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Abstract

The optimal treatment option for end stage heart failure is transplantation; however the shortage of donor organs necessitates alternative treatment strategies such as mechanical circulatory assistance. Ventricular assist devices (VADs) are used to support these cases while awaiting cardiac recovery or transplantation, or in some cases as destination therapy. While left ventricular assist device (LVAD) therapy alone is effective in many instances, up to 50% of LVAD recipients demonstrate clinically significant postoperative right ventricular failure and potentially need a biventricular assist device (BiVAD). In these cases, the BiVAD can effectively support both sides of the failing heart. This article presents a technical review of BiVADs, both clinically applied and under development. BiVADs which have been used clinically are predominantly first generation, pulsatile, paracorporeal systems that are bulky and prone to device failure, thrombus formation and infection. Whilst they have saved many lives, they generally necessitate a large external pneumatic driver which inhibits normal movement and quality of life for many patients. In an attempt to alleviate these issues, several smaller, implantable second and third generation devices that use either immersed mechanical blood bearings or hydrodynamic/magnetic levitation systems to support a rotating impeller are under development or in the early stages of clinical use. Although these rotary devices may offer a longer term, completely implantable option for patients with biventricular failure, their control strategies need to be refined in order to compete with the inherent volume balancing ability of first generation devices. BiVAD systems potentially offer an improved quality of life to patients with total heart failure, and thus a viable alternative to heart transplantation is anticipated with continued development.

Keywords

Ventricular assist device, rotary blood pump, pulsatile blood pump, physiological control, heart failure.

Introduction

With a worldwide shortage of donor hearts, ventricular assist devices (VADs) are being used in end stage heart failure patients as a bridge to decision, bridge to transplant, bridge to myocardial recovery or destination therapy [63, 80]. VADs can be used to provide mechanical circulatory assistance to the left (LVAD), right (RVAD) or both sides of the heart (BiVAD). BiVADs provide simultaneous mechanical circulatory support to the left and right ventricles, pumping blood to the systemic and pulmonary systems. Unlike a total artificial heart (TAH), which requires the removal of the native heart, a BiVAD provides assistance in parallel to the native heart. Implantation of a TAH provides greater anatomical space for device placement through removal of the native ventricles. However, leaving the native ventricles in place for BiVAD support allows the ventricles to act as a natural inflow reservoir, and the remaining ventricular contractility assists in balancing left and right pump flows. Although their function is limited, the remaining ventricles may produce enough cardiac output for patient survival in the event of device malfunction. Retaining the ventricles in BiVAD support also maintains the potential for myocardial recovery and subsequent patient discharge without the requirement for a donor heart [45]. However, some ventricular function is necessary to avoid thrombus formation within the hypostatic ventricles during BiVAD support.

Mechanical circulatory support devices are categorized as first, second and third generation pumps, which are classified depending on their operational characteristics [68, 74]. First generation devices are volume displacement pumps which use pneumatics or electromagnetically actuated pusher plates to deform a membrane to deliver pulsatile flow. These devices have poor durability due to membrane rupture, bearing and mechanical valve wear. They require large

control consoles with limited portability, and have associated risks of postoperative infection, significant haemolysis, thrombus formation and severe postoperative bleeding [70]. Second generation devices use rotary centrifugal, diagonal, or axial impellers that produce continuous outflow, while having few moving, contacting parts. This reduces device wear, while smaller drive consoles promote increased patient mobility. Though they demonstrate marked improvements over first generation devices, these rotary pumps are associated with increased thrombogenicity and acquired platelet dysfunction due to the lack of pulsatile flow and high shear forces near the bearings and seals [9, 32, 36]. Third generation, rotary pumps completely eliminate mechanical wear of the pump components through the use of contactless impeller drive and suspension systems. Electromagnetic and/or hydrodynamic forces are used to levitate the impeller within the housing, while active electromagnetic forces are employed to rotate the impeller. Although clinical experience with third generation devices is limited compared to the vast number of first and second generation device implantations, it is anticipated that they will provide a support system that consumes low power with reduced complications [68].

This article begins by describing the requirement for biventricular assistance and the technical challenges confronting BiVADs such as size limitations and control strategies. The modes of operation and technical characteristics, such as device size, weight and power consumption, are then reviewed for clinically applied devices and several systems which are currently under development. Devices which have been clinically applied hold a current CE mark and/or FDA approval for clinical application of mechanical circulatory support. These include the Abiomed BVS5000 and AB5000, Thoratec PVAD and IVAD, Berlin Heart EXCOR, Medos HIA-VAD, Levitronx CentriMag, Jarvik 2000 and HeartWare HVAD devices. Two of these devices, the

HeartWare HVAD and Jarvik 2000, were specifically designed for left ventricular assistance, however have been implanted as a BiVAD in humans [16, 25]. Devices under development which are reviewed in this article do not have the CE mark or FDA approval for mechanical circulatory support and include the CorAide/Dexaide, Korean AnyHeart, Gyro and BiVACOR BV Assist devices. All BiVADs reviewed in this article are classified according to their generation, surgical placement and clinical implementation (Figure 1), while their drive mechanism, flow profile and clinical purpose are compared in Table 1.

