The future of artificial hearts

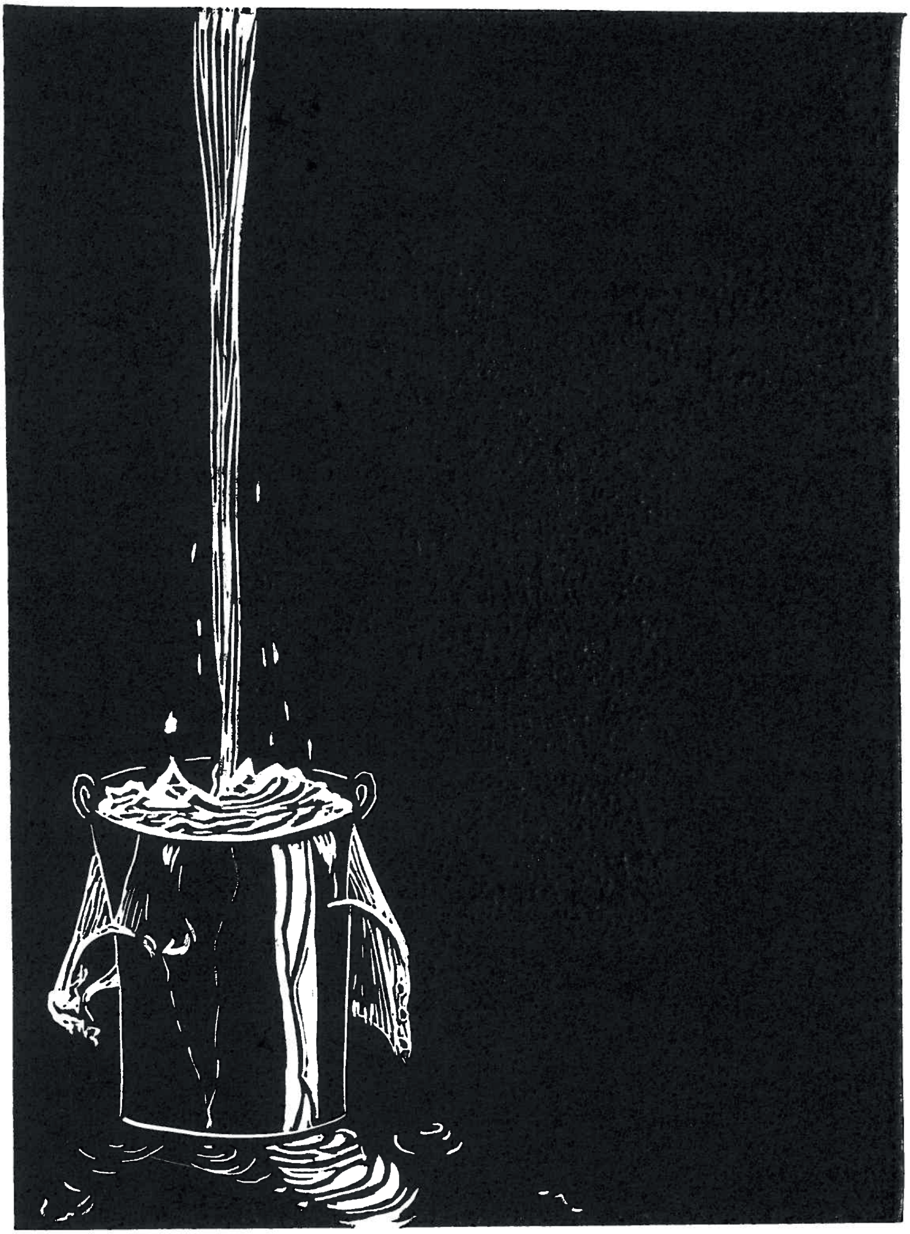
Hearts breakthroughs in becoming biomimetic

Vis, A.

Publication date
2024

Citation for published version (APA):
Vis, A. (2024). *The future of artificial hearts: Hearts breakthroughs in becoming biomimetic*. [Thesis, fully internal, Universiteit van Amsterdam].

3



BALANCING THE VENTRICULAR OUTPUTS OF PULSATILE TOTAL ARTIFICIAL HEARTS

Oskar J. Gülcher*, Annemijn Vis*, Mathias Peirlinck, Jolanda Kluin

*Equal author contribution

Based on: Artificial Organs
2023 Sep 13. doi:
10.1111/aor.14641.
Epub ahead of print.

Abstract

Maintaining balanced left and right cardiac outputs in a total artificial heart (TAH) is challenging due to the need for continuous adaptation to changing hemodynamic conditions. Proper balance in ventricular outputs of the left and right ventricles requires a preload sensitive response and mechanisms to address the higher volumetric efficiency of the right ventricle. This review provides a comprehensive overview of various methods used to balance left and right ventricular outputs in pulsatile total artificial hearts, categorized based on their actuation mechanism. Reported strategies include incorporating compliant materials and/or air cushions inside the ventricles, employing active control mechanisms to regulate ventricular filling state, and utilizing various shunts (such as hydraulic or intra-atrial shunts). Furthermore, reducing right ventricular stroke volume compared to the left often serves to balance the ventricular outputs. Individually controlled actuation of both ventricles in a pulsatile TAH seems to be the simplest and most effective way to achieve proper preload sensitivity and left-right output balance. Pneumatically actuated TAHs have the advantage to respond passively to preload changes. Therefore, a pneumatic TAH that comprises two individually actuated ventricles appears to be a more desirable option – both in terms of simplicity and efficacy – to respond to changing hemodynamic conditions.

