

Annual Review of Biomedical Engineering
Direct Cardiac Compression
Devices to Augment Heart
Biomechanics and Function

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Keywords

heart failure, cardiac biomechanics, mechanical circulatory support, cardiac assist devices, direct cardiac compression, soft robotics

Abstract

The treatment of end-stage heart failure has evolved substantially with advances in medical treatment, cardiac transplantation, and mechanical circulatory support (MCS) devices such as left ventricular assist devices and total artificial hearts. However, current MCS devices are inherently blood contacting and can lead to potential complications including pump thrombosis, hemorrhage, stroke, and hemolysis. Attempts to address these issues and avoid blood contact led to the concept of compressing the failing heart from the epicardial surface and the design of direct cardiac compression (DCC) devices. We review the fundamental concepts related to DCC, present the foundational devices and recent devices in the research and commercialization stages, and discuss the milestones required for clinical translation and adoption of this technology.

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HEART FAILURE

Heart failure (HF) is a complex clinical syndrome caused by a structural or functional cardiac abnormality that results in reduced cardiac output (CO) and/or elevated intracardiac pressures, during effort or at rest (1). HF affects approximately 64 million people worldwide (2) with prevalence increasing with age; ~10% of people older than 70 years of age are affected (3, 4), with a 5-year mortality of ~50% (5). In the United States in 2012, the total direct costs of HF were \$30.7 billion (6) and these costs are expected to increase by 127% in 2030, reaching \$69.8 billion (7). Causes of HF include myocardial disease (e.g., ischemic heart disease, dilated cardiomyopathies), valvular disease (e.g., aortic stenosis), congenital heart disease, anomaly of the pericardium, or high CO etiologies (e.g., chronic anemia, arteriovenous fistula). Common symptoms of HF include fatigue, exercise intolerance, dyspnea, orthopnea, and ankle swelling, while typical clinical signs include peripheral edema, lung congestion, jugular vein distension, and abnormal heart sounds (B3, B4) (8). The severity of symptoms is graded according to the New York Heart Association functional classification and ranges from asymptomatic to severe symptoms at rest (5). HF is further classified as to whether left ventricular ejection fraction (LVEF) is conserved or reduced, using, for example, echocardiography or cardiac magnetic resonance imaging. HF with preserved ejection fraction (HFpEF) is the condition where LVEF >50%, HF with reduced ejection fraction (HFrEF) describes HF with an LVEF of <40%, and HF with mid-range ejection fraction includes patients with an LVEF of 40–50% (3). Depending on the time course of clinical symptoms, HF is described as asymptomatic, chronic stable, chronic decompensated, or acute. Cardiogenic shock (CS) is a reduction of CO leading to organ dysfunction (3). Acute HF and CS represent approximately 6% of admissions to intensive care, with a mortality up to 50% (9). Although HF is generally secondary to left ventricular dysfunction (10), it may also be consequent to right ventricular dysfunction (11).

Heart failure (HF): clinical syndrome describing the inability of the heart to pump enough to satisfy the metabolic needs of the organism

Left ventricular ejection fraction (LVEF): ratio between the volume of blood ejected during systole (stroke volume) and the volume of blood in the ventricle at the end of diastole

Heart failure with preserved ejection fraction (HFpEF): classification of heart failure when LVEF is preserved

PATHOPHYSIOLOGY OF HEART FAILURE

During systole—the ejection phase of the cardiac cycle—the healthy heart ejects sufficient blood or has adequate CO to provide oxygen and nutrients to the body. Similarly, during diastole—the filling phase of the cardiac cycle—the heart fills with blood at low ventricular filling pressures (12). HF may be characterized by either a reduced CO (systolic dysfunction or HFrEF) or an increase in the pressure of blood during ventricular filling [diastolic dysfunction (13) or HFpEF], or both. In HFrEF, clinical manifestations are dominated by fatigue and impaired organ function, while in HFpEF they are primarily related to systemic or pulmonary congestion (peripheral or pulmonary edema) (14).

Systolic and diastolic function can be understood by examining the ventricular pressure-volume (PV) relationship, as depicted in **Figure 1a**. This relationship describes the evolution of ventricular volume and pressure over the cardiac cycle. During diastole, the ventricle fills with blood, while pressure remains low. During systole, contraction of the cardiac muscle increases intraventricular pressure and allows ejection of blood, the amount of which defines the stroke volume (SV), that is, the difference between the end-diastolic volume (EDV) and the end-systolic volume (ESV) (in milliliters), such that $SV = EDV - ESV$. The number of cycles per minute defines the heart rate (HR), and the product of SV and HR is CO ($CO = SV \times HR$), in liters per minute. The ejection fraction (EF) is the ratio between ejected blood (SV) and total available blood at the end of diastole (EDV), or $EF = SV/EDV$. The concept of end-systolic elastance (E_{es}) (**Figure 1b**) provides an assessment of the intrinsic contractility of the heart muscle (15, 16). The maximal pressure developed by the ventricle at any given left ventricle (LV) volume is defined by the end-systolic pressure-volume relationship (ESPVR). The slope and x-intercept of the ESPVR are usually measured experimentally by occluding the inferior vena cava, and this occlusion reduces venous return to the heart. The line joining end-systolic points of consecutive PV loops (point 4 of **Figure 1a**) defines the ESPVR, and its slope is termed E_{es} , the reciprocal of compliance, and is a function of cardiac inotropy but is independent of loading conditions (preload and afterload). Similarly, the connection of end-diastolic points of successive PV curves defines the end-diastolic pressure-volume relationship (EDPVR), and its slope describes the passive elastance of the ventricle in diastole. A PV relationship showing a typical decrease in systolic function is shown in **Figure 1b**.

TREATMENT OF HEART FAILURE

Treatment of HF includes correcting the underlying cause (e.g., percutaneous or surgical coronary revascularization, valvular replacement, metabolic disorder correction), symptomatic treatment of volume overload (diuretics), treatments targeting the activated neurohumoral systems (beta blockers, renin-angiotensin-aldosterone system inhibitors, neprilysin inhibitor), and antiarrhythmic therapies when indicated. In specific situations, cardiac resynchronization therapy may be an option (17). In the acute setting, vasopressive drugs (to increase blood pressure) and inotropic agents (to increase cardiac contractility, including beta-adrenergic compounds, phosphodiesterase inhibitors, and the calcium sensitizer levosimendan) are the cornerstone of therapy for CS (9, 18, 19). For patients who have exhausted medical therapy, therapeutic options include mechanical circulatory support (MCS) and heart transplantation (3).

MCS is an option for patients who are in CS that is unresponsive to medical therapy or in refractory chronic HF (20). In the former, temporary circulatory support (TCS) is a viable option, whereas long-term MCS is typical for the latter. TCS includes intra-aortic balloon pumps (21), venoarterial extracorporeal membrane oxygenation (22, 23), or percutaneous left ventricular assist devices (LVADs) that use a microaxial pump (such as the Impella® heart pump by Abiomed) (24).

Heart failure with reduced ejection fraction (HFrEF): classification of heart failure when LVEF is reduced

End-systolic elastance (E_{es}): load-independent parameter characterizing ventricular inotropy, defined as the slope of ESPVR

End-systolic pressure-volume relationship (ESPVR): relationship between ventricular volume and pressure at the end of systole

End-diastolic pressure-volume relationship (EDPVR): relationship between ventricular volume and pressure at the end of diastole

Mechanical circulatory support (MCS): a set of devices and technologies designed to increase cardiac output

Temporary circulatory support (TCS): a subset of MCS for short periods of use (days to weeks)

Left ventricular assist device (LVAD): surgically implanted long-term MCS that pumps blood from the left ventricle to the aorta