Requirement for biventricular support

As the muscular left ventricle (LV) constitutes the bulk of the myocardial tissue, the majority of ventricular dysfunction is initially seen in this region. Thus, the majority of patients with end stage heart failure treated with mechanical circulatory support receive left ventricular assistance with a LVAD to increase end organ perfusion. However, the incidence of right heart dysfunction after LVAD insertion may vary between 10-50% [12, 25, 30, 53, 55], and is considered the most serious complication within the LVAD postoperative period [62]. Management of acute right ventricular (RV) failure post LVAD is difficult, and although pharmaceutical treatment strategies including pulmonary vasodilators, inotropic agents, and phosphodiesterase agents may temporarily improve RV function, these strategies are generally short term, expensive, and require prolonged intensive care management. Some patients do regain adequate RV function to avoid mechanical RV support, but equally, there are many who fail to adequately respond to these modalities [54]. In fact, the requirement for RVAD placement has been reported in 5-50% of LVAD supported patients [11, 15, 34, 39, 43, 53]. This discrepancy in the reported need for biventricular support is remarkable. Potapov et al. (2008) [53] reported the requirement for

biventricular support in 47.9% of patients in a study of 1025 various VAD implants. Yet the studies by Lee et al. (2010) and Kormos et al. (2010), both completed solely with the HeartMate II LVAD (Thoratec Corporation, Pleasanton, CA, USA), report significantly reduced incidence of RV failure requiring RVAD support (5% of 40 patients and 6% of 484 patients respectively). Comparisons between these studies may indicate a higher degree of RV failure after LVAD implantation with pulsatile devices compared to continuous flow pumps, as found in a multi-institutional study by Slaughter et al. (2009) involving 200 patients [66]. Perhaps the type of VAD and its controller, along with the patient's condition and clinical management, is a defining factor in right ventricular failure post LVAD implantation. Yet until a multi-institutional study is completed with various VAD designs and drive mechanisms, the discrepancy of RVAD requirement remains.

While the statistics of RV failure are commonly presented, it remains uncertain whether the right heart has failed before LVAD insertion due to congestion in the pulmonary system, or post LVAD insertion due to disrupted systolic interaction of the ventricles, or a combination of the two [1, 62]. Regardless, the timing of this diagnosis and subsequent intervention is critical, as mortality in patients with delayed re-admittance to surgery for RVAD implantation is up to 90% [31, 54]. Assisting the function of both ventricles at an earlier stage improves survival by reducing the need for re-operation, improving organ perfusion and allowing patients to leave hospital more rapidly through potentially reversing multi-organ failure [39]. It is for this reason that BiVAD support must be initiated as early as possible, while close attention must be given following surgery for any associated complications such as significant bleeding, thrombus formation or systemic-pulmonary flow imbalance.

Circuit Volume/Flow Balancing

Native human circulation is auto-regulated through a number of closed loop biological control systems. Arterial pressure and ventricular contractility are regulated by baroreceptor stimulation and the Frank-Starling mechanism respectively, both of which influence cardiac output [22, 69]. Auto-regulation of systemic/pulmonary volumes during uni-ventricular support, (e.g. LVAD support), may rely heavily on having one functional ventricle's native control mechanisms. Pulsatile devices operating in full-to-empty mode have an ability to balance outflow, and do not require further flow control for circuit volume balancing [68]. However, the few documented clinical studies of rotary biventricular support warn of haemodynamic instability [13, 47, 48, 58, 77]. All report the importance of continued controller development to prevent pulmonary edema and incidence of suction events in the cannulated heart chamber. Clearly then, balancing of circuit volumes is crucial for any rotary support device, especially rotary BiVADs. In order to balance flows with two Gyro pumps, Nosé et al. (2004) [49] incorporated inlet pressure sensors in each VAD to regulate flow, like the Frank-Starling mechanism. However, blood pump control systems like these can be limited by the low reliability of long term blood pressure and flow sensors [19].

Clinically Applied Devices

Abiomed BVS5000

The Abiomed BVS5000 (Abiomed Inc., Danvers, MA, USA) (Figure 2) was approved in 1992 by the USA Food and Drug Administration (FDA). It is a first generation, extracorporeal, dual-chambered BiVAD with simplicity and low cost as advantages, making it one of the most frequently used BiVADs in the world for treatment of acute cardiogenic shock [61]. The pump is clamped to an IV-type pole, located next to the patient's bed, at a height below the patient's atrium to allow for passive filling [23].

The BVS5000 has two separate 100 mL pumping and filling bladders, and a 660 mL system extracorporeal volume [74]. Allowable pumping rates are between 3 and 140 beats per minute (BPM). Abiomed tri-leaflet Angioflex polyurethane valves are placed at the filling and pumping chamber exits to prevent backflow, while the chamber bladders are made from the same material. Flow stagnation around these valves is a known cause for thrombus formation within the pump. These thrombi may dislodge and potentially contribute to patient mortality.

The pumping chambers are driven by a pulsatile, pneumatic drive console which can operate the LVAD and RVAD separately, or together. This microprocessor-based drive console optimizes and balances left/right pumping ratios by automatically adjusting the systolic/diastolic intervals and beat rate based on measurements of the drive line air flow to/from the console. The large drive console measures 610 x 560 x 845 mm, weighs a substantial 81.6 kg and uses a mean power of 280 W. However, a backup battery is capable of supporting the device for up to one hour in case of power failure. While this device has demonstrated reasonable success bridging

patients to recovery from cardiogenic shock with short term support, portability issues and thrombus incidence present severe limitations should long term VAD support be required [60].

