-stage heart failure patients. It can work in synchrony with the heart without the aid of sensors for over 30 days. This is the first time that a miniaturized pericardial pump has achieved this synchronisation.This study [22] done by French heart device company CorWave demonstrated sensorless synchronisation of a pericardial pump with the native heart for over 30 days. This study is an important step towards making the next-generation heart pump available to patients with advanced heart failure. CorWave LVAD can be implanted sternotomy and/or thoracotomy (Fig. 3B). Its ability to reproduce a physiological pulsatile flow aims to reduce existing complications and improve patients' lives.



A **B**

Figure 3. Corwave [19]

(A) CorWave physiological Heart Pump; (B) CorWave LVAD implant

Aeson, The CARMAT total artificial heart

The CARMAT total artificial heart was first implemented by Prof. Jan D. Schmitto and his associate Heart Team of the Department of Cardiothoracic and Transplant Surgery at Hannover Medical School, in Germany [23]. Aeson is an electro-hydraulic device with a shape like that of a human heart. It includes an implantable bio-prosthesis and a movable external power supply system. Once linked, the device mimics the performance of a normal heart, giving mechanical circulatory support and maintaining optimal blood flow throughout the body.

Corvia InterAtrial Shunt Device

The InterAtrial Shunt Device (IASD, Corvia Medical, Tewksbury, MA, USA) is the first transcatheter device (*Fig. 4C*) developed to target heart failure with preserved ejection fraction (HFpEF) or mid-range ejection fraction (HFmrEF) [24]. The IASD implantation, is placed after a tiny opening is made in the atrial septum, establishing a route between the left and right atria (*Figure 4A*) that allows the left atrium to loosen up at rest and during exercise, decreasing left atrial tension. The implant method entails trans-septal catheterization, which is performed using standard methods

and supported by either transesophageal or intracardiac echocardiography (*Fig. 4B*).

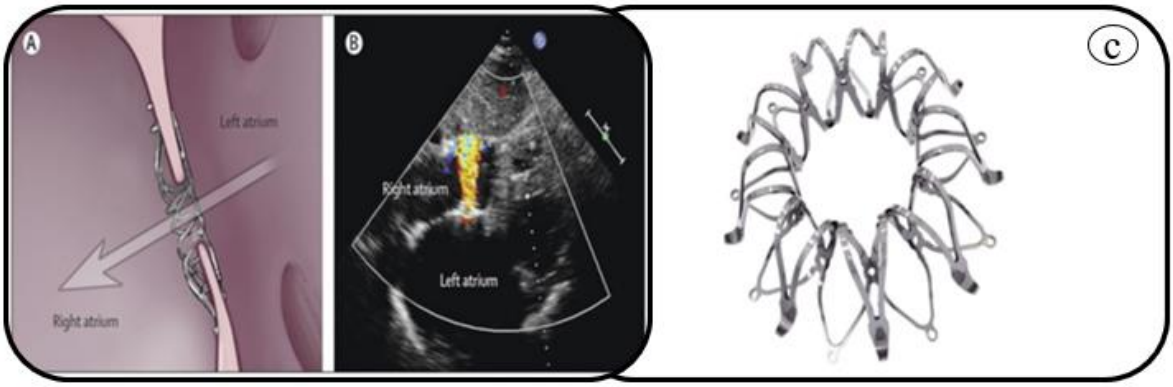


Figure 4. Device schematics and applicability [24]

(A) Device placement in the interatrial septum, blood flow from right to left;

(B) An echocardiographic image showing left to right blood flow;

(C) The InterAtrial Shunt Device (IASD)

Second Body Cavity

A single mechanical aid to support the ventricle and the treatment of biologically active substances has made great progress in heart failure. Therefore, further research on the combination of mechanical therapy and biological therapy is a particularly attractive treatment strategy for patients with heart failure. Based on this, a new concept "second body cavity ventricular assist device" is proposed, which is in direct contact with the epicardium, and the body is filled with liquid or gas. When it is filled with liquid or gas, it plays a role of physical support for the hydrodynamic skeleton. The microporous structure or permeable material can deliver drugs and other substances to the surface of the epicardium to promote the formation of blood vessels and the repair of tissues. It can not only provide support for the ventricle, prevent bad remodeling, but also serve as a reservoir for drugs, cells, etc., slow-release and repeated delivery to the epicardial surface, resulting in a local therapeutic effect. In addition to the above functions, we also hope that this kind of device can detect the physiological, biochemical, and pathological signals of the heart, and provide clearer scheme for the diagnosis and treatment of diseases. This type of device is a comprehensive treatment effect for advanced heart failure and provides a new development for ventricular assist devices.