Background

Heart transplantation remains the golden standard treatment for patients suffering from end-stage heart failure. However, due to donor shortage, not all patients can receive a heart transplantation in time[1]. To overcome the gap between the high number of patients and the low number of donor hearts, researchers have been working on developing a total artificial heart (TAH) to serve as a bridge to heart transplantation or destination therapy[2]. A TAH is a mechanical device that completely takes over the native heart's pump function and is implanted in the thoracic cavity after removal of the patient's heart. For more than half a century, several TAHs have been developed. Currently, two TAHs: SynCardia (SynCardia Systems, Tucson, AZ, USA) [3,4] and Carmat (Aeson; Carmat, Vélizy-villacoublay, France) [5,6] are approved for clinical use, and many other TAHs are under development[7-10].

Achieving and maintaining a balance between the left and right ventricular outputs is a major hurdle that has to be overcome when developing a TAH. A TAH has to continuously adapt its cardiac outputs to changing hemodynamic conditions. Additionally, some blood ejected by the left ventricle is shunted to the bronchial circulation that converges with the pulmonary circulation and returns directly to the left atrium. Due to this phenomenon, the left ventricle must provide a higher output relative to the right ventricle. Under normal physiological conditions, the bronchial shunt flow accounts for approximately 1% of the systemic cardiac output. However, under certain conditions, the bronchial shunt flow can reach up to one third of the left ventricular output[11]. Therefore, a TAH must be able to dynamically increase left versus right stroke volume ratios in response to changing hemodynamic conditions. Given the higher afterload of the left ventricle compared to the right, it is challenging for the left ventricle to obtain higher stroke volumes. If a TAH cannot maintain balance in ventricular outputs, severe clinical complications such as lung oedema and respiratory failure arise[12]. Respiratory failure is amongst the most reported reasons of death during chronic animal trials with TAHs[2].

The human heart adapts to increased end diastolic volume (EDV), and thus preload, by increasing stroke volume. This is called the Frank-Starling mechanism [13]. TAHs should show Frank Starling-like behaviour in response to varying hemodynamic perturbations to maintain balanced outputs between the left and right ventricles. For TAHs, two additional criteria should be met: 1. a more forceful contraction of the left ventricle compared to the right, to compensate for its lower volumetric efficiency and 2. a higher left stroke volume compared to the right stroke volume to compensate for the bronchial shunt flow.

This review focuses balancing mechanisms utilized in pulsatile TAHs. We address the challenges associated with balanced ventricular outputs in various working mechanisms of pulsatile TAHs and propose potential solutions to address this issue.

Methods to balance ventricular outputs

Pulsatile TAHs with individually controlled actuation of both ventricles

We can categorize pulsatile TAHs based on working mechanisms. TAHs with individually controlled actuation of both ventricles can be 1. pneumatically actuated: SynCardia[3], Vienna TAH (University of Vienna, Vienna, Austria) [14], BRNO TAH (Vacord Bioengineering Research Company, Brno, Czech Republic) [15], Mushroom TAH (The University of Utah, Salt Lake City, USA) [16], 2. hydraulically actuated: Carmat[5] or 3. mechanically actuated: RealHeart (Linköping University, Linköping, Sweden) [17]. Fluid driven TAH's have a flexible membrane in the base of the ventricle, separating the blood compartment from a gas/liquid filled compartment. By increasing pressure and volume in the gas/liquid filled compartment, blood is ejected from the ventricle. The mechanically driven RealHeart TAH is actuated by two planes moving up and down, thereby increasing pressure in the ventricle. Because these type of TAHs can individually control their ventricles, they allow for individual setting of pump parameters, that facilitate balance in ventricular outputs (Figure 1A).

The SynCardia is a clinically available TAH used for temporary support. The ventricles of the SynCardia are purposely under-filled (70-85%) to leave a gas filled "cushion" in the ventricle base that allows for augmentation of increased venous return. Driving pressures, percent systole time and beat rate are adjusted based on continuously monitored hemodynamic parameters. The filling states of the ventricles can be calculated based on gas flow through the drive lines. The SynCardia driving pressure is constantly monitored using sensors in the external pneumatic driver. The TAH itself is sensor-free. For the SynCardia, the driving pressure of the right ventricle is set 30 mmHg higher than the pulmonary pressure and for

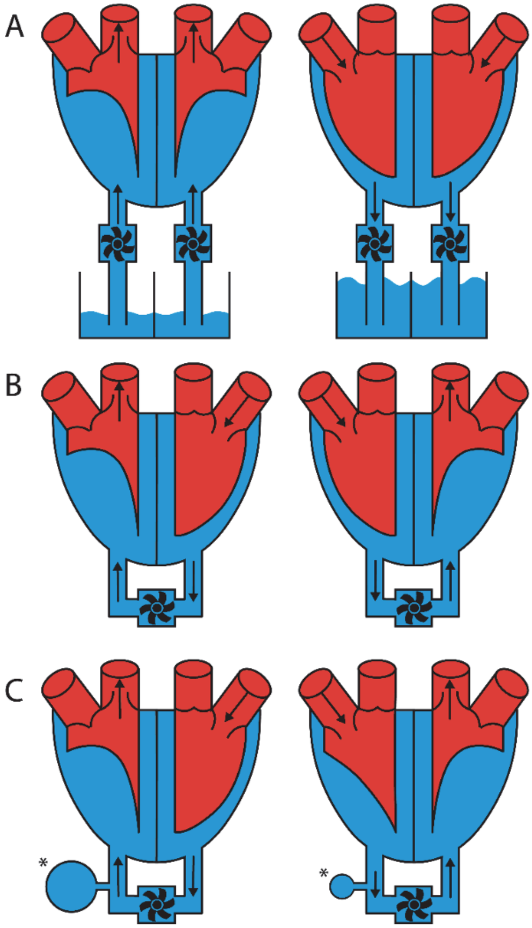


Figure 1. Schematic overview of TAH categories, based on working mechanism. Red colour depicts blood inside the ventricles. Blue colour depicts the actuation mechanism. A) Pulsatile TAHs with Individually controlled actuation of both ventricles. B) Single actuation mechanism, volumetrically coupled ventricles. C) Single actuation mechanism, volumetrically decoupled ventricles. * indicates the compliance chamber.

the left ventricle 60 mmHg higher than the systemic pressure to overcome the higher volumetric efficiency of the right ventricle[3].