Abiomed AB5000

The Abiomed AB5000 (Abiomed Inc., Danvers, MA, USA) (Figure 3) was approved by the FDA in 2003. Similar to the BVS5000, it is a first generation, pneumatically driven, volume displacement pump; however its paracorporeal location means that it can be used as a first choice VAD treatment or as a replacement to the BVS5000 should greater patient mobility be desired. In this latter case, the device can connect to the existing cannulae of the BVS5000, thus eliminating the need for additional surgery. Offering univentricular or biventricular assistance for cardiogenic or postcardiotomy shock, the small number of pumps implanted to date have demonstrated safety and reliability [40, 84].

The pump weighs 300 g when primed and has a 100 mL blood sac. The total extracorporeal system priming volume is less than 200 mL, which is less than the BVS5000. The outlet port uniquely exits centrally from the pump chamber in an attempt to improve flow dynamics and thus better chamber washout. The drive system automatically controls the AB5000 pump at a fixed rate mode, which usually outputs a 70-80 mL stroke volume. However, this stroke volume is reduced at high beat rates up to a maximum of 150 BPM, which results in a maximum output of 6 L min⁻¹. The drive console is a fully automatic, vacuum-assisted console designed to support both Abiomed blood pumps. The drive console has dimensions of 584 x 305 x 737 mm and a weight of 43.5 kg (without the portable cart), and consumes a maximum power of 250 W. Air supply pressures of 420 and 300 mmHg are regulated for LVAD and RVAD systole respectively,

while negative pressures of -100 mmHg assist filling in both pumps. While the AB5000 pump and drive console improved portability from the BVS5000, significant further development would be required to improve patient mobility.

Thoratec PVAD

The Thoratec PVAD (Thoratec Corporation, Pleasanton, CA, USA) was approved by the FDA for bridge to transplant in 1995 and postcardiotomy support in 1998. It is a first generation, pneumatically actuated, paracorporeal VAD suitable for left, right or biventricular assistance, however it has also been used as a total artificial heart [33].

The PVAD, shown in Figure 4, consists of a rigid plastic chamber which houses a polyurethane multipolymer (BPS-215M polyurethane elastomer) pumping sac to provide extensive flex life, strength and thromboresistance. Mechanical valves are also included to provide unidirectional flow [14]. The total size of the device is approximately 125 x 80 x 60 mm, with a total displacement volume of 318 mL and weight of 417 g [56]. As the device is located external to the body, in front of the abdomen, the size and weight of the Thoratec PVAD can pose problems to patient mobility. To ensure balanced flow between the systemic and pulmonary circulations, the PVAD features a full-to-empty actuation mode. A Hall-effect switch attached to the PVAD chamber senses when the pumping chamber is full and sends a signal to the controller which triggers the supply of compressed air to initiate systole. The vacuum assisted pump has a fixed stroke volume of 65 mL and a variable pulse rate, producing a minimum and maximum pump output of 1.3 and 7.2 L min⁻¹ respectively. The drive system can also operate in a fixed rate mode or synchronized with the patient's ECG [74].

Either the 231 kg Thoratec Dual Drive Console (DDC) (battery life of 40 minutes) or the much lighter, 9.8 kg, Thoratec TLC-II portable driver can be used to operate the VAD system, potentially allowing the patient to return home [74]. Like most first generation devices, valves in the pneumatic driver generate a significant amount of noise and are a constant cause for patient complaint [6] .

Thoratec IVAD

The intracorporeal, pneumatically actuated, pulsatile Thoratec IVAD (Thoratec Corporation, Pleasanton, CA, USA) has been approved by the FDA since 2004 to support the systemic and/or pulmonary circulations in a left, right or biventricular assist configuration.

With dimensions of 120 x 80 x 50 mm, a total displacement volume of 252 mL and a weight of 339 g, the IVAD is sufficiently smaller and lighter than the extracorporeal PVAD, yet provides the same 65 mL stroke volume and maximum VAD output of 7.2 L min^{-1} [56]. The size of this first generation device does, however, limit BiVAD implantation to larger patients, with children and small women usually ineligible for biventricular IVAD support. The IVAD, displayed in Figure 5, incorporates similar internal pump materials and mechanical valves to the PVAD, however a titanium alloy housing improves external surface biocompatibility.

Usually operating in full-to-empty mode, optical infrared sensors are used to detect the end systolic and diastolic position of the membrane, providing adequate systemic/pulmonary flow balancing. A 9 mm percutaneous pneumatic line with electrical cable for the sensor connects the

IVAD to either of the drivers used to operate the Thoratec PVAD (DDC or TLC-II). The implantable design of the IVAD allows for improved patient mobility and reduced infection, however eliminates advantages seen in the PVAD such as ease of replacement and direct pump visualization to identify malfunctions such as thrombus formation within the pump.

Berlin Heart EXCOR

Developed by Berlin Heart (Berlin Heart AG, Berlin, Germany), the EXCOR device (Figure 6) is a pneumatically actuated, paracorporeal, first generation VAD capable of left, right or biventricular support.