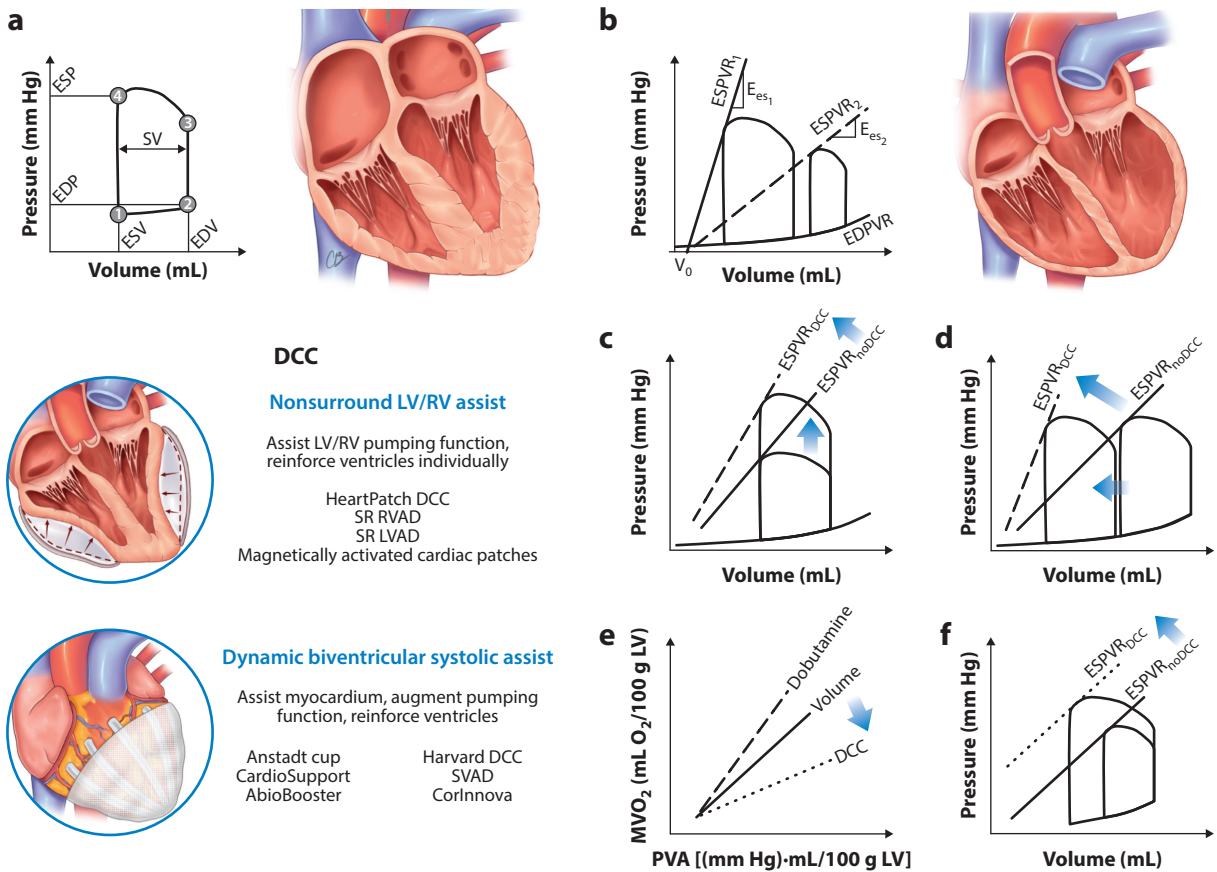


Figure 1

(a) Ventricular PV relationship. The cardiac cycle begins at point ① and corresponds to the opening of the mitral valve, and the beginning of ventricular filling, until point ②, the end of the diastolic phase. At this point, the end-diastolic volume and pressure can be measured. At point ②, the mitral valve closes and begins isovolumetric contraction until point ③, where the aortic valve opens and ejection begins, until point ④, where the end-systolic pressure and volume are measured. At point ④, the aortic valve closes and isovolumetric relaxation begins, until point ①.

(b) PV loops for normal (ESPVR₁) and decreased (ESPVR₂) systolic function.

(c–f) Proposed physiological effect of DCC on cardiac function. DCC improves ventricular ejection by increasing the slope of the ESPVR in different experimental conditions: (c) under constant preload and SV, and (d) under various preload and constant SV. (e) For a comparable increase in ventricular work (the area enclosed by the PV loop), DCC exhibits superior mechanical efficiency (defined as the ratio PVA/MVO₂) compared with dobutamine or volume loading. (f) DCC increases ventricular ejection by shifting the ESPVR to the left, without changing its slope. Abbreviations: DCC, direct cardiac compression; EDP, end-diastolic pressure; EDPVR, end-diastolic pressure-volume relationship; EDV, end-diastolic volume; E_{es}, end-systolic elastance; ESP, end-systolic pressure; ESPVR, end-systolic pressure-volume relationship; ESV, end-systolic volume; LV, left ventricle; LVAD, left ventricular assist device; MVO₂, myocardial oxygen consumption; PV, pressure-volume; PVA, pressure-volume area; RV, right ventricle; RVAD, right ventricular assist device; SR, soft robotic; SV, stroke volume; SVAD, soft ventricular assist device; V₀, relaxation volume. Panels c–e adapted with permission from Reference 48; copyright 1992 Elsevier. Renderings by BioHues Digital.

Long-term MCS comprises surgically implanted LVADs for LV failure, or total artificial hearts (TAHs) for biventricular failure (25) (e.g., Carmat or SynCardia TAHs) (see the sidebar titled Total Artificial Heart Technology). LVADs are employed as a destination therapy (26, 27), as a bridge to cardiac transplantation (28–30), or until there is partial recovery of native cardiac function (31). Several generations of LVADs have been developed, with the latest generation being centrifugal

TOTAL ARTIFICIAL HEART TECHNOLOGY

Total artificial heart technology is rapidly growing with devices such as SynCardia and Carmat and associated recent successes in clinical trials. A subset of the technologies described herein for direct cardiac compression may also be applicable to the development of total artificial hearts.

continuous-flow pumps driving blood from the LV to the aorta at flow rates of up to 10 L/min (32), requiring open-heart surgery for implantation. A detailed discussion of LVADs is beyond the scope of this work, and we refer the interested reader to extensive recent reviews on this topic (33, 34).

LVADs are not without limitations. First, they contain blood-contacting surfaces, thereby increasing the risk of thrombosis and necessitating that the recipient receives long-term anticoagulation therapy. As such, hemocompatibility-related complications such as pump thrombosis, stroke, hemorrhages, or hemolysis (35–37) remain unacceptably high (38, 39). Further complications include driveline infection (40), right HF (41), cardiac arrhythmia (42), or immune system dysregulation (43–45).

Conceptually, the ideal MCS should (a) provide systolic enhancement that increases CO, (b) operate at low filling pressures to avoid congestion problems, (c) avoid blood exposure to artificial surfaces, and (d) adapt rapidly and autonomously to variations of loading conditions (preload and afterload). These considerations led to the principle of direct cardiac compression (DCC), which has the potential to meet these requirements. Owing to recent developments in soft robotics (46) and material science, there is a renewed interest in using this method to assist the failing heart. In this review, we discuss important concepts related to DCC and give examples of devices in this area.

PATHOPHYSIOLOGY OF DCC

Complications related to the exposure of blood to the artificial surfaces of cardiac assist devices have prompted researchers to develop alternative forms of MCS. The idea to compress the failing heart from its external surface (the epicardium), to avoid any contact between blood and the assisting device, emerged more than 50 years ago (47), giving rise to the concept of DCC. Pioneering work from Suga and colleagues (48–50) and the Burkhoff group (51) provided crucial information in understanding the influence of DCC on cardiac physiology.

With an experimental setup consisting of a canine heart in cross-circulation with ventricles surrounded by an inflatable airtight chamber, Kawaguchi et al. (48) modeled systolic compressions by applying cyclic variations of the chamber air volume. Instantaneous left ventricular pressure and volume, coronary blood flow, and myocardial oxygen consumption (MVO_2) were measured. Results showed that—at a constant SV—DCC increased the slope of the ESPVR (albeit without a direct effect on cardiac contractility, per se), at both constant end-diastolic volume (**Figure 1c**) and pressure (**Figure 1d**). In the first condition, DCC enhanced external mechanical work without changing MVO_2 , while in the second, DCC did not change external work but reduced MVO_2 , indicating significant metabolic benefits. These effects contrasted with those of dobutamine and volume loading, which both increased MVO_2 to produce mechanical effects comparable with those of DCC (**Figure 1e**). Furthermore, the influence of DCC on systolic function appeared independent of the native ventricular contractility and was more effective in the dilated heart (49).

Artrip et al. (51) later used a more sophisticated canine model with DCC assisting both the right ventricle (RV) and the LV, with isovolumic and ejecting conditions. Their results indicated that DCC increased the overall pumping efficiency of the heart by increasing intraventricular

Direct cardiac compression (DCC) devices:

cardiac assist devices that assist the heart by compressing the epicardial surface; also known as direct mechanical ventricular assistance

Soft robotics:

subset of robotics using compliant and continuously deformable materials that are actuated in response to a stimulus or trigger, most commonly pressurized fluid

pressure, without directly enhancing its contractility. This result is illustrated by a leftward shift of the ESPVR, with no change in its slope (**Figure 1f**), in contrast to the data by Kawaguchi et al. (48–50). This study showed that the DCC-mediated improvement of ventricular SV was dependent on the conditions of ventricular filling (preload), did not increase MVO_2 , and occurred independently from any influence of the DCC on ventricular diastolic function. In summary, these physiological studies provided essential clues to elucidate the effects of DCC on cardiac physiology and its ability to significantly increase the pumping strength of the heart at a low metabolic cost, supporting a global improvement of its mechanical efficiency (50). For further details on this work, we refer the interested reader to a comprehensive review of these results (52).

FOUNDATIONAL DCC DEVICES

Here, we present initial DCC devices in chronological order, including a historical perspective, as well as a description of important milestones in the development and understanding of DCC devices and physiology. DCC, or direct mechanical ventricular actuation, was first introduced in the 1950s.

Pneumomassage

DCC devices were initially developed to provide circulatory support during refractory cardiac arrest (CA). Bencini & Parola (53) conceptualized and realized a version of DCC therapy in 1956 known as pneumomassage. The pericardial space—the space between the epicardium and the pericardial membrane—was inflated and deflated with air to compress the failing heart. This technique, which employs the native cardiac structures for assistance, was not efficacious because the simultaneous compression of the atrial and ventricular cavities prevented their adequate filling. These preliminary results underlined the importance of designing for the diastolic function in addition to the systolic function.