The hydraulically actuated Carmat has recently been approved for clinical use. It individually controls the ventricles by two actuators that are volumetrically decoupled using a compliant fluid reservoir. During diastole, sensors in the hydraulic compartment continuously monitor the pressure inside the ventricle, providing an evaluation of the venous return. The membrane movement is dynamically adjusted to establish an optimal stroke volume[5]. To precisely calculate the filling status of the ventricles, the Carmat TAH has incorporated ultrasonic transducers in both ventricles to monitor the membrane position[5].

The RealHeart TAH is currently under development and no mechanisms for preload sensitivity have been reported yet. However, initial characterisation of the TAH showed insufficient passive preload sensitivity, indicating the need for automated control[17].

The Vienna TAH, BRNO TAH and mushroom TAH are older TAH devices that are no longer in development. The Vienna TAH uses a complete filling/partial ejection mode for the ventricles. The cardiac output is manually changed, based on a left master control method that adjusts the right ventricular performance based on left atrial pressure[18]. In the BRNO TAH, the beat rate is adjusted such that the right pump fills to 90% of the maximum stroke to create a cushion that allows for passive preload sensitivity[15]. Vienna TAH and BRNO TAH both use higher driving pressures for the left ventricle compared to the right. The Mushroom TAH has ventricles made from soft, compliant materials. Due to the passive filling and stretching of the ventricles under higher preloads, a Frank Starling-like behaviour is obtained[16].

We calculated the preload sensitivity values (l/min/mmHg) of the TAHs, by determining the slope of the linear regressing of the preload sensitivity curve. For calculating the linear regression, we utilized preload sensitivity data obtained from literature, which covered a preload pressure range of 0-15 mmHg. These results are shown in Figure 2A, Table 1 and 2. The preload sensitivity of the native heart is 0.241[19]. All the pulsatile TAHs with individually controlled actuation of both ventricles show steep preload sensitivity curves, indicating that they adequately respond to preload changes by changing stroke volume. The Mushroom TAH is very preload sensitive due to its compliant ventricles (0.791)[16]. The combination of active and passive mechanisms in the BRNO result in a relatively high preload sensitivity (0.595)[15]. The solely passive mechanisms of the SynCardia and Vienna had lower preload sensitivity values (0.344 and 0.262 respectively) as well as the fully active mechanism of the Carmat TAH (0.214)[5,14,20].

Single actuation mechanism, volumetrically coupled ventricles

Pulsatile TAHs with single actuation mechanism and volumetrically coupled ventricles have two blood compartments separated from the actuation compartment by a membrane, similar to the TAHs with individually controlled actuation of both ventricles. However, these types of TAHs are actuated by a single actuator that either alternatingly or simultaneously ejects both ventricles. The ventricles are volumetrically coupled and individual adjustment in stroke volume of one ventricle is not possible. This means that stroke volume of both ventricles is equal since the volume reduction caused by one ventricle is compensated for by filling of the opposing ventricle (Figure 1B). Two alternatingly actuated, volumetrically coupled TAHs were developed in the past, but are no longer in use: the Electrohydraulic TAH (EH-TAH, Artificial Organs Department, Osaka, Japan)[21] and the AbioCor TAH (Abiomed, Danvers, MA, USA) [22]. Both systems are hydraulically actuated.

Because alternatingly actuated and volumetrically coupled TAHs do not facilitate passive filling, active control schemes are required to allow for preload sensitivity. In both TAHs, beat rate is adjustable based on changes in ventricular filling pressure. With an increase in

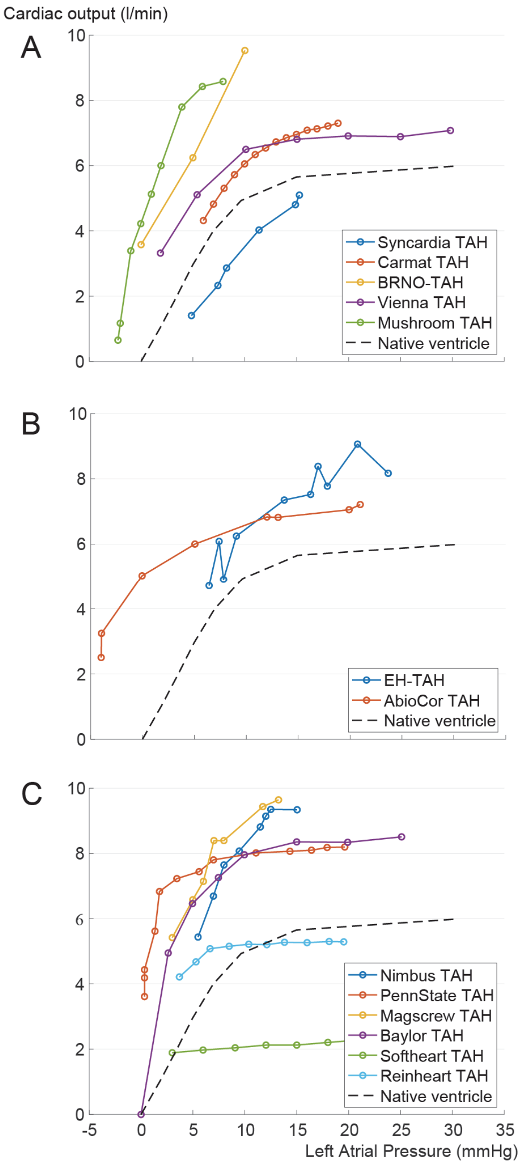


Figure 2. Preload sensitivity for pulsatile TAHs. Plots represent the relation between left atrial pressure (preload) and cardiac output. A) Pulsatile TAHs with individually controlled actuation of both ventricles. B) Pulsatile TAHs with single actuation mechanism, volumetrically coupled ventricles. C) Pulsatile TAHs with single actuation mechanism, volumetrically decoupled ventricles.