Adult pumps, available for use only outside the USA, come in 50, 60 and 80 mL sizes, while pediatric pumps, which were granted investigational device use status by the FDA in 2008, have smaller volumes at 10, 20 and 35 mL. Inside the transparent polyurethane housing, a triple layered polyurethane membrane separates the air and blood chambers [8]. Including the tri-leaflet inlet and outlet valves, all blood contacting surfaces of the EXCOR pump are coated with Carmeda bioactive surface coating. Despite this coating, thrombus formation is often seen in the pump's valves, indicating the pump or valve design hasn't been optimized to improve washout.

The drive system, Ikus, is a large, 93 kg electro-pneumatic drive unit which can produce pulse rates of 30-150 BPM, systolic pressures of 60-350 mmHg, diastolic pressures of -100 to 0 mmHg and systolic duration of 20-70% of the cardiac cycle. The higher pressure limits of -100 mmHg and 350 mmHg may be required to overcome the resistance of smaller pediatric cannulae at high heart rates [24]. A smaller, 9 kg portable drive unit, the EXCOR mobile driving system, can be

used in a biventricular configuration with up to 5 hours of battery life [4]. The mobile driving system is only available for adult pump sizes, thus the mobility of the pediatric population is limited with the larger driver. This is of particular importance with the EXCOR system as it is used extensively in Europe as a bridge to transplant device, which may confine pediatric patients to a hospital or specialist centre for long periods of time [8].

Medos HIA-VAD

With transparent pump chamber sizes varying from 9-80 mL, the paracorporeal Medos HIA-VAD (MEDOS Medizintechnik, GmbH, Stollberg, Germany) can be used in adult, infant and pediatric cases. Implanted for mechanical circulatory support since 1994, this pneumatically actuated, first generation blood pump is capable of assisting the left, right or both sides of the heart at flow rates ranging from 5-6 L min⁻¹ [3]. Adult sized pumps are 60 mL while pediatric versions come in 25 and 10 mL sizes (Figure 7). To account for the extra bronchial circulation on the left side, the right side pumps have smaller pump membranes to deliver 10% less cardiac output in a fixed rate operational mode [82].

The drive system is capable of applying systolic pressures of 50 to 300 mmHg and diastolic pressures of -1 to -99 mmHg, with systolic times of 20 to 50% and pulse rates of 40 to 180 BPM depending on the pump size [42]. The three-leaflet valves in the inflow and outflow tracts, and the seamless transparent pump casing, are made of biocompatible polyurethane [81]. Similar to most first generation devices, flow paths through the device appear sub-optimal which commonly leads to thrombus formation in the outflow tracts of both LVADs and RVADs [28].

Meanwhile, the large drive system again confines patients to hospital while receiving VAD support, which severely limits their quality of life.

Levitronix CentriMag

The Levitronix CentriMag (Levitronix LLC, Waltham, MA) obtained CE mark approval in 2002 for short term support of up to 30 days. This device is capable of providing short term support to the left and/or right side of the heart and as extracorporeal life support, including ECMO [2]. The CentriMag is a third generation, electrically operated, extracorporeal, centrifugal blood pump. With FDA approval for up to 6 hours of ventricular support only, trials are underway in the US to investigate longer term support of up to 30 days [73].

Frequently used as a ‘bridge to decision’ device [10], the CentriMag contains a disposable rotor and polycarbonate pump housing assembly which is fitted to an external magnetic motor that controls radial rotor position and speed (Figure 8). Each pump head has a total priming volume of just 31 mL. Using bearing-less motor technology, the impeller is magnetically levitated and rotated at speeds of 1500-5500 RPM to provide maximum pump flow of 9.9 L min^{-1} .

Pump speed is altered using an interface on the 6.6 kg drive console, which is connected to the 1.7 kg magnetic motor. While the introduction of this third generation pump for provision of biventricular support is a reasonable step forward, the large drive console and actuator severely limits patient mobility. Also, the advantages of third generation pumps such as improved device lifetime and durability may not be noticeable for very short term support.

Jarvik 2000

The Jarvik 2000 device (Jarvik Heart Inc., New York, USA) (Figure 9) has been included in a BTT trial since 2008 for FDA approval, subsequent to CE mark approval for the same application in 2005. The device is a second generation, axial flow LVAD that has also been used to support right ventricular function in humans [16, 31].

With a weight of just 90 g, length of 55 mm, diameter of 25 mm and total pump displacement of 25 mL, the Jarvik 2000 is small enough for BiVAD implantation in almost any patient. This electrically powered VAD can deliver flow rates of 3-7 L min⁻¹ against 100 mmHg at 8000-12000 RPM while using 4-8 W of power [27]. The brushless electromagnetic DC motor inside the sealed pump housing powers the rotor through electromagnetic fields that cross the blood flow path.

A power cable passes through the abdominal wall and connects to an external controller, while the system receives power from lithium-ion or lead acid batteries [67]. RVAD support was achieved with reduced VAD speeds (6000-10000 RPM) to compensate for the lower pulmonary pressures [31]. While presenting exceptional reliability as an LVAD, the long term effects as an RVAD have not been published and there appears to be no plan to modify the LVAD's design for RV specific support.

HeartWare HVAD

Originally developed as an LVAD and receiving CE mark approval for BTT applications in 2009, the HeartWare HVAD (HeartWare Inc, Massachusetts, USA) has also been used for biventricular support in humans [25, 71].