The Anstadt Cup

Anstadt et al. (47) proposed a DCC device, the Anstadt cup, that aimed to assist heart function during CA. A contoured cup, made of a semirigid outer layer and an inflatable inner layer (the diaphragm), was designed to circumferentially surround the ventricles and compress them on pneumatic actuation (**Figure 2a**). Inflation of the diaphragm provided systolic assistance, while active deflation generated negative pressure, thereby assisting ventricular filling (diastolic assistance). Attachment of the inner layer to the epicardial surface was maintained by means of a constant negative pressure generated at the apex by the command system, which also controlled the rate of compression, actuation pressure, systolic duration, and rate of pressurization (47, 54). The insertion of the device required a left anterior thoracotomy, without cardiopulmonary bypass (55).

The device was first used in 6 patients with refractory CA (56) and restored adequate arterial blood pressure and reasonable CO for up to 4 h of use. In one patient, return of spontaneous circulation was obtained, but the patient died after 6 days as a result of his initial condition (kidney failure). Thereafter, a larger feasibility study was performed (57). The device was used in 22 refractory CA patients. This study demonstrated that the device could be quickly implanted (less than 2 min from skin incision) and provided significant hemodynamic improvement, compared with conventional chest compression or open-chest cardiac massage. Among the 22 patients, 6 patients underwent successful return of spontaneous circulation, but all died later from respiratory or circulatory failure. The outcome of this study may be, at least in part, attributed to the duration between CA and the device implantation, which was approximately 90 min. Informed

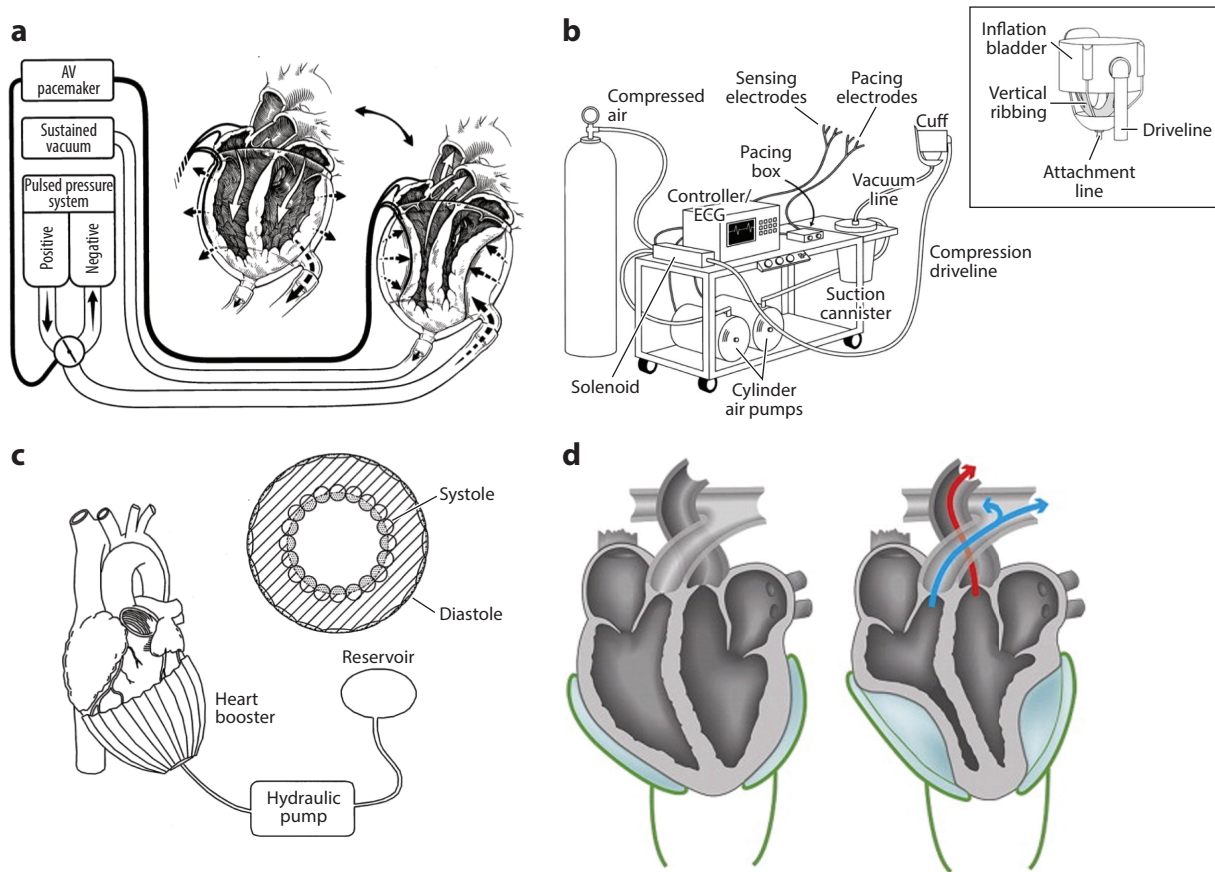


Figure 2

Examples of foundational DCC devices. (a) The Anstadt cup. Panel adapted with permission from Reference 102; copyright 2002 Elsevier. (b) The CardioSupport system. Panel adapted with permission from Reference 67; copyright 1999 Wolters Kluwer Health, Inc. (c) The AbioBooster. Panel adapted with permission from Reference 70; copyright 1999 Elsevier. (d) The HeartPatch. Panel reproduced with permission from Reference 73; copyright 2011 Elsevier. Abbreviations: AV, atrioventricular; DCC, direct cardiac compression; ECG, electrocardiogram.

consent required by the study protocol may have contributed to the delay. The device was then used in 2 patients who developed CS while awaiting cardiac transplantation (58). One patient was successfully bridged to transplantation after 56 h of DCC therapy, while the second patient suffered CA before DCC implantation and died from irreversible neurologic injury.

Further preclinical investigations with the Anstadt cup enriched the fundamental understanding of DCC pathophysiology. First, DCC may promote myocardial salvage in a canine model of myocardial infarction (59) and delay depletion of adenosine triphosphate compared with cardiopulmonary bypass (60). The proposed mechanisms may reside in the elimination of the asynchronous motion of the infarcted wall, the restoration of baseline arteriovenous gradients, the reduction of MVO_2 , and a possible increase in coronary blood flow induced by the negative pressures generated during the assisted diastole. Second, in a canine model of CA, a study suggested that DCC did not show an increase in cardiac trauma, compared with cardiopulmonary bypass reanimation (61). Third, DCC is as effective as internal manual cardiac massage to provide

regional cerebral blood flow (62). Fourth, this device was investigated for longer duration of assistance and demonstrated the ability to maintain adequate circulatory support in dogs for 2–3 days (63) and later in sheep for up to 7 days (64). The device was subsequently applied to the pediatric population using a small-animal model of acute (65) and chronic (66) HF. These studies showed that DCC augments both systolic and diastolic function in a failing heart with a smaller anatomy.

To the best of our knowledge, the Anstadt cup remains the only DCC device used in a human trial to date. Preliminary results could be improved by earlier administration of the device (especially for CA). Overall, however, the aforementioned studies demonstrated the feasibility and the potential of this method for both CA and CS.

The CardioSupport System

The CardioSupport system (Cardio Technologies Inc., Pine Brook, New Jersey, USA) comprised a plastic cuff surrounding the ventricles with an inflation bladder from the outflow tract to the midwall of the heart, covering approximately 50% of the epicardial surface. Negative pressure applied to the apex of the heart secured the position of the inflation bladder, preventing its migration (**Figure 2b**). The device was synchronized with an electrocardiogram (ECG) (67, 68).

In a canine model of HF assisted with the CardioSupport, Artrip et al. (67) showed an upward shift of ESPVR and a leftward shift of EDPVR for both the LV and the RV without a modification of E_{es} , reflecting, as mentioned above, the fact that DCC enhances contraction without modifying native ventricle inotropy. Approximately 40% of the pressure generated by DCC was effectively transmitted to the ventricular chambers, corresponding to the amount of the upward shift of ESPVR. In addition, the authors underlined the importance of ventricular filling; owing to its increased pumping performance, the assisted ventricle emptied more efficiently and therefore worked at lower EDVs (i.e., lower preload). This phenomenon reduced the possible increase of end-systolic pressure and SV. In vivo experiments confirmed that DCC increased LV systolic pressures and SV and was more effective with reduced baseline ventricular function. However, the DCC-assisted heart was not able to reach baseline CO, owing to the aforementioned reduction in ventricular filling (preload).

The same group further studied the effect of loading conditions during DCC with an ex vivo and in vivo canine heart model (69). They confirmed that initiation of DCC decreased filling volume and pressure, thereby limiting the augmentation provided by the cardiac assistance. They demonstrated that active manipulation of preload (increasing with saline infusion), afterload (decreasing with hypotensive drugs), or both, enabled restoration of healthy CO with DCC in the failing heart. As manipulations of preload and afterload are commonly performed in the setting of critical care medicine, they could be easily translated for use with a DCC device.