filling pressures, beat rate is increased and/or the relative diastole time is reduced. We calculated preload sensitivity values for both devices (Figure 2B, Table 1). It should be noted that these devices can adapt to preload changes for both ventricles simultaneously but are not able to balance their ventricular outputs individually. The EH-TAH and the AbioCor have sensors in the hydraulic compartment, to continuously monitor atrial pressures[22,23]. Additionally, the AbioCor TAH uses Hall sensors to monitor the filling state of the ventricles[22]. Because the left and right ventricular outputs cannot be changed independently, additional flow balancing mechanisms have been introduced. In the AbioCor TAH, a hydraulic shunt is placed between the right hydraulic chamber and a flow compensation chamber located between the left atrium and the mitral valve. High left atrial pressures (LAP) will cause a hydraulic shunt flow towards the right chamber, reducing the right pump capacity that eventually lowers the LAP [24] (Figure 3). In the EH-TAH an inter-atrial shunt (IAS) is used for maintaining balance between the LAP and right atrial pressure (RAP) [23].

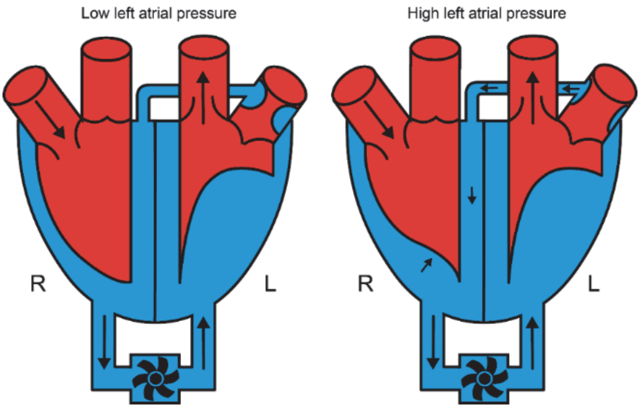


Figure 3. Schematic presentation of a hydraulic shunt, as used by AbioCor. High left atrial pressure will cause a hydraulic shunt flow towards the right hydraulic chamber. This limits the right pump capacity that eventually lowers the left atrial pressure.

Single actuation mechanism, volumetrically decoupled ventricles

These type of pulsatile TAHs have a single actuation mechanism but have volumetrically decoupled ventricles by an additional mechanism that compensates for the volume change. Often, a compliance chamber is used as a volume compensator. The compliance chamber is a separate implanted device that is connected to the TAH's actuation compartment. It is filled with gas, and capable of reducing its volume to compensate for volume differences (Figure 1C). We identified the following TAHs in this category: Baylor TAH (Baylor College of Medicine, Houston, TX, USA) [25], PennState TAH (Pennsylvania State University, Hershey, Pennsylvania, USA) [26], Magscrew TAH (Cleveland Clinic, Cleveland, OH, USA)[27], Nimbus TAH (Cleveland Clinic) [28], and Reinheart TAH (Helmholtz Institute, Aachen, Germany)[29]. These TAHs are actuated by an alternating pusher plate placed in between both ventricles. In general, these TAHs achieve preload sensitivity through a left master alternate control scheme. In a left master control method, pumping parameters are adjusted based on left ventricular filling parameters. Alternatively, one pneumatically actuated TAH in this category has been identified: the Softheart (ETH Zurich, Zurich, Switzerland). In the Softheart, both ventricles are actuated by the same actuator, namely in the form of an inflatable ventricular septum. The ventricles are decoupled due to the flexible nature of the material used. None of the TAHs in this category are currently in development.

The Baylor TAH, Magscrew, Nimbus TAH and PennState TAH are controlled by a left master alternate control method. This control method adjusts the pump speed, and thus beat rate, in response to an increased filling of the left ventricle. If a low end-diastolic volume is detected in the left ventricle, the beat rate is decreased, providing the ventricle more time to fill[28]. For the Baylor TAH, complete filling of the left ventricle serves as the main control parameter. After complete ejection of the right ventricle, the motor is turned off, adding a short pause in the cardiac cycle. Only after complete filling of the left ventricle is detected, the motor is turned back on and left ventricular ejection is initiated[30]. The right pump runs at 85-90% of its maximum stroke volume, allowing some passive buffer capacity for higher RAPs[30,31]. The Magscrew uses a similar left master alternate control method. Additionally, the Magscrew has a 20% lower stroke volume on the right side compared to the left[27]. This lower right-sided stroke volume is established by inhibiting the filling of the right ventricle, and by reducing the voltage supply to the right pump, that in turn reduces the right pump speed[27]. The Nimbus TAH uses a left master control method to limit the filling of the left ventricle to 90% of its maximum capacity, serving as a buffer to handle sudden increases in LAP[28]. The PennState TAH's control system allows for amplification or suppression of the Frank Starling-like response. More specifically, when the RAP rises, the right filling time of the ventricle is decreased, resulting in a higher pump speed. This leads to higher cardiac outputs on both sides. Importantly, the PennState can adjust the left ventricular filling time independently. For example, when the right ventricular filling time is reduced due to an increase in RAP, the left ventricular filling time can be prolonged if desired, resulting in a moderate Frank Starling response. Alternatively, a simultaneous reduction of both the left and right ventricular filling times results in a strong Frank Starling response mimicking the human heart [32]. Furthermore, the PennState TAH deliberately uses a slightly regurgitant pulmonary valve, a smaller pusher plate for the right pump, and a longer left ventricular filling time compared to the right [26,33]. In the Baylor TAH, Magscrew, Nimbus TAHs and PennState, the filling status of the left ventricle are measured using Hall sensors[28,31,34,35].