This third generation blood pump weighs 145 g and is capable of providing up to 10 L min^{-1} of blood flow with a wide-blade centrifugal impeller that rotates at a maximum speed of 4000 RPM [79]. A combined/hybrid passive magnetic and hydrodynamic thrust bearing suspend the impeller within the titanium-ceramic housing to improve device durability, while device reliability is improved with the use of independently driven dual motor stators. Each motor stator has a separate cable which passes through the 4.2 mm diameter fatigue-resistant percutaneous driveline and connects to the external controller and power supply. Power is delivered through either an AC power supply, a 12 V DC supply, or two rechargeable batteries which can provide up to 12 hours of power.

With a device displacement volume of just 50 mL, the HVAD (Figure 10) is small enough to be implanted in the pericardial cavity [38]. This eliminates the need for extensive abdominal dissection which is required for placement of larger implantable VADs. Integrated into the device, the smooth titanium inflow cannula (25 mm long and 21 mm outer diameter) is inserted through the left ventricular apex for the LVAD and the free wall of the right ventricle for the RVAD. To prevent septal occlusion of the RVAD inflow, spacers are added between the outer RV free wall and the pump to reduce cannula insertion length [25]. The HVAD-myocardial interface is secured with a sewing ring which comprises a Dacron polyester suture ring and titanium frame that screws onto the inflow cannula. The decreased pulmonary pressures are

compensated by banding/restricting the HVAD outflow cannula to a smaller diameter, however little work has been completed to characterize the degree of banding which may vary from patient to patient [25, 35].

The controller estimates flow by the electrical current, impeller RPM and a clinically determined blood viscosity value. Sensor-less suction detection and cyclic controlled speed change (to decrease areas of blood stasis) systems have been incorporated into the controller algorithm to improve support safety [38]. For biventricular support, patients are required to carry two controllers and power supplies. Although they could be incorporated into one controller and power supply, the reduction in size and weight still presents an advantage over previous first generation pump control units. Meanwhile, manual adjustment of pump speed to ensure flow balancing in a biventricular configuration has been reported, indicating the potential need for an automatic speed controller developed specifically for biventricular support [41].

Devices currently under development

CorAide/DexAide

Developed at the Cleveland Clinic, the CorAide (LVAD) and DexAide (RVAD) (Figure 11) pumps (Arrow International, Reading, U.S.A.) are third-generation, implantable, centrifugal VADs which use hydrodynamic and magnetic forces to passively support the rotor. Both devices are characterized by their inverted motor configuration, with each consisting of an impeller mounted on a 'hollow' rotor surrounding the cylindrical motor stator. The devices, developed for bridge-to-transplant applications, were designed to be simple, reliable and reduce contact, wear and potential thrombus formation.

The CoreAide has a displacement volume of 84 mL, pump weight of 293 g, a portable power supply (6 hour battery life) and controller weight of 1350 g [58]. It can achieve flow rates from 2 to 8 L min⁻¹ and has an operational pump speed range of 2000 to 3000 RPM. Pumping 5 L min⁻¹ against 100 mmHg, the CorAide LVAD uses less than 6 W of power at 2850 RPM [18]. The DexAide RVAD was developed by modifying the CorAide device and has a diameter, length, weight and device displacement volume of 44 mm, 48 mm, 280 g and 69 mL respectively [51]. The implantable centrifugal RVAD was developed by reducing the size of each primary vane, decreasing the number of primary vanes from seven to five and redesigning the volute. The DexAide can pump at speeds ranging from 1800 to 3600 RPM to provide over 5 L min⁻¹ cardiac output to the pulmonary circulation. Using only 2.6 W of power while supplying a flow rate of 5.2 L min⁻¹ at 2500 RPM, the DexAide has a battery life of over 12 hours on two fully charged batteries [17]. Meanwhile, Saeed et al. (2010) [59] demonstrated that Zirconium Oxide

can replace titanium in RVAD blood journal bearing applications to increase motor efficiency with no additional platelet activation or biological deposition.

A 4 mm percutaneous cable connects each VAD to the controller, which has a fixed speed mode or a variable speed mode that responds to the patient's physiological demands. When used for biventricular support, the LVAD is set to an automatic mode, which adjusts pump speed to obtain a target flow. LVAD flow pulsatility is also incorporated as a suction detection mechanism [18]. Meanwhile, the RVAD uses fixed flow control with an added observer suction detection system which compares changes in flow with speed variation [57]. However if low LVAD flow pulsatility is recorded, the dual pump controller responds by increasing the RVAD pump speed until either the LVAD flow pulsatility is restored, or the RVAD controller senses excessive RV unloading [57].

Korean AnyHeart

The Korean AnyHeart (BiomedLab Co., Seoul, Korea), is an electrically driven, pulsatile BiVAD which is also capable of operating as a total artificial heart [46]. The left and right pumping chambers are each approximately 100 mL in volume, while the entire device and connectors require about 500 mL of blood to prime [52]. These pumping chambers reside either side of a pendulum driver which swings side to side providing left systolic function during right side filling and vice versa. A brushless DC motor drives the pendulum actuator via an epicyclic gear train to reduce motor shaft speed and increase torque. The shaft and gear system, which control the pendulum actuator, are housed within the casing along with the ventricle chambers.