The AbioBooster

The AbioBooster (Abiomed Inc., Danvers, Massachusetts, USA), formerly named the Heart Booster, was a DCC device made of contractile polyurethane tubular elements, longitudinally assembled to form a closed circular sleeve that surrounded the ventricles (70) (**Figure 2c**). Inflation of the tubes with fluid reduced the inner diameter of the sleeve, therefore assisting the heart in systole, while active deflation assisted the heart in diastole. The insertion required a left thoracotomy and was performed without cardiopulmonary bypass. Preliminary studies performed in an animal model of acute HF (bovine, $n = 3$) showed an increase of 0.5 L/min in CO. The limited increase in CO was partially attributed to undersized devices (approximately 20% of the epicardium was not covered). Further in vivo experiments (ovine, $n = 12$) with HF demonstrated an increase in descending aortic flow to approximately baseline value (71). The effect of the device on coronary

artery bypass grafting was studied in six animals, showing no effect on graft flow and maintenance of patency in the anastomosis. To avoid epicardial tissue ingrowth, a silicone-coated device was used, and no cardiac contusions were detected on histological examination.

PediBooster

The PediBooster is a pediatric biventricular (BiV) extracardiac assist device made of two polyurethane balloons inserted in a polypropylene mesh, circumferentially wrapped around the heart. The epicardial face of the mesh is coated with a hydrogel to provide a reversible adhesion to the heart. The balloons are pneumatically actuated, and contraction is synchronized with an ECG. The PediBooster was developed to provide cardiac support for CS after cardiac surgery for the repair of complex congenital heart disease, for example, hypoplastic left heart syndrome (HLHS) (72).

The device was first assessed in a porcine model of congenital heart disease mimicking HLHS. However, the procedure led to major hemodynamic instability and high mortality, motivating the investigators to create a simpler model consisting of a surgically created atrial septal defect (i.e., a communication between right and left atria) and pulmonary stenosis (i.e., a reduction in the diameter of the pulmonary artery), resulting in right ventricular failure and eventually CS. The device was implanted and tested in four piglets with this model of CS. Although actuation provided some cardiac augmentation (as measured by an increase in aortic pressure), the device implantation induced diastolic restriction, resulting in an increase in LV end-diastolic pressure and a progressive attenuation of the augmentation effect. Moreover, areas of bruising were observed on the epicardial surface. These results highlight again the importance of diastolic function and ventricular filling, which are as important as the systolic augmentation of DCC devices.

The HeartPatch

The HeartPatch (Heart Assist Technologies, St Leonards, New South Wales, Australia) is composed of two independent inflatable silicone patch elements attached to the epicardial surfaces of the LV and the RV (see **Figure 2d**). A porous silicone material allows biointegration and adhesion of the device to the epicardium. The edges of the HeartPatch are sutured to the pericardium to secure the position. The patches are pneumatically actuated by an extracorporeal pump and are synchronized to features in the ECG tracing. Insertion is made through a left thoracotomy without cardiopulmonary bypass. To achieve biointegration, the device was left in place at least 1 week before evaluation in animal experiments, limiting its current possible use to chronic HF.

Unlike the surround devices described above, the HeartPatch is a non-surround device (73). This key element could help in reducing its preload dependency, compared with other devices, such as the CardioSupport. Moreover, the two chambers are actuated independently, permitting the device to assist the RV, the LV, or both ventricles and separately adjust actuation pressure. Independent actuation is fundamentally important, as the pulmonary circulation has lower pressures and lower resistances than the systemic circulation, therefore requiring lower actuation forces and energy. Indeed, applying too much actuation to the right side of the heart could have adverse consequences and ultimately reduce CO corresponding to a leftward shift of the EDPVR (67).

In an animal model of acute HF, Gallagher et al. (74) compared the effect of RV, LV, and BiV assistance with the HeartPatch. They showed that BiV assistance significantly increased CO and restored hemodynamic parameters to their baseline value. Both univentricular RV and LV assistance provided an augmentation of equal magnitude but less than that provided by BiV assistance. Using a similar experimental setting, the effect of DCC on coronary circulation was investigated (75). Although the flow pattern was modified, anterograde coronary blood flow was maintained,

suggesting that DCC does not impede myocardial perfusion. Finally, the impact of DCC on 3D ventricular geometry was evaluated using sonomicrometry crystal transducers implanted in the myocardium (76). The researchers found that DCC increased septal-lateral axial shortening, while the anteroposterior axis was not affected to the same extent, consistent with the placement of the device on the ventricular free walls.

While the HeartPatch provided innovative solutions to address some of the limitations of previous devices, it is not without potential shortcomings that warrant further evaluation. The non-uniform forces applied to myocardium and their resultant wall stress may induce an inflammatory reaction, as well as traumatic injury, and may even increase the risk of myocardial rupture, which is especially concerning when the HeartPatch is applied to infarcted, or weakened, myocardium. The abnormal inverted ventricular wall motion generated may also induce or worsen valvular dysfunction (e.g., mitral valve regurgitation), as the valvular apparatus is particularly vulnerable to mechanical or geometrical modifications of the myocardium. Furthermore, long-term studies are required to evaluate the durability of the device, specifically the risk of delamination from the epicardial wall.

APPLYING SOFT ROBOTIC TECHNIQUES TO DCC

The advent of soft robotics, a field that burgeoned in the last decade, enabled programmable motion with fluidic actuators composed of soft materials, with moduli that approximated that of cardiac tissue. Research groups endeavored to rethink the way that assist devices could be designed to augment myocardial function. Some groups relied on interventricular components, and others described exclusively extracardiac structures. We review each of these categories in turn in the subsequent sections.

DCC Devices with an Intraventricular Component

A series of studies from Harvard University and Boston Children's Hospital proposed the concept of using external soft actuators in combination with septal bracing to engage the interventricular septum and maximize the amount of ventricular assistance provided to either the left or right side of the heart (77–82). The first realization of this concept was a McKibben actuator in the RV that would approximate the RV free wall and the septum when pressurized (**Figure 3a,b**). It consisted of an inner elastomeric balloon, an outer mesh, and a surrounding elastomeric bladder to assist with recoil and emptying. A polyether ether ketone anchor in the LV was attached to the RV components via a threaded screw, and a polyurethane tip stabilized the fixation on the right side of the septum (78, 79). This concept was developed further by using a passive connecting rod in the RV to connect an external soft actuator to an epicardial brace (80, 81) (**Figure 3c**). When the actuator was pressurized, the free wall and the interventricular septum were pulled together. A similar approach with an intracardiac/extracardiac brace and an epicardial soft actuator was used to augment both LV (81, 82) and mitral valve (82) function (**Figure 3d**), with the bracing bar in the LV.

In a separate study, acute RV failure was created by ligation of the right coronary artery, which led to a reduction in SV of 63% (83). A copulsion balloon was secured over the RV free wall, suturing it to the opened pericardium. RV SVs and pulmonary artery pressures were restored to baseline, and tricuspid regurgitation was not noted; however, although improvements were noted in mean aortic pressure (MAP), they did not return to baseline. This result demonstrated that cardiac compression via balloon copulsion can support the pulmonary circulation acutely and motivated study in long-term models.