The Reinheart TAH adaptation to increased preload is solely achieved through passive filling of the ventricles[29,36]. In addition, the right ventricle is 10% smaller compared to the left and a larger mitral valve (23 mm) is used compared to the tricuspid valve (19 mm)[29,36].

In the Softheart some preload sensitivity is achieved due to the soft, elastic nature of the materials used. Its right ventricle is designed to be smaller than the left ventricle[37,38].

We found that the mean preload sensitivity for mechanically actuated TAHs in this category was highest for TAHs that are regulated by a left master alternate control system, mean 0.397 (Baylor TAH[25], PennState[26], Magscrew[27] and Nimbus TAH[28]) (Figure 2C and Table 1). In contrast, the passive preload regulated Reinheart TAH[29] and Softheart[37] exhibit poorer preload sensitivity, mean 0.039 (Table 1). This implies that the mechanically actuated TAHs in this category benefit from active preload regulation.

TAH	Preload Sensitivity mechanism	Preload Sensitivity (l/min/mmHg)	Mean Preload Sensitivity (l/min/mmHg)	Working mechanism TAH	Refs
Carmat	Automatic control	0.214	0.405	Individually controlled actuation of both ventricles	[5]
BRNO		0.595			[15]
SynCardia	Passive	0.344	0.466		[20]
Vienna		0.262			[14]
Mushroom		0.791			[16]
EHTAH	Automatic control	0.269	0.313	Single actuation mechanism, volumetrically *coupled* ventricles	[21]
Abiocor		0.356			[22]
Baylor	Automatic control	0.487	0.397	single actuation mechanism, volumetrically *decoupled* ventricles.	[25]
PennState		0.280			[26]
Magscrew		0.403			[27]
Nimbus		0.415			[28]
Reinheart	Passive	0.059	0.039		[29]
Softheart		0.020			[37]
Native human heart	Passive	0.241		Frank-Starling mechanism	[19,45]

Table 1. Preload sensitivity values for all TAHs. We calculated the preload sensitivity values (l/min/mmHg) of all TAHs, by determining the slope of the linear regressing of the preload sensitivity curve. We used data obtained between 0-15 mmHg preload pressure for calculating the linear regression.

In vivo performances

To evaluate proper output balance between both ventricles during changing hemodynamic conditions, in-vivo preclinical trials or even clinical trials deliver the most valuable information. In these trials, even a small imbalance is likely to cause clinical complications, such as respiratory failure and lung edema. Only with excellent ventricular balance, long support times can be achieved. The SynCardia has been implanted in over 1700 patients and reports duration of support up to 4.5 years, indicating sufficient adaptation to hemodynamic conditions[39]. Similarly, the Carmat has been shown to successfully balance its ventricular outputs. A currently ongoing clinical trial has reported a maximum duration of support of 308 days[40]. Although SynCardia and Carmat can effectively balance their ventricular outputs, their balance mechanisms come with constraints. The SynCardia is sensor-free but requires a large external driver next to the patient. The Carmat has integrated complex sensors into the system, that increases the risk of device failure.

The AbioCor TAH (no longer in development) has been implanted in 14 patients, with a maximum survival of 512 days[41], indicating that the cardiac outputs remained balanced. The EH-TAH, Nimbus TAH and the PennState TAH have not been implanted in patients, but reported long follow-up durations in animals >90 days, suggesting successful ventricular balancing mechanisms[33,42,43]. The other TAHs (Reinheart, Softheart, Baylor TAH, Vienna, BRNO and Mushroom TAH), did not report on long term support during (pre)clinical studies.

Implications for current and next generations of TAHs

Reported strategies to enable a pulsatile TAH to dynamically adapt to changing hemodynamic conditions include the incorporation of compliant materials and/or air cushions inside the ventricles, passive shunts (hydraulic or intra-atrial) or active control mechanisms to regulate ventricular filling state. Additionally, relative downsizing of the right ventricle was frequently reported as an additional (static) tool to balance the ventricular outputs.

Passive preload sensitivity mechanisms offer important advantages over automatically controlled mechanisms. The absence of sensors and complex control mechanisms reduce the risk of device failure. In pneumatically actuated TAHs, such passive mechanisms have been used. By purposely under filling the ventricle, a cushion of air is created around the ventricle, which enables a passive response. Alternatively, compliant materials can be used to invoke larger end-diastolic volumes at increased filling pressures. However, the use of compliant materials also comes with challenges. The compliant ventricles of the Softheart TAH demonstrated greater afterload sensitivity than preload sensitivity, which is highly undesirable[37]. This means that with an increase in systemic blood pressure, the pumping performance of the TAHs rapidly declines.

For mechanically and hydraulically actuated TAH devices, effective *passive* mechanisms to obtain preload sensitivity have not been reported yet. The mechanically actuated Reinheart TAH relied solely on passive filling of the ventricles, which was reported to be insufficient as it resulted in lung complications during animal trials[36]. Integrating passive preload sensitivity mechanisms such as air cushions or compliant materials in mechanically of hydraulically driven TAHs would be in interesting topic for future research.