How the alternating motion of the pendulum is achieved from this drive has not been defined in the literature and so the nature of the periodic motion is unclear.

This implantable or wearable design, with dimensions of approximately 110 x 88 x 66 mm and mass of 780 g, can supply a pulse rate of up to 170 BPM without compromising pump filling [52]. However, the device size, similar to two Thoratec IVADs, would pose problems with small patients. The maximum ejection fraction and cardiac output of the AnyHeart (Figure 12) is approximately 65% and 9 L min⁻¹ respectively with a power consumption of 28.8 W [46]. With 4 L min⁻¹ pump flow against 100 mmHg, a total system efficiency of 8% and power consumption of less than 9 W has been reported [44]. The ventricle chambers are made of smooth, seamless segmented polyurethane encased in a rigid polyurethane chamber, with 26 mm polymer valves at the inflow and outflow ports [46]. The difference between left and right stroke volumes is reportedly compensated by a flexible 56 × 90mm polyurethane membrane, however the operation and placement of this membrane is unclear in the literature.

An automated control system uses motor current waveforms to alter the AnyHeart pumping conditions. Decreased ventricular filling due to decreased preload results in increased time before the pendulum motion comes into contact with the blood sac. The control system recognizes this delay through changes in motor current and adjusts the pump rate to compensate. The external monitoring system communicates with the device through a transcutaneous infrared system, while power is also supplied transcutaneously [52]. The addition of a transcutaneous power supply and reduction of overall pump size through a single drive mechanism for LVAD and RVAD does present some advantage over previously developed first generation pumps.

However, the apparent complex nature of the epicyclic gear train to drive the rotating pendulum combined with mechanical valves and a flexible compliance window is sure to result in device wear in the short term.

Gyro

Contributions to the development of this second generation device have been made by the Baylor College of Medicine (Houston, USA), Miwatec (Tokyo, Japan), and the New Energy and Industrial Technology Development Organization (NEDO) (Kawasaki, Japan).

The Gyro BiVAD (Figure 13) incorporates two permanently implantable centrifugal pumps, whose rotating impellers include additional secondary blades to accelerate blood flow beneath the impeller and reduce potential thrombus formation from blood circulation on the impeller back face. The seal-less titanium alloy pump housing encloses the impeller which is supported by a double pivot bearing. The double pivot bearing arrangement provides axial limits to the impeller movement within both the RVAD and LVAD pump casings. The female and male pivot bearings are made of aluminium oxide ceramics and ultra-high molecular weight polyethylene (UHMWPE) respectively. The VAD impellers, with a diameter of 50mm, are magnetically driven, and during operation the magnetic forces approximately balance the induced axial hydrodynamic forces upon the rotor, allowing the impeller to float between the pivot bearings. High device lifetimes of 8 and 10 years for LVAD and RVAD respectively are therefore expected [49, 83], however, blood compatibility of the contacting pivots are yet to be demonstrated in a clinical setting.

The magnetic drive actuator includes the pump controller and locates below the pump within the housing. The actuator has a brushless DC motor with coils fixed in a plastic mount surrounding a rotating disc with permanent magnets. The active magnetics of the RVAD, however, have an increased clearance between the impeller and magnetic coupling to reduce the magnetic force compared to the LVAD. Herein lies the only design difference between the two devices, permitting the lower pressure generation in the RVAD [26]. The VAD inlet port is placed off centre in an attempt to circulate the flow around the upper pivot bearing to decrease the risk of thrombus formation. Meanwhile, an emergency clamp is included on the LVAD outflow to prevent backflow in the event of pump malfunction.

The Gyro pump has a priming volume of 20 mL and, combined with the housed motor, a weight of 305 g, height of 53 mm and diameter of 65 mm [49]. The overall system, including the pump and actuator, has a displacement volume and weight of 155 mL and 480 g respectively. While representing a significant reduction in size compared to first generation pumps, the Gyro's displacement volume is nearly double that of the CorAide device. Therefore, intracorporeal biventricular support with the Gyro system may be problematic in small patients. The LVAD is capable of pumping 5 L min^{-1} against 120 mmHg, while the RVAD can pump the same flow against 40 mmHg. Left-right flow control was reported to be achieved with a Starling-like regulation, which increases flow with increased preload, however no mention was made on how preload will be measured in the long-term [49]. Meanwhile, a transcutaneous energy transfer system has been developed for the Gyro pump, with a maximum transmission efficiency of 87.3% [50].

BiVACOR BV Assist

The BiVACOR BV Assist (BiVACOR Pty Ltd., Brisbane, Australia) is a third generation BiVAD capable of providing complete circulatory support to treat end stage heart failure. A non-functional prototype of the device is shown in Figure 14. This rotary device will use two centrifugal type impellers to simultaneously support the left and right ventricles on either side of a single rotating hub. This essentially forms a double sided, rotary heart pump with one single moving part. Passive radial stability of the rotor is managed via a hydrodynamic radial bearing between the outer cylindrical face of the rotating hub and the outer casing. To achieve axial stability, active magnetic bearings and active motor magnet arrays oppose each other on the RVAD and LVAD casings respectively, allowing suspension and rotation of the impeller hub [20, 37]. The interaction between the magnetic bearing and motor system can alter the axial position of the hub and therefore the respective clearance above the RVAD and LVAD semi-open impeller blades. These actively controlled and coupled impeller clearances result in diverging hydraulic efficiency control, meaning that an increase in the hydraulic output of the LVAD can be created while decreasing that of the RVAD [72].