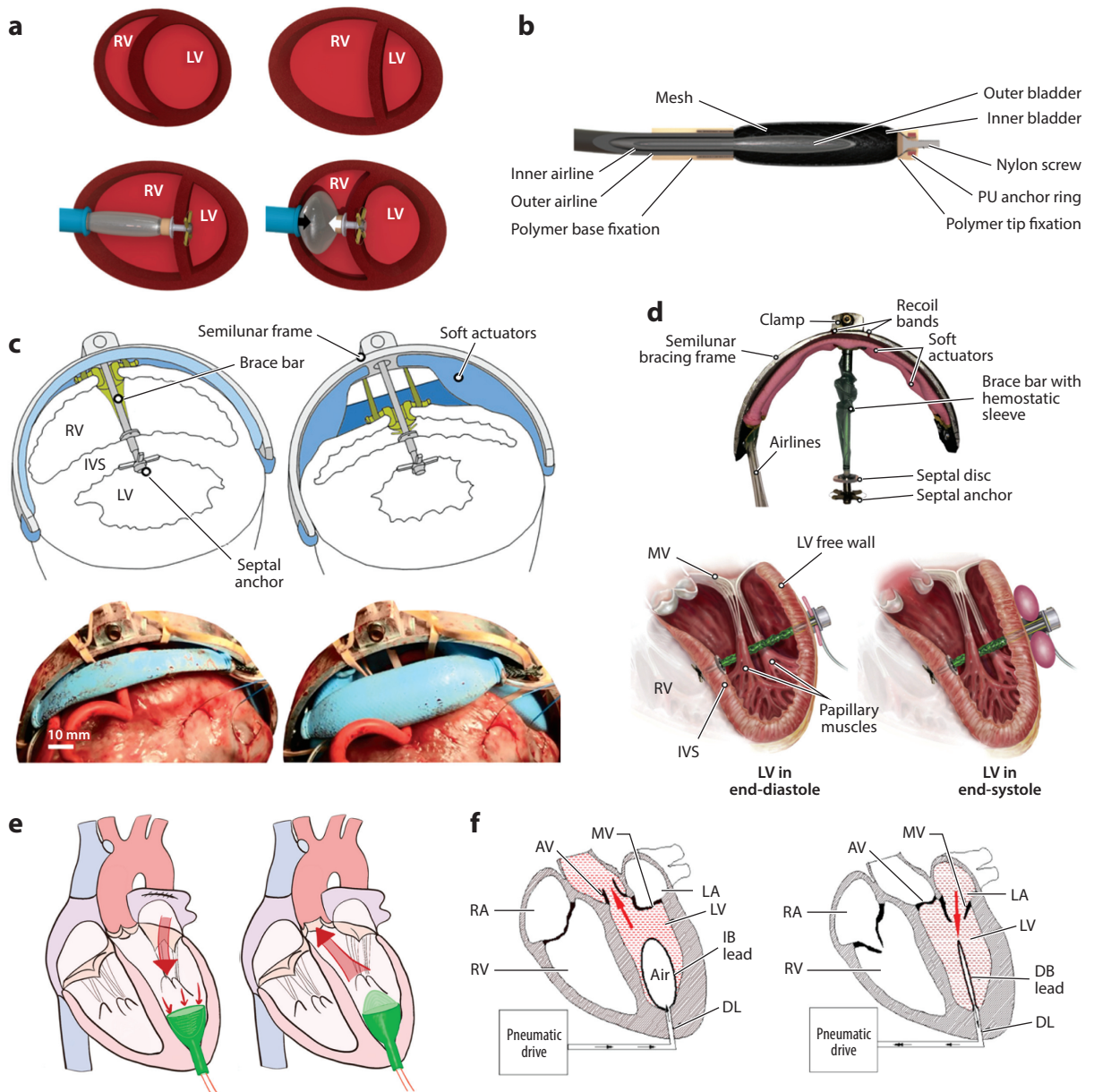


Figure 3

DCC devices with an intraventricular component. (a) The McKibben RVAD. Panel adapted with permission from Reference 78; copyright 2017 Springer Nature. (b) The intraventricular pneumatic artificial muscle. Panel adapted with permission from Reference 78; copyright 2017 Springer Nature. (c) A soft robotic system with an epicardial brace and passive rod in the RV (also demonstrated for the LV in this work). Panel adapted with permission from Reference 81; copyright 2017 AAAS. (d) A soft robotic system similar to that shown in panel c, used here in the LV to augment mitral valve function. Panel adapted with permission from Reference 82; copyright 2020 Elsevier. (e) The IVMP. Panel reproduced with permission from Reference 84; copyright 2020 John Wiley and Sons. (f) The soft ventricular assist device based on an intraventricular balloon technology. Panel adapted with permission from Reference 85; copyright 2019 ASME. Abbreviations: AV, aortic valve; DCC, direct cardiac compression; DB, dedicated bipolar; DL, driveline; IB, integrated bipolar; IVMP, intraventricular membrane pump; IVS, interventricular septum; LA, left atrium; LV, left ventricle; MV, mitral valve; PU, polyurethane; RA, right atrium; RV, right ventricle; RVAD, right ventricular assist device.

In a more recent study, researchers introduced an intraventricular membrane pump (IVMP) and tested it for efficacy and safety. The IVMP is implanted in the apex of the LV (**Figure 3e**), and it is evacuated during diastole to help with filling and pressurized during systole to enhance ejection. In an ex vivo porcine model, the group demonstrated a significant increase of the CO ($+1.4 \pm 0.2$ L/min, $P < 0.001$) and MAP ($+13 \pm 6$ mm Hg, $P = 0.008$) when the IVMP was supporting the circulation. Mitral valve function was not negatively affected, motivating future development of a catheter-based IVMP (84). Finally, a soft ventricular assist device (SVAD) system was developed with an intraventricular polyurethane balloon (**Figure 3f**); the system operates in a similar fashion to the IVMP, generating pulsatile flow by displacing volume within the LV during inflation and aiding with filling during deflation. In an ex vivo porcine model, the SVAD system generated an EF of $50.18 \pm 1.52\%$. This system is designed to be inserted transapically via a minithoracotomy and may be assessed in chronic large-animal studies in the future (85).

Extracardiac Devices in the Research Stage

Our group has designed a bioinspired soft active material that can simulate the twisting motion of the heart (86). This led to the development of a DCC device consisting of pneumatic artificial muscles (PAMs) embedded in silicone. PAMs are arranged in both helical and circumferential orientations to provide compression and twist to the heart simultaneously (87). The silicone sleeve was capable of achieving a squeezing and twisting motion (81, 87). In preclinical studies (swine, $n = 6$), the device restored a baseline CO of 3 L/min following CA or an esmolol-induced reduction in contractility. In subsequent studies, the concept was redesigned and optimized for coupling to the epicardium and synchronization with the heart rhythm (88). The sleeve was then redesigned with a medical textile mesh with integrated channels for helical and circumferential actuators. The mesh allowed a controlled level of tissue integration for optimal coupling (89). These devices are being developed further, with a focus on the robustness of the actuators and minimization of the associated hardware to enable future chronic studies.

More recently, groups have been investigating electrically contractile polymer-based actuators (90) or magnetically active patches (91) (**Figure 4a**) to impart assistance to the heart. Other groups have reported muscle-powered extracardiac devices (92), where an internal muscle energy converter is used to drive a DCC sleeve for long-term circulatory support, avoiding the need for an external driveline and eliminating the issues associated with their use.

EXTRACARDIAC DEVICES IN CLINICAL TRANSLATION

Although there have been major achievements and technological advancements toward the development of DCC devices, most of them remain at an experimental stage to date. The Anstadt cup, although demonstrating promising results, has not been used in humans for several years. Still, with a resurgence of interest in the field in the past decade, some devices have recently reached important milestones in their preclinical development and are presented below.

The CorInnova Cardiac Assist Device

The CorInnova cardiac assist device (CorInnova Inc., Houston, Texas, USA) is a cup-shaped device made of two layers of polyurethane bladders separated by a nitinol wire scaffold (see **Figure 4c**). Each bladder has a helical orientation. The inner layer is passive and fluid filled, and it interfaces with the epicardium. The outer layer is active, air filled, and actuated to compress the heart during systole. An epicardial sensing electrode is positioned at the apex, providing

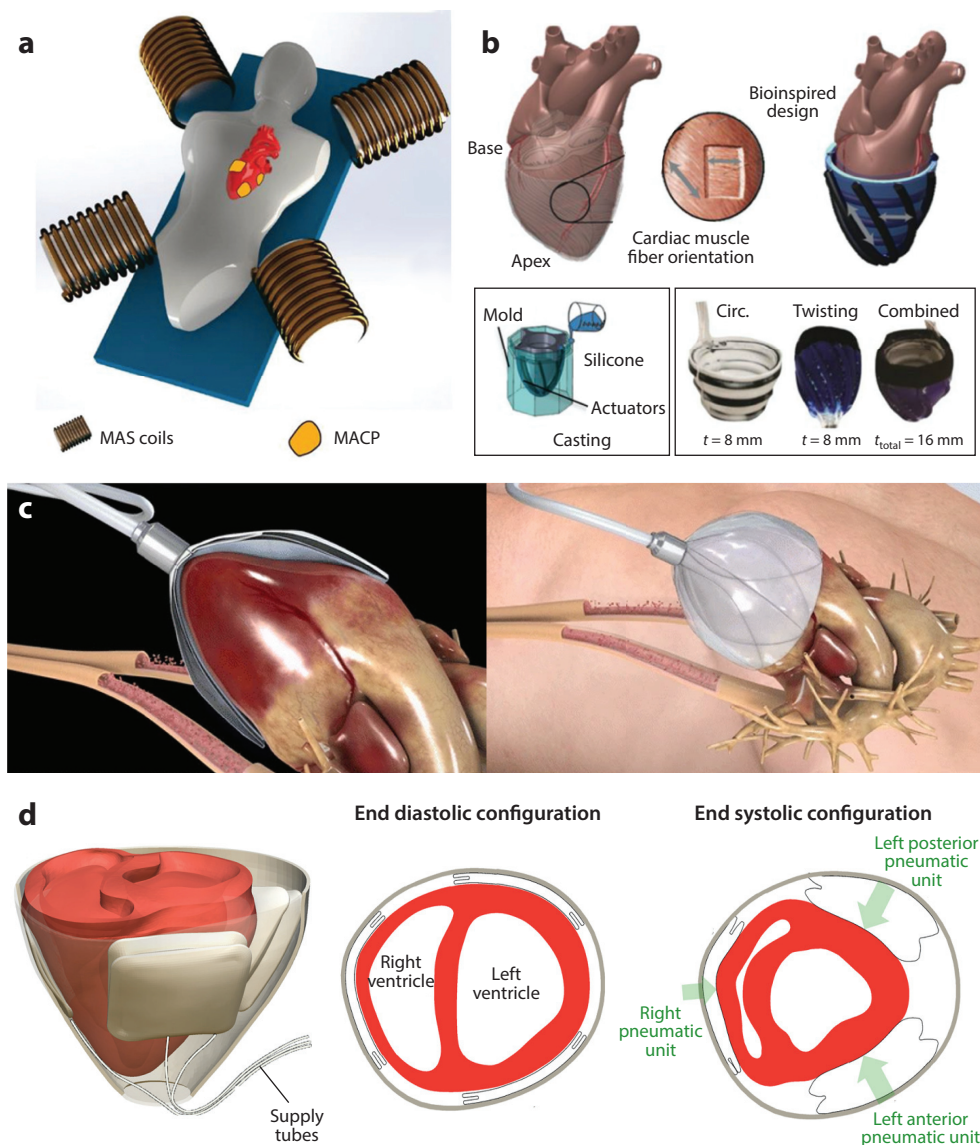


Figure 4

(a) Magnetically active patches attached to the epicardium. Panel adapted from Reference 91 (CC BY 4.0). (b) Extracardiac DCC device developed at Harvard and Boston Children's Hospital. Panel adapted with permission from Reference 87; copyright 2017 AAAS. (c) CorInnova cardiac assist device. Panel reproduced from Reference 96 (CC BY 4.0). (d) AdjuCor BEAT device. Panel adapted with permission from Reference 100; copyright 2019 John Wiley and Sons. Abbreviations: Circ., circumferential; DCC, direct cardiac compression; MACP, magnetically active cardiac patch; MAS, magnetic actuation system.

a synchronized actuation with the HR (93). The insertion requires a minimally invasive intervention. Owing to its material properties, the device can be compressed and inserted in a deployment tube. After incision of the pericardium, the distal end of the insertion tube is placed inside the pericardium. Under fluoroscopy, the device is progressively advanced to the heart and

self-expands around the epicardium. It can provide different modes of assistance: First, it can deliver an ECG-synchronized active cardiac compression to augment systolic function; second, without active contraction but by filling the passive chambers to various volumes, the device functions as a passive LV restraint to reduce the size of heart chambers and eventually attenuate the remodeling processes (94). Finally, it can be left in place without interfering with cardiac function. Owing to its helical conception, the CorInnova DCC device does not invert the normal curvature of the heart. It therefore provides a more physiological systolic augmentation that may positively impact cardiac remodeling and recovery.