Besides being sensitive to preload changes, TAHs should also be able to eject different stroke volumes for each ventricle. For this, TAHs with an individual actuation system per ventricle outperform TAHs with a single actuator. This is confirmed by the fact that the only two clinically approved TAHs (SynCardia and Carmat) both have individually actuated ventricles. In TAHs that use a single actuator, additional balancing mechanisms are often needed. For TAHs with volumetrically decoupled ventricles, these balancing mechanisms include smaller right ventricles compared to the left, as well as larger left ventricular inflow valves. These measures have the disadvantage of being static and are therefore unable to account for large hemodynamic changes. Additionally, in TAHs with a single actuation mechanism, a shunting mechanism can be used to achieve a balanced cardiac output. An intra-atrial shunt increases the risk for thrombi and the mixing of oxygenated and non-oxygenated blood[44]. A hydraulic shunt (used in the AbioCor) seems to be an interesting solution to aid ventricular balance, because it works passively and has less limitations. Also, the long-term clinical implantation of the AbioCor TAH in the past indicates proper functioning of the hydraulic shunt. Further investigation of such a hydraulical shunt may be of interest for future TAH prototypes with single actuation mechanism.

Conclusions

In this paper, different methods for controlling preload sensitivity and balance in pulsatile TAHs have been presented. In the case of individually controlled actuation of both ventricles, proper preload sensitivity seems to be sufficient for balancing the left and right cardiac outputs. TAHs containing one actuator driving both ventricles require additional left-right balancing mechanisms. While preload sensitive behaviour is relatively simple to achieve for pneumatically driven TAHs due to the natural compliant behaviour of gas, hydraulic and mechanically driven TAHs require more advanced control algorithms and active monitoring of hemodynamic parameters. Therefore, with regard to responsiveness to changing hemodynamic conditions, a pneumatic TAH that comprises two individually actuated ventricles appears to be a more desirable option in terms of both simplicity and efficacy.

TAH	Actuation	Basic preload sensitivity mechanism	Additional preload sensitivity mechanism	Preload sensi-tivity	Mean preload sensi-tivity	Additional mechanisms to maintain ventricular balance	Sensors	(Pre)clinical results: max follow-up	Develop-ment status	Refs
Carmat	Hydraulic	Automatic control	Individual control for both ventricles	0.214	0.405	Individual drive setup	Pressure sensor in hydraulic compartment and incorporated ultrasonic transducers to measure filling status.	308 days (human)	In clinical use	5,40,46,47
BRNO	Pneumatic		Beat rate adjustments to maintain 90% filling of the RV	0.595		Individual drive setup	Pressure in the gas compartment is monitored using a catheter	10 days (human)	Terminated	15,48,49
Syncardia	Pneumatic	Passive	Air cushion	0.344	0.466	Individual drive setup	Sensors in the pneumatic driver, so no sensors are placed inside the body	4.5 years (human)	In clinical use	3,20,50,51
Vienna	Pneumatic		Air cushion	0.262		Individual drive setup	Catheters with pressure transducers were inserted into the radial artery, the vena cava superior and the left atrium	22 days (human)	Terminated	14,18
Mushroom	Pneumatic		Compliant materials	0.791		Individual drive setup	No sensors	Not applicable	Terminated	16
EHTAH	Hydraulic	Automatic control	Adjusting T_{RD} and T_{LD} based on pressure inside hydraulic compartment during diastole. This pressure should be slightly negative.	0.269	0.313	IAS	Pressure sensor in hydraulic compartment	159 days (animal)	Terminated	21,23,52,53
Abiocor	Hydraulic		Adjusting T_{RD} and T_{LD} based on pressure inside hydraulic compartment during diastole. If under- or overfilling of both ventricles is detected, overall beat rate is increased.	0.356		Hydraulic shunt	Pressure sensor in hydraulic compartment and Hall sensor to measure membrane position	512 days (human)	Terminated	24,41,54-57
Baylor	Mechanical	Automatic control	LMA, pause after RV ejection until complete LV filling is detected.	0.487	0.397	Right SV reduction	Hall sensors are used for measuring the filling status of the LV	2 days (animal)	Terminated	25,30,31,58,59
Penn state	Mechanical		LMA, T_{RD} adjustments to maintain LV filling at 90%	0.280		Right SV reduction Adjusted right valve Diastase after left diastole	Indirectly determine end diastolic volume of the ventricles based on motor current	388 days (animal)	Terminated	26,32,33,60-62
Magscrew	Mechanical		LMA, beat rate adjustments to maintain LV filling at 90%	0.403		Right SV reduction Right voltage reduction	Hall sensors are used for measuring the filling status of the LV	92 days (animal)	Terminated	27,35,63,64
Nimbus	Mechanical		LMA, beat rate adjustments to maintain LV filling at 90%	0.415		Right SV reduction Right voltage reduction	Hall sensors are used for measuring the filling status of the LV	120 days (animal)	Terminated	28,43
Reinheart	Mechanical	Passive	Passive, preload sensitive filling	0.059	0.039	Right SV reduction; Syst/diast ratio adjustments.	No sensors	2 days (animal)	Ongoing	29,36,65-68
Softheart	Pneumatic		Compliant materials	0.020		Right SV reduction	No sensors	Not applicable	Ongoing	37

Table 2. Preload sensitivity methods for all included TAHs. RV=right ventricle, T_{RD}=right diastolic time, T_{LD}=left diastolic time, LMA=left master alternate control scheme, LV=left ventricle.

References

1 *Organ Donation Statistics* <https://www.organdonor.gov/learn/organ-donation-statistics > (2023).

2 Vis, A. *et al.* The ongoing quest for the first total artificial heart as destination therapy. *Nature Reviews Cardiology* 19, 813-828, (2022).