Both speed changes and axial clearance adjustment allow mutually increased and divergent fluid outputs respectively of the left and right pumps, making this device adequately suited to control systemic and pulmonary perfusion. The Frank-Starling like flow balancing controller uses the current within the magnetic bearing to detect changes in inlet/outlet pressures, and automatically adjust the impeller position accordingly [78]. Flow rates of 5 L min^{-1} are obtainable with systemic and pulmonary mean arterial pressures of 100 mmHg and 20 mmHg respectively at a pump speed of 2300 RPM and equal axial clearances above the LVAD and RVAD impeller

blades of 0.5 mm. While maintaining rotational speed and arterial pressures, an impeller axial displacement of +/-0.3 mm can lead to a relative left-right flow differential of 1.8 L min^{-1} [75]. The current prototype has a diameter of 60 mm and a length of 70 mm [76]. The rotor is capable of reaching speeds up to 3750 RPM to deliver 8 L min^{-1} cardiac output, while a power consumption of less than 15 W is used at 2500 RPM. As the LVAD and RVAD impellers are housed on a common rotating hub, one would expect an overall increased BiVAD efficiency compared to two separate centrifugal pumps. However, the reported high power consumption of the initial prototype indicates that further development is required to improve device efficiency.

Summary

Despite major advances in the management of acute and chronic end stage heart failure, the prevalence of heart failure is increasing due to the lack of donor organs [5]. The requirement for biventricular mechanical assistance is not only highlighted by the number of patients who present with end stage biventricular failure, but also the looming risk of right heart failure following LVAD implantation. Developed through either form, biventricular failure is a serious issue affecting a substantial demographic of heart disease patients. Unfortunately though, there are limited options compared to left heart failure treatment.

This paper reviewed BiVAD systems which have been clinically applied in humans or are currently under development. The technical characteristics for these devices are summarized in Table 2. First generation, pulsatile devices, including the Abiomed BVS5000 and AB5000, Thoratec PVAD and IVAD, Berlin Heart EXCOR, and Medos HIA-VAD, provide short or medium term solutions to support patients to transplant, or even myocardial recovery. Significant progress has been made over previous decades to improve these first generation devices with the development of smaller, battery powered drive consoles which help to improve the quality of life of end stage heart failure patients. Meanwhile, the Thoratec IVAD is the only implantable first generation device aimed at providing medium term biventricular support for chronic heart failure patients. However, the moving and contacting parts of these first generation pumps promote device wear, and even the use of smaller drive consoles still limit patient mobility. The only third generation rotary device which has reasonable clinical experience providing biventricular support, the Levitronix CentriMag, appears to have resolved the issue of device wear; however this extracorporeal device is only available for short term support while the patient is confined to

the hospital bed. Although the Jarvik 2000 and HeartWare HVAD devices have been implanted many times with success as an LVAD, there is currently only limited experience of biventricular support provided by these pumps [36, 64].

Systems currently under development include first generation (Korean AnyHeart), second generation (Gyro), and third generation (CorAide/DexAide and BiVACOR BV Assist) devices. The AnyHeart is designed to be completely implantable and operate with a moving actuator mechanism; however its large size limits the potential patient pool. The Gyro and CorAide/DexAide systems require the implantation of two independently controlled centrifugal pumps to support both ventricles, which may limit implantation to larger patients. The DexAide pump is still the only device designed specifically for RVAD support. However, specific RVAD development may be delayed further as clinicians have started to use modified second and third generation LVAD systems with reduced speed or clamped RVAD outflow cannulae to reduce pressure sufficiently to be suitable for pulmonary support. This reduces the regulatory workload in providing viable right ventricular support options, as seen with the Jarvik 2000 and HeartWare HVAD devices [54, 71]. Modified LVADs are, however, not ideal as reduced speed or clamped outflow grafts may encourage thrombogenesis around mechanical bearings or in cannula folds caused by the partial occlusion. Meanwhile, flow balancing issues may arise unless BiVAD specific controllers are developed for dual LVAD application. The BiVACOR BV Assist device accommodates for flow balance issues through its axially dynamic, dual impeller hub system that will automatically respond to changes in inlet and outlet pressure, although it is still in the early stages of development.

As physiological control is increasingly becoming a research focus for LVAD development, the fine tuning of physiologically sensitive BiVAD systems will follow the availability of the devices themselves. Preload monitoring measures, alongside active control systems, may be crucial to provide elevated cardiac output for low level exercise and depressed cardiac output during sleep. This is particularly pertinent for rotary BiVADs in order to prevent pulmonary edema or ventricular suction [57]. Sensor-less systems using pulsatility as a surrogate for preload will benefit individually actuated pumps such as dual rotary devices, although their safety in biventricular support scenarios must to be assessed [7, 21]. Combined pumps such as the AnyHeart and BiVACOR may not be able to easily infer preload from pulsatility as the left and right ventricular pulsatility will be transmitted to a common actuator/hub, however suitable force/pressure signals may be extracted from the magnetic bearing to achieve this in a sensor-less fashion. Nevertheless, this emphasizes the need for long term pressure measuring options with which to manage these devices.