Introduction and concept

Interventional therapy for cardiovascular disease (defined by our group as an "intramural" strategy) has become increasingly widespread, especially in the treatment of myocardial infarction. However, this method is mainly used for intravascular operation. And the direct contact of instruments with blood and vascular endothelium causes more post-operative complications. Moreover, the operation space of this method is relatively limited, which results in a small degree of expansion of the operation itself, related instruments, and therapeutic effects.

Correspondingly, the epicardium has unique anatomical and histological structure. It is one of the anatomical structures closest to the normal or diseased heart tissue and is a more direct and clearer site for detecting various physiological and pathological signals of the heart. In addition, due to its origin from the same progenitor cell pool as cardiomyocytes, many recent literatures have proved that epicardium plays an important role in heart development, regeneration, injury repair, and clinical diagnosis. More importantly, there is a huge potential gap between the epicardium and other organs in the thoracic cavity. Therefore, focusing on the diagnosis and treatment of cardiac lesions, our research group proposed an "external intervention" diagnosis and treatment strategy with the epicardium as the target organ. By establishing a cavity between the body surface and the epicardium, an artificial independent cavity structure that exists both in the body (attached to the outside of the heart), and the outside of the body. Our research team defines it as " The second body cavity". Many instruments or devices for detecting sensing, pressure delivery, and drug release can be placed in it. Unlike the internal intervention method, the following functions can be realized in an integrated and multimodal manner:

① by implanting various physical and chemical signal detectors in the second body cavity, a variety of cardiac physiological, biochemical, and pathological signals can instantly be detected. It can also directly collect epicardial in situ exudate for multi-omics joint analysis, and then conduct real-time, dynamic, and diversified cardiac function monitoring and assessment.

② by connecting with the external pressure generating device.

The second body cavity can directly support and restrain the heart physically, and even generate active and arbitrarily adjustable pressure outside the ventricle, which in turn generates a direct auxiliary pumping effect, thereby inhibiting, or even reversing it myocardial remodeling and energy metabolism disorders in heart failure.

③ by connecting with the in vitro drug delivery system. The second body cavity is filled with various chemicals, traditional Chinese medicines, biological agents, stem cells, and a mixture of the ingredients to achieve the function of local epicardial delivery.

It can provide high-concentration, individualized, and dynamically adjusted precision drug treatment programs for local heart disease, thereby improving the effectiveness of medication. Because it does not directly contact the blood and vascular intima, meaning that it is not a systemic method of administration, so the systemic side effects of the drug will also be significantly low, thereby improving the safety of medication. In short, the "external intervention" diagnosis and treatment strategy may achieve a more excellent effect, wider expansion, and better safety than the "internal intervention" strategy. Cardiac patches and non-blood contact devices belong to the strategy of external interventional therapy, which play a very important role in the treatment of cardiac diseases.

Non-Blood contacting Cardiac Assist Devices

Despite numerous CAD models and material progress made over the years in order to alleviate chronic pump thrombosis, the problem persists, and the proper prescription and frequency of long-term antithrombotic therapy is still unknown. Numerous companies are now developing non-blood contact devices to overcome this obstacle.

The Anstadt Assistor Cup

In 1945, Anstadt proposed the concept of a non-blood contact dual-ventricular assist device, called direct mechanical ventricular actuation or Anstadt cup [26], which was first used clinically in 965. It is composed of an outer shell and an internal flexible diaphragm. It is attached to the two ventricles through a continuous vacuum at the top. In many animal experiments, it has been found that the device not only compresses the ventricle to produce contraction, but also assists the diastolic ventricle to enhance filling. At the same time, studies have found that the device can improve the contraction and diastolic expansion of small failing hearts. This beneficial effect can be used in pediatrics and provides a new treatment method [27].