3 Slepian, M. J. *et al.* The Syncardia™ total artificial heart: in vivo, in vitro, and computational modeling studies. *Journal of Biomechanics* 46, 266-275, (2013).

4 US Food and Drug Administration. *SynCardia Temporary Cardio West Total Artificial Heart (TAH-T).*https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=P03 0011 (2004).

5 Netuka, I. *et al.* First Clinical Experience With the Pressure Sensor–Based Autoregulation of Blood Flow in an Artificial Heart. *ASAIO Journal* Publish Ahead of Print, (2021).

6 Carmat receives the CE marking for its total artificial heart. *Carmat*, <https://www.carmatsa.com/en/press-release/carmat-receives-ce-marking-total-artificial-heart/> (2020).

7 Pieper, I. L., Sonntag, S. J., Meyns, B., Hadi, H. & Najar, A. Evaluation of the novel total artificial heart Realheart in a pilot human fitting study. *Artif Organs* 44, 174-177, (2020).

8 Greatrex, N., Kleinheyer, M., Nestler, F. & Timms, D. The Maglev Heart. *IEEE Spectrum* 56, 22-29, (2019).

9 Jurney, P. L. *et al.* Characterization of a pulsatile rotary total artificial heart. *Artif Organs* 45, 135-142, (2021).

10 Miyamoto, T. *et al.* Analysis of Cleveland Clinic continuous-flow total artificial heart performance using the Virtual Mock Loop: Comparison with an in vivo study. *Artif Organs* 44, 375-383, (2020).

11 Ley, S., Kreitner, K. F., Morgenstern, I., Thelen, M. & Kauczor, H. U. Bronchopulmonary shunts in patients with chronic thromboembolic pulmonary hypertension: evaluation with helical CT and MR imaging. *AJR Am J Roentgenol* 179, 1209-1215, (2002).

12 Cohn, W., Timms, D., Frazier, O., Bhunia, S. K. & Kung, R. T. Total artificial hearts: Past, present, and future Indirect bronchial shunt flow measurements in AbioCor implantable replacement heart recipients. Nature reviews. Cardiology 12, (2015).

13 Jacob, R., Dierberger, B. & Kissling, G. Functional significance of the Frank-Starling mechanism under physiological and pathophysiological conditions. *European Heart Journal* 13, 7-14, (1992).

14 Rokitansky, A. *et al.* The New Small Viennese Total Artificial Heart: Experimental and First Clinical Experiences. *Artificial Organs* 15, 129-135, (1991).

15 Vasku, J. *et al.* Control and Driving of Pneumatic Total Artificial Hearts TNS-BRNO-II and-III in Long-Term Experiments. *Artificial Organs* 10, 145 - 152, (1986).

16 Kolff, A., Kolff, C. & Kolff, W. J. The soft-shell mushroom heart remembered. *Artificial Organs* 15, 225-240 (1991).

17 Fresiello, L. *et al.* Hemodynamic characterization of the Realheart® total artificial heart with a hybrid cardiovascular simulator. *Artificial Organs* 46, 1585-1596, (2022).

18 Schima, H. *et al.* Control of the Total Artificial Heart: New Aspects in Human versus Animal Experience. *Artificial Organs* 13, 545-552, (1989).

19 Fukamachi, K. *et al.* Preload Sensitivity in Cardiac Assist Devices. *The Annals of Thoracic Surgery* 95, 373-380, (2013).

20 Crosby, J. R. *et al.* Physiological Characterization of the SynCardia Total Artificial Heart in a Mock Circulation System. *ASAIO Journal* 61 (2015).

21 Kim, H. C., Khanwilkar, P., Bearnson, G. & Olsen, D. Development of a microcontroller-based automatic control system for the electrohydraulic total artificial heart. *IEEE transactions on bio-medical engineering* 44, 77-89, (1997).

22 Kung, R. T. V. & Ochs, B. in *3rd International Symposium on Artificial Heart and Assist Devices* 173-181 (Springer Japan, Tokyo, Japan, 1990).

23 Olsen, D. B., White, R. K., Long, J. W. & Khanwilkar, P. S. Right-Left Ventricular output Balance in the Totally Implantable Artificial Heart. The International Journal of Artificial Organs 14, 359-364, (1991).

24 Kung, R. T. V., Yu, L.-S., Ochs, B., Parnis, S. & Frazier, O. H. An Atrial Hydraulic Shunt in a Total Artificial Heart A Balance Mechanism for the Bronchial Shunt. *ASAIO Journal* 39 (1993).

25 Orime, Y. *et al.* Versatile One-Piece Total Artificial Heart for Bridge to Transplantation or Permanent Heart Replacement. *Artificial organs* 16, 607-613, (1993).

26 Weiss, W. J. *et al.* Steady State Hemodynamic and Energetic Characterization of the Penn State/3M Health Care Total Artificial Heart. *ASAIO Journal* 45 (1999).

27 Weber, S. *et al.* In Vitro Controllability of the MagScrew Total Artificial Heart System. *ASAIO Journal* 48 (2002).

28 Massiello, A. *et al.* The Cleveland Clinic-Nimbus total artificial heart. Design and in vitro function. *The Journal of Thoracic and Cardiovascular Surgery* 108, 412-419 (1994).

29 Hildebrand, S. *et al.* Controlling the flow balance: In vitro characterization of a pulsatile total artificial heart in preload and afterload sensitivity. *Artificial Organs* 46, 71-82, (2022).

30 Takatani, S. *et al.* Left and Right Pump Output Control in One-Piece Electromechanical Total Artificial Heart. *Artificial Organs* 17, 176-184, (1993).