Current, generally accepted options for clinicians to provide biventricular support beyond 30 days are limited to first generation devices. Although the inherent Frank Starling-like flow balancing full-to-empty mode of these devices allows for simple physiological control, limitations in patient mobility, comfort and quality of life exist until a donor heart is found [57, 66]. The lack of focus on RVAD development has probably hindered the clinical progression and availability of a third generation, implantable BiVAD. This is not surprising considering the requirement for left ventricular assistance compared to right ventricular assistance [29, 52]. Despite this, development of the CorAide/DexAide, Gyro and BiVACOR devices are focusing on RV specific hydraulic and magnetic design. However, the control of these devices in response

to the patients' physiological demands must be addressed before a long term solution can be anticipated. With the exception of dual device, pneumatically driven VAD arrangements which allow a full-to-empty type function; VAD control appears to have become an after-thought in some devices, especially where the LVAD controller has already been developed. We postulate that perhaps existing LVAD controllers with seemingly complimentary RVAD controllers may not be sufficient for long term rotary devices. A more holistic approach may be needed which incorporates the interaction between the VADs as well as their combined interactions with the cardiovascular system as a complete system.

The various implantation techniques may also contribute to the long term success or failure of these devices to infiltrate the clinical market. First generation devices are not implantable and therefore not suitable for long term biventricular support, excluding the Thoratec IVAD and Korean AnyHeart which require considerable abdominal dissection for placement. The CentriMag system is also incapable of intracorporeal placement and thus can only be used for short-term applications. Pericardial placement of the HeartWare or Jarvik devices is an undoubted advantage, however the cost of the combined pumps for BiVAD support must be considered. The Gyro, CorAide/DexAide and BiVACOR devices are currently suitable for sub-diaphragmatic placement, however with continued development of these systems it is possible that pericardially placed versions will become available. Meanwhile, the easily attachable sewing ring of the HeartWare device [79] may be favored by surgeons, and additional techniques to easily attach the cannulae while reducing the high rates of postoperative bleeding should be investigated [65].

The continued improvement of the presented devices is necessary to achieve the goal of a long term device capable of supporting critically ill patients as a destination therapy. Successful development of a reliable, durable BiVAD will ultimately lead to an improved patient survival rate and quality of life for those suffering from end stage biventricular heart failure.

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Table and Figure Captions

Table 1 – BiVAD drive mechanism, flow profile and clinical purpose for applied and under development devices. PD – pneumatically driven, ED – electrically driven, FP – filled passively, FV – vacuum assisted filling, AX – axial flow pump, CE – centrifugal flow pump, MA – mechanically actuated pump. Short term support indicates bridging to recovery, transplant or longer term support. Medium term support indicates bridging to recovery or transplant. Long term support indicates bridging to recovery, transplant or destination therapy.

Table 2 – Reported technical characteristics of clinically applied and under development BiVADs. * indicates the weight of the device including cannulae, - indicates the information is not available in the literature, + indicates values for LVAD/RVAD.

Figure 1 – Flow chart of the three generations of intracorporeal and paracorporeal/extracorporeal BiVADs including those applied clinically (not shaded) and under development (shaded).

Figure 2 – The Abiomed BVS5000 device with pneumatic driveline and inflow and outflow cannulae

Figure 3 – The Abiomed AB5000 device with pneumatic driveline.

Figure 4 – The Thoratec PVAD with pneumatic driveline (Courtesy of Thoratec Corporation).

Figure 5 – The Thoratec IVAD with percutaneous pneumatic driveline (Courtesy of Thoratec Corporation).

Figure 6 – The Berlin Heart EXCOR (Courtesy of Berlin Heart AG).

Figure 7 – The Medos HIA-VAD with pneumatic driveline.

Figure 8 – The Levitronix CentriMag drive console, magnetic motor and disposable pump head (Courtesy of Levitronix LLC).

Figure 9 – The Jarvik 2000 VAD with electrical lead (Courtesy of Jarvik Heart Inc.).

Figure 10 – The HeartWare HVAD with electrical lead (Courtesy of HeartWare Inc.).

Figure 11 – The DexAide RVAD assembly including the new zirconia stator housing (bottom left) and the previous FEP-coated titanium stator housing (bottom right). (Reprinted with permission from Saeed, D., et al., In vivo evaluation of zirconia ceramic in the DexAide right ventricular assist device journal bearing. *Artificial Organs*, 2010. 34(6): p. 512-516).

Figure 12 – The Korean AnyHeart, implanted sub-diaphragmatically as a BiVAD. (Reprinted with permission from Park, C.Y., et al., Development of totally implantable pulsatile biventricular assist device. *Artificial Organs*, 2003. 27(1): p. 119-123).

Figure 13 – The Gyro PI-710 device including schematic sectioned view (right). (Reprinted with permission from Nose, Y. and K. Furukawa, Current status of the Gyro centrifugal blood pump - Development of the permanently implantable centrifugal blood pump as a biventricular assist device (NEDO Project). *Artificial Organs*, 2004. 28(10): p. 953-958.).

Figure 14 – Non-functional fitting prototype of the BiVACOR BV Assist (Courtesy of BiVACOR Pty. Ltd.).