Preliminary results in an acute animal HF model highlighted these important features (93, 95). When turned off, the device did not modify PV curves and did not affect CO or central, pulmonary wedge, or aortic pressures. The device is therefore nonobligatory, and the patient is not entirely dependent on its function. The minimally invasive approach and the possible ease of removal make this device an interesting candidate as a bridge-to-recovery or bridge-to-removal indication. When the device was used as an LV restraint, the authors observed a leftward and upward shift in the EDPVR, pointing toward a reduction of the size of the LV chamber. During active functioning, there was a significant increase in CO and stroke work.

Criscione's group (96) performed further experiments with a preclinical acute HF model. Implantation was successful, and time from skin incision to cardiac assistance was, impressively, less than 10 min. The device permitted recovery of CO and SV of 74% and 86% of the healthy baseline, respectively, and an increase in stroke work of 102%. Although these investigations provided encouraging results, further studies are required in areas such as chronic testing, the effect of the device on cardiac remodeling, and the host/device interaction.

AdjuCor BEAT

The AdjuCor BEAT (AdjuCor GmbH, Munich, Germany) is a BiV DCC device consisting of a nitinol structure bonded to a polyurethane sleeve (see **Figure 3d**). This structure, designed to conform to the shape of the ventricle, contains three inflatable bladders, positioned so that two are in contact with the LV and one is in contact with the RV. The inflation pressures delivered to the LV- and RV-facing bladders can be independently controlled, and actuation is synchronized with an ECG.

The first preclinical studies in a porcine HF model have demonstrated encouraging results (97). For a patient-specific design, computed tomography images were used to derive the shape of the outer surface of the heart and guide the device geometry. The device was implanted using either an open chest or a minimally invasive approach using a procedure similar to that described for the CorInnova device (98). The correct placement was confirmed after a partial sternotomy. The presence of the passive device did not affect PV curves, notably the LV filling. All device actuation modes (BiV assist, RV assist, and LV assist) increased LV end-systolic pressure and SV proportionally to the pressure support delivered. Both LV assist and BiV assist, but not RV assist, decreased LV end-diastolic pressure. BiV assist was tested in the case of CA and provided a CO up to 2.8 L/min. The authors did not observe myocardial or great vessel injuries. In brief, the AdjuCor BEAT is a customizable, patient-specific, minimally invasive DCC device that provides adjustable BiV cardiac assistance, without affecting ventricular diastolic function when it is not actuated. Moreover, this device is nonobligatory, that is, it can be left in place without affecting the native heart function. This feature may enable weaning of the patient from the assist, and could improve safety in case of device dysfunction.

Two other studies were aimed at developing multiscale computational models of the circulatory system (99) and provided a reliable framework for the development and optimization of the device

(100). In a recent preclinical study (103), Schueler et al. investigated the safety and functioning of the device in a porcine model for two conditions: acute drug-induced HF ($n = 5$) and a 30-day survival model ($n = 2$). The former condition confirmed previous results and showed an increase in cardiac performance (significant increases in SV, CO, and stroke work, as well as a decrease in end-diastolic pressure for both ventricles), while the latter condition demonstrated safe use with normal tissue morphology. Investigators used a subxyphoid approach in the chronic model and a partial sternotomy in the acute model, with an estimated implantation time of 15–30 min. Moreover, electromechanical coupling with epicardial ECG provided accurate and reliable synchronization for both acute and chronic studies. These promising results pave the way to first-in-human use in the near future.

CONCLUSION AND PERSPECTIVE

There are a number of design criteria that are important to consider in the quest for an ideal DCC device (101). They should be adaptable to different loading conditions and feature autoregulation mechanisms to achieve a cardiac output that satisfies metabolic needs during rest and exercise (5–20 L/min). They should be non-blood-contacting and have robust design and manufacturing techniques, with a fatigue life of years. Methods of attachment to the heart should prevent injury, contusions, and blockage of coronary flow but enable efficient coupling. Ideally, they would be powered by transcutaneous energy transfer to obviate the need for external drivelines. Finally, it would be desirable if the device could be turned off without harming the patient, and if the patient could be weaned from assistance if the heart recovers some function. As actuator design and durability improve, these goals become more attainable. In the future, the combination of DCC with pacing, or the delivery of biologics or stem cells, may enable recovery of function of the heart, supporting cardiac output, and unloading the heart while it is healing and regenerating.

SUMMARY POINTS

1. Treatment of heart failure has evolved in the past few decades, notably with the use of mechanical circulatory support. However, current devices expose blood to artificial surfaces, and such exposure can lead to numerous complications.
2. Direct cardiac compression (DCC), a concept that has been studied for decades, avoids blood-contacting surfaces. Initial in vitro and in vivo studies have demonstrated that DCC can augment heart function and improve myocardial efficiency.
3. Technical issues limited the translation of initial DCC devices into the clinical field. Recent progress in soft robotics and material science has sparked a renewed interest in DCC.
4. Newer devices can be classified into two broad categories: extracardiac devices and devices with an intraventricular component. Some of these devices have reached important milestones in their preclinical development, and clinical trials are expected in the near future.

DISCLOSURE STATEMENT

E.T.R. consults for Holistick Medical and is an inventor on patent US20160346449A1 (Biomimetic actuation device and system, and methods for controlling a biomimetic actuation device and system).

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LITERATURE CITED

1. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, et al. 2021. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Eur. J. Heart Fail.* 23:352–80
2. Lippi G, Sanchis-Gomar F. 2020. Global epidemiology and future trends of heart failure. *AME Med. J.* 5:15
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, et al. 2016. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. J. Heart Fail.* 18:891–975
4. Vasan RS, Benjamin EJ. 2016. The future of cardiovascular epidemiology. *Circulation* 133:2626–33
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., et al. 2013. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 128:e240–327
6. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. 2018. National burden of heart failure events in the United States, 2006 to 2014. *Circ. Heart Fail.* 11:e004873
7. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, et al. 2020. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation* 141:e139–596
8. Metra M, Teerlink JR. 2017. Heart failure. *Lancet* 390:1981–95
9. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, et al. 2017. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 136:e232–68
10. Ziaieian B, Fonarow GC. 2016. Epidemiology and aetiology of heart failure. *Nat. Rev. Cardiol.* 13:368–78
11. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, et al. 2018. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation* 137:e578–622
12. Guyton AC, Hall JE. 2006. *Textbook of Medical Physiology*. Philadelphia: Elsevier Saunders. 11th ed.
13. Borlaug BA. 2014. The pathophysiology of heart failure with preserved ejection fraction. *Nat. Rev. Cardiol.* 11:507–15
14. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, et al. 2020. Acute heart failure. *Nat. Rev. Dis. Primers* 6:16
15. Suga H, Sagawa K. 1974. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circ. Res.* 35:117–26
16. Suga H, Sagawa K, Shoukas AA. 1973. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ. Res.* 32:314–22
17. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., et al. 2017. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 136:e137–61
18. Farmakis D, Agostoni P, Baholli L, Bautin A, Comin-Colet J, et al. 2019. A pragmatic approach to the use of inotropes for the management of acute and advanced heart failure: an expert panel consensus. *Int. J. Cardiol.* 297:83–90
19. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, et al. 2019. SCAI clinical expert consensus statement on the classification of cardiogenic shock. *Catheter. Cardiovasc. Interv.* 94:29–37
20. Combes A. 2017. Mechanical circulatory support for end-stage heart failure. *Metabolism* 69:S30–35
21. Thiele H, Schuler G, Neumann FJ, Hausleiter J, Olbrich HG, et al. 2012. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock: design and rationale of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial. *Am. Heart J.* 163:938–45