The AbioBooster

Although the AbioBooster and Anstadt cup are both pericardial devices and have a cup-like structure, there are obvious differences between the two. The device is designed and manufactured by ABIOMED [25, 28]. It is an inflatable cuff whose shape roughly conforms to the shape of a natural heart. The cuff is formed by a series of interconnected closed tubes. Flexible, non-expandable, fluid-tight material is formed and can be filled with gas. The expansion of the tube results in a smaller closed volume, while the contraction of the tube results in a larger closed volume. Its role is to synchronize with the heart during the systole to assist the heart to expel blood during the systole, and to relax with the heart during the diastole without hindering the diastolic filling. To enhance the long-term performance of DCCSs, researchers have been attracted to new soft robotic technologies lately, such as The Soft Robotic Sleeve and The Adjucor Beat Device.

The Soft Robotic Sleeve

The Roche team from Harvard University created a soft robotic sleeve, which is placed around the damaged heart, and the pneumatic and soft contraction actuators are arranged in a ring and spiral form to act as a ventricular assist device [29]. Custom-designed soft pneumatic artificial muscles (PAMs) are used as a single contraction element or actuator in a layered spiral and circular manner, imitating the direction of the two outer muscle layers of the mammalian heart, both in contraction and relaxation. Closely consistent with the heart. The device provides a multifunctional platform to manipulate the mechanical environment of the heart to achieve the purpose of cardiac rehabilitation.

The Adjucor Beat Device

The new product developed by Adjucor company is different from the listed instrument treatment device [30]. It is a special anatomical structure product customized based on the patient's ventricular

size. It is sleeved around the heart to avoid contact with blood. At the same time, it enhances the blood pumping function by giving the heart contractile force and synchronizing with the natural rhythm of the heart. In a 60 days pre-clinical study, it was found that the device showed chronic physiological acceptability, individualized anatomical fitting, and no complications. Therefore, there is no need for strong pharmacological intervention after operation, such as anticoagulation.

Heart patch

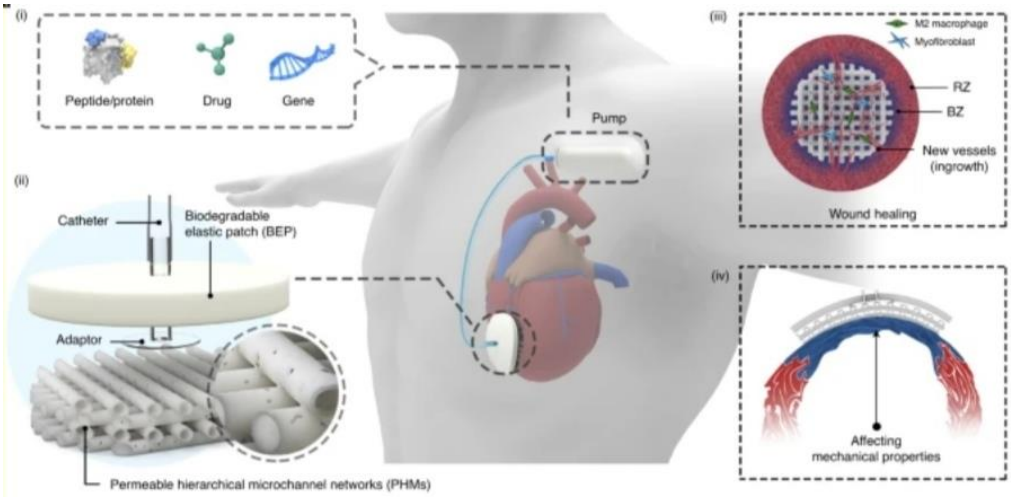
Heart patch is an engineered material and structure attached to the surface of the epicardium to repair myocardial damage caused by myocardial infarction (*Fig.7*). It is composed of a therapeutic component and a matrix scaffold. The therapeutic components of heart patch range from cells (such as skeletal myoblasts, mesenchymal stem cells, and human pluripotent stem cells) to biologically active molecules (including growth factors, microRNAs and extracellular vesicles) [31]. Scaffolds can improve the survival, retention, and repair of cells after implantation, and are composed of natural or synthetic biological materials, such as chitosan, hydrogel, and fibrin. Heart patches made of biological materials, provide a potential treatment for severe myocardial infarction (MI) and subsequent heart failure. Based on the delivery of active substances such as drugs and stem cells to the epicardial surface of the heart patch to produce effective treatment for cardiovascular diseases, the current research results of combining biomaterials and cells to treat myocardial infarction, and a further second body cavity device provides the idea as described earlier.