22. Combes A, Brodie D, Chen YS, Fan E, Henriques JPS, et al. 2017. The ICM research agenda on extracorporeal life support. *Intensive Care Med.* 43:1306–18
23. Broman LM, Taccone FS, Lorusso R, Malfertheiner MV, Pappalardo F, et al. 2019. The ELSO Maas-tricht Treaty for ECLS Nomenclature: abbreviations for cannulation configuration in extracorporeal life support—a position paper of the Extracorporeal Life Support Organization. *Crit. Care* 23:36
24. Combes A, Price S, Slutsky AS, Brodie D. 2020. Temporary circulatory support for cardiogenic shock. *Lancet* 396:199–212
25. Arabia FA. 2020. The total artificial heart: Where are we? *Cardiol. Rev.* 28:275–82
26. Mehra MR, Uriel N, Naka Y, Cleveland JC Jr., Yuzefpolskaya M, et al. 2019. A fully magnetically levitated left ventricular assist device—final report. *N. Engl. J. Med.* 380:1618–27
27. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, et al. 2009. Advanced heart failure treated with continuous-flow left ventricular assist device. *N. Engl. J. Med.* 361:2241–51
28. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, et al. 2007. Use of a continuous-flow device in patients awaiting heart transplantation. *N. Engl. J. Med.* 357:885–96
29. Moonsamy P, Axtell AL, Ibrahim NE, Funamoto M, Tolis G, et al. 2020. Survival after heart transplan-tation in patients bridged with mechanical circulatory support. *J. Am. Coll. Cardiol.* 75:2892–905
30. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, et al. 2001. Long-term use of a left ventricular assist device for end-stage heart failure. *N. Engl. J. Med.* 345:1435–43
31. Jakovljevic DG, Yacoub MH, Schueler S, MacGowan GA, Velicki L, et al. 2017. Left ventricular assist device as a bridge to recovery for patients with advanced heart failure. *J. Am. Coll. Cardiol.* 69:1924–33
32. Aissaoui N, Jouan J, Gourjault M, Diebold B, Ortuno S, et al. 2018. Understanding left ventricular assist devices. *Blood Purif.* 46:292–300
33. Han J, Trumble D. 2019. Cardiac assist devices: early concepts, current technologies, and future innovations. *Bioengineering* 6:18
34. Schramm R, Morshuis M, Schoenbrodt M, Boergermann J, Hakim-Meibodi K, et al. 2019. Current perspectives on mechanical circulatory support. *Eur. J. Cardiothorac. Surg.* 55:i31–37
35. Eckman PM, John R. 2012. Bleeding and thrombosis in patients with continuous-flow ventricular assist devices. *Circulation* 125:3038–47
36. Hilal T, Mudd J, Deloughery TG. 2019. Hemostatic complications associated with ventricular assist devices. *Res. Pract. Thromb. Haemost.* 3:589–98
37. Samura T, Yoshioka D, Toda K, Sakaniwa R, Shimizu M, et al. 2019. Risk of stroke early after implantation of a left ventricular assist device. *J. Thorac. Cardiovasc. Surg.* 157:259–67
38. Mehra MR, Cleveland JC, Uriel N, Cowger JA, Hall S, et al. 2021. Primary results of long-term out-comes in the MOMENTUM 3 pivotal trial and continued access protocol study phase: a study of 2200 HeartMate 3 left ventricular assist device implants. *Eur. J. Heart Fail.* 23:1392–400
39. Devore AD, Patel PA, Patel CB. 2017. Medical management of patients with a left ventricular assist device for the non-left ventricular assist device specialist. *JACC Heart Fail.* 5:621–31
40. Aburjania N, Hay CM, Sohail MR. 2021. Continuous-flow left ventricular assist device systems infections: current outcomes and management strategies. *Ann. Cardiothorac. Surg.* 10:233–39
41. Rivas-Lasarte M, Kumar S, Derbala MH, Ferrall J, Cefalu M, et al. 2021. Prediction of right heart failure after left ventricular assist implantation: external validation of the EUROMACS right-sided heart failure risk score. *Eur. Heart J. Acute Cardiovasc. Care* 10:723–32
42. Maradey JA, Singleton MJ, O'Neill TJ, Bhavne PD. 2020. Management of ventricular arrhythmias in patients with LVAD. *Curr. Opin. Cardiol.* 35:289–94
43. Ankersmit HJ, Tugudea S, Spanier T, Weinberg AD, Artrip JH, et al. 1999. Activation-induced T-cell death and immune dysfunction after implantation of left-ventricular assist device. *Lancet* 354:550–55
44. Itescu S, John R. 2003. Interactions between the recipient immune system and the left ventricular assist device surface: immunological and clinical implications. *Ann. Thorac. Surg.* 75:S58–65
45. Ko B-S, Drakos S, Kfoury AG, Hurst D, Stoddard GJ, et al. 2016. Immunologic effects of continuous-flow left ventricular assist devices before and after heart transplant. *J. Heart Lung Transplant.* 35:1024–30
46. Rus D, Tolley MT. 2015. Design, fabrication and control of soft robots. *Nature* 521:467–75
47. Anstadt GL, Blakemore W, Baue AE. 1965. A new instrument for prolonged mechanical massage. *Circulation* 31/32:43–44

26. Recent clinical trial evaluating the use of LVAD for the treatment of terminal heart failure.

46. Comprehensive review of soft robotics and its current and future applications.

48. Kawaguchi O, Goto Y, Futaki S, Ohgoshi Y, Yaku H, Suga H. 1992. Mechanical enhancement and myocardial oxygen saving by synchronized dynamic left ventricular compression. *J. Thorac. Cardiovasc. Surg.* 103:573–81
49. Kawaguchi O, Goto Y, Futaki S, Ohgoshi Y, Yaku H, Suga H. 1994. The effects of dynamic cardiac compression on ventricular mechanics and energetics. Role of ventricular size and contractility. *J. Thorac. Cardiovasc. Surg.* 107:850–59
50. Kawaguchi O, Goto Y, Ohgoshi Y, Yaku H, Murase M, Suga H. 1997. Dynamic cardiac compression improves contractile efficiency of the heart. *J. Thorac. Cardiovasc. Surg.* 113:923–31
51. Artrip JH, Wang J, Leventhal AR, Tsitlik JE, Levin HR, Burkhoff D. 1999. Hemodynamic effects of direct biventricular compression studied in isovolumic and ejecting isolated canine hearts. *Circulation* 99:2177–84
52. **Oz MC, Artrip JH, Burkhoff D. 2002. Direct cardiac compression devices. *J. Heart Lung Transplant.* 21:1049–55**
53. Bencini A, Parola PL. 1956. The pneumo-massage of the heart; experimental research. *Surgery* 39:375–84
54. Anstadt GL, Schiff P, Baue AE. 1966. Prolonged circulatory support by direct mechanical ventricular assistance. *Trans. Am. Soc. Artif. Intern. Organs* 12:72–79
55. Lowe JE, Hughes GC, Biswas SS. 1999. Blood-contacting biventricular support: direct mechanical ventricular actuation. *Oper. Tech. Thorac. Cardiovasc. Surg.* 4:345–51
56. Baue AE, Tragus ET, Anstadt GL, Blakemore WS. 1968. Mechanical ventricular assistance in man. *Circulation* 37:II33–36
57. **Anstadt MP, Bartlett RL, Malone JP, Brown GR, Martin S, et al. 1991. Direct mechanical ventricular actuation for cardiac arrest in humans. A clinical feasibility trial. *Chest* 100:86–92**
58. Lowe JE, Anstadt MP, Van Trigt P, Smith PK, Hendry PJ, et al. 1991. First successful bridge to cardiac transplantation using direct mechanical ventricular actuation. *Ann. Thorac. Surg.* 52:1237–45
59. Anstadt MP, Malone JP, Brown GR, Nolan DS, Quinones JD, Anstadt GL. 1987. Direct mechanical ventricular assistance promotes salvage of ischemic myocardium. *ASAIO Trans.* 33:720–25
60. Anstadt MP, Hendry PJ, Plunkett MD, Menius JA Jr., Pacifico AD Jr., Lowe JE. 1990. Mechanical myocardial actuation during ventricular fibrillation improves tolerance to ischemia compared with cardiopulmonary bypass. *Circulation* 82:IV284–90
61. Anstadt MP, Tedder SD, Heide RS, Tedder M, Hilleren DJ, et al. 1992. Cardiac pathology following resuscitative circulatory support. Direct mechanical ventricular actuation versus cardiopulmonary bypass. *ASAIO J.* 38:75–81
62. Griffith RF, Anstadt M, Hoekstra J, Van Ligten PF, Anstadt GV, et al. 1992. Regional cerebral blood flow with manual internal cardiac massage versus direct mechanical ventricular assistance. *Ann. Emerg. Med.* 21:137–41
63. Anstadt GL, Rawlings CA, Krahwinkel DT, Casey HW, Schiff P. 1971. Prolonged circulatory support by direct mechanical ventricular assistance for two to three days of ventricular fibrillation. *Trans. Am. Soc. Artif. Intern. Organs* 17:174–82
64. Perez-Tamayo RA, Anstadt MP, Cothran RL Jr., Reisinger RJ, Schenkman DI, et al. 1995. Prolonged total circulatory support using direct mechanical ventricular actuation. *ASAIO J.* 41:M512–17
65. Anstadt MP, Budharaju S, Darner RJ, Schmitt BA, Prochaska LJ, et al. 2009. Ventricular actuation improves systolic and diastolic myocardial function in the small failing heart. *Ann. Thorac. Surg.* 88:1982–88
66. McConnell PI, Anstadt MP, Del Rio CL, Preston TJ, Ueyama Y, Youngblood BL. 2014. Cardiac function after acute support with direct mechanical ventricular actuation in chronic heart failure. *ASAIO J.* 60:701–6
67. Artrip JH, Yi G-H, Levin HR, Burkhoff D, Wang J. 1999. Physiological and hemodynamic evaluation of nonuniform direct cardiac compression. *Circulation* 100:II236–43
68. Williams MR, Artrip JH. 2001. Direct cardiac compression for cardiogenic shock with the Cardio-Support system. *Ann. Thorac. Surg.* 71:S188–89