Ventricular Assist Device

The PerMed

A perfusion multifunctional epicardial device called PerMed (*Fig.5*). It is assembled by biodegradable elastic patch (BEP), permeable hierarchical microchannel networks (PHMs) and conveying system. BEP exhibits bionic elasticity and strength, provides effective mechanical signals for the weak ventricular wall, and promotes tissue repair. Bionic vascular-like PHMs have a hierarchical framework, interconnected microchannels and permeable walls, which promote the mass exchange and infiltration of endothelial cells, myofibroblasts and macrophages, and can be used as a reservoir for therapeutic reagents, including drugs, genes, and growth factors to achieve sustained release of therapeutic drugs. Complementary design produces a comprehensive synergistic effect in tissue repair [32]. Studies have found that after myocardial infarction, PerMed implantation can improve ventricular function and poor ventricular remodeling. BEPs can reduce the end-diastolic diameter of the left ventricle, increase the left ventricular ejection fraction, significantly inhibit the dilation of the left ventricle, and improve heart function.

a



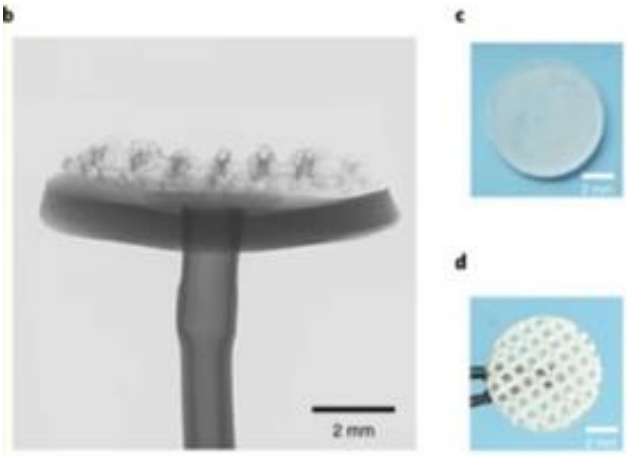


Figure 5(a) Schematic of PerMed components and its use for treating myocardial infarction; (b) 3D structure of the PerMed device by micro-CT; (c) Gross image of the BEP; (d) Gross image of a PHM **[32]**

An active hydraulic ventricular support drug delivery system (ASD)

ASD, a Silicone mesh-like device [33], designed by Dr.Xiaohui Zhou, is a non-transplant novel ventricular restraint device which has the ability to deliver a therapeutic drug directly to the heart.

The ASD is a non-transplant novel ventricular restraint mesh-like device [33], designed by Dr. Xiaohui Zhou. Composed of numerous hollow tubules, that encloses both ventricles of the heart which can relate to each other; the tubules have apertures (or without apertures) throughout the body on the side facing the epicardium (*Fig.6).*The hollow ASD tubules are linked together to form several independent areas, and the independent regions are interacting from the inner side but not interacting from the outer side. All the independent areas are forming a net-like structure, which has two or more than two ends that is tunneled to the outside of the body. The tubules of ASD can be filled with fluid, and it can contract and relax synchronically with the recipient heartbeat. Furthermore, the fluid in ASD tubules provides a proper microenvironment for stem cell survival. The ASD has potential to deliver drugs as well as stem cells locally from the apertures in the tubules

to the epicardium. Utilizing ASD to deliver the TCM drug, Salvia miltiorrhiza, in the treatment of heart failure, showed a reversal in cardiac function, and provided additional support to the dilated ventricle of HF rats according to Naveed et al. (2017) [34]. It has been observed by Yue et al. (2018) that ASD can deliver BMSCs to the cardiomyocytes successfully and broaden the therapeutic efficacy, in comparison to the restraint device alone. Li et al. (2019) concluded that ASD administration of nitroglycerine (NTG) improves systolic and diastolic LV function after Acute myocardial infarction (AMI) [35]. Liu et al. (2020) research concluded that bone marrow-derived mesenchymal stem cells (BMSCs) through ASD delivery, resulted in a significant increase of the left ventricular systolic pressure (LVSP), the maximum rate of left ventricular pressure rise (+dP/dt), the maximum rate of left ventricular pressure decline (-dP/dt). It was also confirmed that cells reached the myocardium more efficiently through ASD than IV delivery which has been considered effective for global myocardial injury [36].

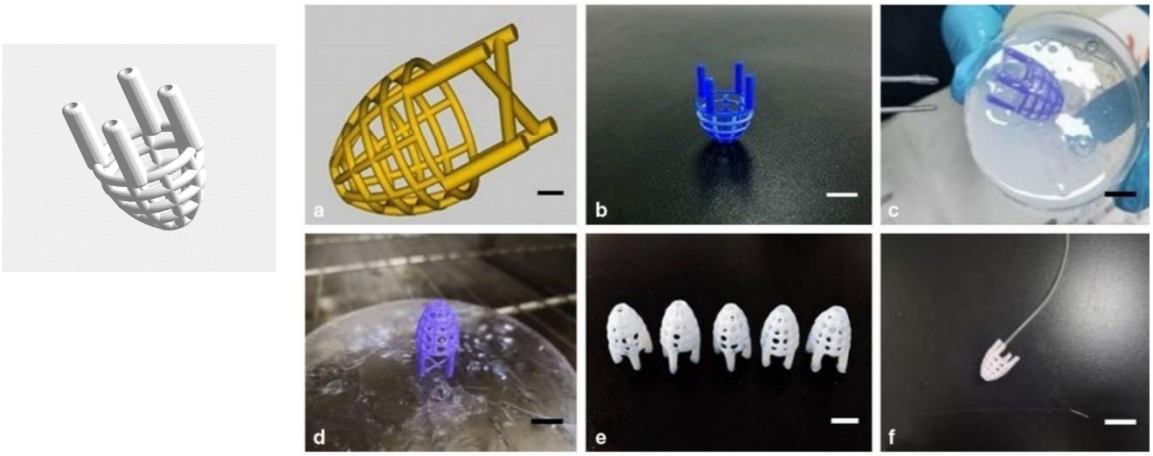


Figure 6 Active hydraulic ventricular support drug delivery system [35]

(a) 3D design of ASD, (b) ASD Blue wax printing model of ASD; (c) Blue wax model of ASD dropped into liquid silicone; (d) Blue wax melting from the ASD model in oven at 100℃ for 30 min; (e) ASD from pure silicone; (f) ASD attached with implantable catheter, scale bar100μm.

Summary:

Limitations and future development

As medical therapy for heart failure patients reaches a plateau, the upcoming years will have good prospects for heart failure patients. The future of device therapy will almost certainly be spectacular, given the growing need for hearts and the severe scarcity of donors. Optimized reliability will surely result from advancements in device design and construction. Several axial flow and updated centrifugal pumps are presently being tested in clinical trials around the world. According to preliminary data, the devices' durability has significantly improved. Furthermore, the smaller sizes

result in greater applicability to patients with smaller bodies, minimize infections previously associated with pump pockets (because they do not necessitate the development of a pump pocket), and ultimately lead to facilitating devices that involve comprehensive implantation within the body without exiting drivelines. Furthermore, these new technological improvements, combined with a better understanding of the cellular and molecular mechanisms of heart failure, may result in the final therapeutic goal: strategies that allow ruptured myocardium to be repaired through cellular or molecular engineering of the underlying substrate. ASD is made of silicon, so it is likely that 3D printed tiny ECG sensors and others desired multiple kinds of sensors can be loaded on a silicon membrane. It is believed that this advanced ASD 3D technology would improve the observation and estimation of heart function and conduct with more accurate electrophysiological treatment. In addition to conventional memory sensor signal detection, ASDs can also be used to collect pericardial exudates for in vitro laboratory analysis. At present, our laboratory under supervision of Professor Zhou Xiaohui, has successfully collected early epicardial exudation of acute myocardial infarction through ASD, and performed in vitro multi-omics analysis to screen new targets for disease treatment and identify diagnostic markers (based on new unpublished data from the laboratory) (*Fig.7*)