52. In-depth review of the pathophysiology of DCC.

57. Early clinical study where DCC was applied on 22 patients with refractory cardiac arrest.

69. Artrip JH, Yi GH, Shimizo J, Feihn E, Sciacca RR, et al. 2000. Maximizing hemodynamic effectiveness of biventricular assistance by direct cardiac compression studied in ex vivo and in vivo canine models of acute heart failure. *J. Thorac. Cardiovasc. Surg.* 120:379–86
 70. Kung RTV, Rosenberg M. 1999. Heart Booster: a pericardial support device. *Ann. Thorac. Surg.* 68:764–67
 71. Kavarana MN, Helman DN, Williams MR, Barbone A, Sanchez JA, et al. 2001. Circulatory support with a direct cardiac compression device: a less invasive approach with the AbioBooster device. *J. Thorac. Cardiovasc. Surg.* 122:786–87
 72. Kavarana MN, Loree HM 2nd, Stewart RB, Milbocker MT, Hannan RL, et al. 2013. Pediatric mechanical support with an external cardiac compression device. *J. Cardiovasc. Dis. Diagn.* 1(2):1000105
 73. Mau J, Menzie S, Huang Y, Ward M, Hunyor S. 2011. Nonsurround, nonuniform, biventricular-capable direct cardiac compression provides Frank-Starling recruitment independent of left ventricular septal damage. *J. Thorac. Cardiovasc. Surg.* 142:209–15
 74. Gallagher GL, Huang Y, Morita S, Zielinski RR, Hunyor SN. 2007. Efficacy and mechanisms of biventricular and left/right direct cardiac compression in acute heart failure sheep. *Artif. Organs* 31:39–44
 75. Huang Y, Gallagher G, Plekhanov S, Morita S, Brady PW, Hunyor SN. 2003. HeartPatch implanted direct cardiac compression: effect on coronary flow and flow patterns in acute heart failure sheep. *ASAIO J.* 49:309–13
 76. Gallagher GL, Huang Y, Zielinski RR, Morita S, Hunyor SN. 2007. Effect of direct cardiac compression on left ventricular axial dynamics in sheep. *ASAIO J.* 53:292–97
 77. Bautista-Salinas D, Hammer PE, Payne CJ, Wamala I, Saeed M, et al. 2020. Synchronization of a soft robotic ventricular assist device to the native cardiac rhythm using an epicardial electrogram. *J. Med. Devices* 14:031003
 78. Horvath MA, Wamala I, Rytkin E, Doyle E, Payne CJ, et al. 2017. An intracardiac soft robotic device for augmentation of blood ejection from the failing right ventricle. *Ann. Biomed. Eng.* 45:2222–33
 79. Park E, Mehandru N, Lievano Beltran T, Kraus E, Holland D, et al. 2014. An intraventricular soft robotic pulsatile assist device for right ventricular heart failure. *J. Med. Devices* 8:020908
 80. Wamala I, Payne CJ, Saeed MY, Bautista-Salinas D, Van Story D, et al. 2022. Importance of preserved tricuspid valve function for effective soft robotic augmentation of the right ventricle in cases of elevated pulmonary artery pressure. *Cardiovasc. Eng. Technol.* 13:120–28
 81. Payne CJ, Wamala I, Bautista-Salinas D, Saeed M, Van Story D, et al. 2017. Soft robotic ventricular assist device with septal bracing for therapy of heart failure. *Sci. Robot.* 2:eaan6736
 82. Saeed MY, Van Story D, Payne CJ, Wamala I, Shin B, et al. 2020. Dynamic augmentation of left ventricle and mitral valve function with an implantable soft robotic device. *JACC Basic Transl. Sci.* 5:229–42
 83. Trumble DR, Park CS, Magovern JA. 1999. Copulsation balloon for right ventricular assistance: preliminary trials. *Circulation* 99:2815–18
 84. van Dort DIM, Thannhauser J, Gommans FDH, Ten Cate TJ, Duncker DJ, et al. 2020. Proof of principle of a novel co-pulsating intra-ventricular membrane pump. *Artif. Organs* 44:1267–75
 85. Gharaie SH, Amir Moghadam AA, Al'Aref SJ, Caprio A, Alaie S, et al. 2019. A proof-of-concept demonstration for a novel soft ventricular assist device. *J. Med. Devices* 13:021009
 86. Roche ET, Wohlfarth R, Overvelde JT, Vasilyev NV, Pigula FA, et al. 2014. A bioinspired soft actuated material. *Adv. Mater.* 26:1200–6
 87. Roche ET, Horvath MA, Wamala I, Alazmani A, Song SE, et al. 2017. Soft robotic sleeve supports heart function. *Sci. Transl. Med.* 9:eaaf3925
 88. Payne CJ, Wamala I, Abah C, Thalhoffer T, Saeed M, et al. 2017. An implantable extracardiac soft robotic device for the failing heart: mechanical coupling and synchronization. *Soft Robot.* 4:241–50
 89. Horvath MA, Varela CE, Dolan EB, Whyte W, Monahan DS, et al. 2018. Towards alternative approaches for coupling of a soft robotic sleeve to the heart. *Ann. Biomed. Eng.* 46:1534–47
 90. Kongahage D, Ruhparwar A, Foroughi J. 2021. High performance artificial muscles to engineer a ventricular cardiac assist device and future prospective of a cardiac sleeve. *Adv. Mater. Technol.* 6:2000894
 91. Gu H, Bertrand T, Boehler Q, Chautems C, Vasilyev NV, Nelson BJ. 2021. Magnetically active cardiac patches as an untethered, non-blood contacting ventricular assist device. *Adv. Sci.* 8:2000726
-
87. Describes the development of a soft robotic sleeve to provide cardiac assistance in an acute heart failure model.

92. Han J, Kubala M, Trumble DR. 2018. Design of a muscle-powered soft robotic Bi-VAD for long-term circulatory support. In *Proceedings of the 2018 Design of Medical Devices Conference, Minneapolis, MN, USA, April 9–12, 2018*. New York: ASME
93. Moreno MR, Biswas S, Harrison LD, Pernelle G, Miller MW, et al. 2011. Assessment of minimally invasive device that provides simultaneous adjustable cardiac support and active synchronous assist in an acute heart failure model. *J. Med. Devices* 5:041008
94. Mann DL, Bristow MR. 2005. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation* 111:2837–49
95. Moreno MR, Biswas S, Harrison LD, Pernelle G, Miller MW, et al. 2011. Development of a non-blood contacting cardiac assist and support device: an in vivo proof of concept study. *J. Med. Devices* 5:041007
96. Hord EC, Bolch CM, Tuzun E, Cohn WE, Leschinsky B, Criscione JC. 2019. Evaluation of the CorInnova heart assist device in an acute heart failure model. *J. Cardiovasc. Transl. Res.* 12:155–63
97. Jagschies L, Hirschvogel M, Matallo J, Maier A, Mild K, et al. 2018. Individualized biventricular epicardial augmentation technology in a drug-induced porcine failing heart model. *ASAIO J.* 64:480–88
98. Dolan EB, Hofmann B, De Vaal MH, Bellavia G, Straino S, et al. 2019. A bioresorbable biomaterial carrier and passive stabilization device to improve heart function post-myocardial infarction. *Mater. Sci. Eng. C Mater. Biol. Appl.* 103:109751
99. Hirschvogel M, Bassilious M, Jagschies L, Wildhirt SM, Gee MW. 2017. A monolithic 3D-0D coupled closed-loop model of the heart and the vascular system: experiment-based parameter estimation for patient-specific cardiac mechanics. *Int. J. Numer. Methods Biomed. Eng.* 33:e2842
100. Hirschvogel M, Jagschies L, Maier A, Wildhirt SM, Gee MW. 2019. An in silico twin for epicardial augmentation of the failing heart. *Int. J. Numer. Methods Biomed. Eng.* 35:e3233
101. Criscione JC. 2017. Cardiovascular devices: soft hugs for healing hearts. *Nat. Biomed. Eng.* 1:0046
102. Anstadt MP, Schulte-Eistrup SA, Motomura T, Soltero ER, Takano T, et al. 2002. Non-blood contacting biventricular support for severe heart failure. *Ann. Thorac. Surg.* 73:556–62
103. Schueler S, Bowles CT, Hinkel R, Wohlfarth R, Schmid MR, et al. 2022. A novel intrapericardial pulsatile device, reBEAT, for individualized, biventricular circulatory support without direct blood contact. *J. Thorac. Cardiovasc. Surg.* In press. <https://doi.org/10.1016/j.jtcvs.2021.11.093>

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CorInnova cardiac assist device: <https://www.corinnova.com/indication-overview>
 AdjuCor BEAT biventricular DCC device: <https://www.adjucor.com>