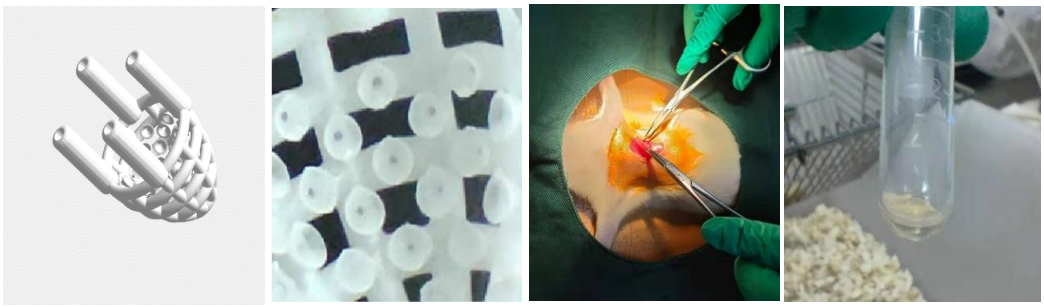


Figure 7 Collecting early epicardial exudation of acute myocardial infarction through ASD
(A) micropores in the inner wall combined with A micro-sucker structure attached to the epicardium; (B) Physical drawing of ASD inner wall mini sucker; (C) ASD was implanted on the epicardial surface of rats with early acute myocardial infarction; (D) Collected early epicardial exudate of acute myocardial infarction was analyzed in vitro. On the other hand, the mechanism of ASD utilizing nitroglycerine (NTG) through ASD showed a remarkable vasodilator effect, but further study will still be needed for the advancement of this technology to get a clear vision whether ASD influenced electrophysiology on the heart surface. Studies have also confirmed that cells reached the myocardium more efficiently through ASD than IV delivery which has been considered effective for global myocardial injury, but it remains to determine the BMSC differentiation in the myocardial, and the proper paracrine factors released by bone marrow stem cells (BMSC) that are beneficial for myocardial improvement. So, understanding paracrine mechanisms, mediated by stem cells, is

essential if stem cells through ASD are ever going to reach clinical importance. Thus, it is important to understand the potential benefits of the paracrine effects for myocardial repair. More animal studies of ASD will be essential to focus on several factors when delivering cells to the heart, such as the nature of the injury, timing of the treatment, and ability of cells to survive. Future advanced studies are needed to strengthen treatment benefits, especially to evaluate the effects of long-term drug delivery.

2. CONCLUSION

Heart failure therapy is extremely multifarious, and it is always improving, both clinically and scientifically. End-stage heart failure therapeutic interventions have evolved through the years, and include a combination of medications, plant-derived medications, mechanical devices, and surgical treatments that can help patients' symptoms and life expectancy. The drug classes responsible for this effect are Angiotensin-converting enzyme inhibitors (ACEi) that's indicated to expanding blood vessels, reduce blood pressure, and increase blood flow to assist the heart to pump blood easier. Beta-blockers, angiotensin II-AT 1 receptor blockers (ARBs), and angiotensin II-AT 1 receptor blockers (ARBs) are complementary medications for decreasing blood pressure and increasing blood flow, beta-blockers which decrease myocardial oxygen consumption and improve symptoms, Calcium Channel Blockers (CCBs) dilate blood vessel which results in a lowering of the blood pressure, while symptoms of fluid overload and congestion are treated with loop diuretics, which enhance the kidneys to rinse more fluid and salt from the body to help alleviate edema (swelling). Patients with symptomatic heart failure and low ejection fraction may benefit from surgical therapy such as coronary artery bypass grafting (CABG), implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy (CRT), while an effective therapy for severe aortic valve stenosis is surgical aortic valve replacement (sAVR). Instrumental therapy may be used to improve ventricular function, patient symptoms, and survival. To support the ventricle and the treatment of biologically active substances, a Second body cavity ventricular assist device can be used. Active hydraulic Ventricular Support delivery System (ASD) is a novel ventricular assist device based on the "second body chamber" concept, which is predicted to be a comprehensive therapy platform in treating superior cardiovascular diseases. In previous studies, drug delivery through ASD as a combination therapy, showed excellent therapeutic outcomes. In addition to this, different potent drugs can be delivered to the heart through novel ASD device more safely and effectively. Future studies about the clinical impacts and modification of the treatment process, as well as changes in patient eligibility criteria, are required to encourage further advancements in survival rates and patient quality of life, particularly in the setting of long-term circulatory support. This present study reviewed the implantation, drug administration, the benefits, and drawbacks of current and potential pharmacological, surgical, and instrumental treatment options of HF, and the concept of "second body cavity".

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest

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