31 Takatani, S. *et al.* One Piece Ultracompact Totally Implantable Electromechanical Total Artificial Heart for Permanent Use. *ASAIO Journal* 48 (2002).

32 Snyder, A. J., Rosenberg, G. & Pierce, W. S. Noninvasive Control of Cardiac Output for Alternately Ejecting Dual-Pusherplate Pumps. *Artificial Organs* 16, 189-194, (1992).

33 Snyder, A. J. *et al.* An electrically powered total artificial heart. Over 1 year survival in the calf. *ASAIO journal* 38, M707—712, (1992).

34 Kuroda, H. *et al.* Postoperative pulmonary complications in calves after implantation of an electric total artificial heart. *Asaio j* 44, M613-618, (1998).

35 Weber, S. *et al.* MagScrew TAH: An Update. *ASAIO Journal* 51 (2005).

36 Diedrich, M. *et al.* Experimental investigation of right-left flow balance concepts for a total artificial heart. *Artificial Organs* 45, 364-372, (2021).

37 Cohrs, N. H. *et al.* A Soft Total Artificial Heart—First Concept Evaluation on a Hybrid Mock Circulation. *Artificial Organs* 41, 948-958, (2017).

38 Guex, L. G. *et al.* Increased Longevity and Pumping Performance of an Injection Molded Soft Total Artificial Heart. *Soft Robot* 8, 588-593, (2021).

39 Syncardia Systems. *Turkish Man Becomes World’s Longest Supported SynCardia temporary Total Artificial Heart Patient*, <https://syncardia.com/news/turkish-man-becomes-worlds-longest-supported-syncardia-temporary-total-artificial-heart-patient/>

40 Netuka, I. *et al.* Initial bridge to transplant experience with a bioprosthetic autoregulated artificial heart. *Journal of Heart and Lung Transplantation* 39, 1491--1493, (2020).

41 Frazier, O. H. *et al.* The Total Artificial Heart: Where We Stand. *Cardiology* 101, 117-121, (2004).

42 Taenaka, Y. *et al.* An electrohydraulic total artificial heart with a separately placed actuator. *ASAIO Trans* 36, M242-245 (1990).

43 Harasaki, H. *et al.* Progress in Cleveland Clinic--Nimbus Total Artificial Heart Development. *ASAIO Journal* 40 (1994).

44 Tatsumi, E. *et al.* In Vitro and In Vivo Evaluation of a Left-Right Balancing Capacity of an Interatrial Shunt in an Electrohydraulic Total Artificial Heart System. *ASAIO Journal* 43 (1997).

45 Salamonsen, R. F., Mason, D. G. & Ayre, P. J. Response of Rotary Blood Pumps to Changes in Preload and Afterload at a Fixed Speed Setting Are Unphysiological When Compared With the Natural Heart. *Artificial Organs* 35, E47-E53, (2011).

46 Jansen, P., Oeveren, W., Capel, A. & Carpentier, A. In vitro haemocompatibility of a novel bioprosthetic total artificial heart. *European Journal of Cardio-Thoracic Surgery* 41, e166-172, (2012).

47 Carpentier, A. *et al.* First clinical use of a bioprosthetic total artificial heart: Report of two cases. *Lancet (London, England)* 386, (2015).

48 Hanzelka, P. *et al.* BRNO-I, An Implantable, Diaphragm-Type Total Artificial Heart: Technical Aspects of Design. *Artificial Organs* 4, 65-67, (1980).

49 Vašků, J. *et al.* 150-Day Survival of a Calf with a Polymethylmethacrylate Total Artificial Heart: TNS-BRNO-II. *Artificial Organs* 5, 388-400, (1981).

50 Copeland, J. G. *et al.* Total artificial hearts: Bridge to transplantation. *Cardiology Clinics* 21, 101-113, (2003).

51 Kawai, J. *et al.* Implantation of a total artificial heart in calves under hypothermia with 10 day survival. *The Journal of Thoracic and Cardiovascular Surgery* 64, 45-60, (1972).

52 Lioi, A. P. *et al.* In Vitro Development of Automatic Control for the Actively Filled Electrohydraulic Heart. *Artificial Organs* 12, 152-162, (1988).

53 Long, J. W. *et al.* Right-Left Ventricular Balance in Implanted Electrically Powered Artificial Hearts. *ASAIO Journal* 36 (1990).

54 Kung, R. T. V. & Ochs, B. in *Artificial Heart 3* (eds Tetsuzo Akutsu *et al.*) 173-181 (Springer Japan, 1991).

55 Kung, R. T. V., Ochs, B. & Singh, P. I. A Unique Left-Right Flow Imbalance Compensation Scheme for an Implantable Total Artificial Heart. *ASAIO Journal* 35 (1989).

56 Samuels, L. The AbioCor Totally Implantable Replacement Heart. *The American Heart Hospital Journal* 1, 91-96, (2003).

57 Dowling, R. D. *et al.* Initial experience with the AbioCor implantable replacement heart system. *The Journal of Thoracic and Cardiovascular Surgery* 127, 131-141, (2004).

58 Takatani, S. *et al.* Development of a Totally Implantable Electromechanical Total Artificial Heart: Baylor TAH. *Artificial Organs* 16, 398-406, (1992).

59 Yukihiko, O. *et al.* Current Status of The Baylor Total Artificial Heart. *人工臓器* 24, 383-390, (1995).

60 Rosenberg, G. *et al.* An Electric Motor-Driven Total Artificial Heart: Seven Months Survival in the Calf. *ASAIO Journal* 30 (1984).

61 Rosenberg, G., Snyder, A. J., Weiss, W. J., Sapirstein, J. S. & Pierce, W. S. in *Assisted Circulation 4* (ed Felix Unger) 236-248 (Springer Berlin Heidelberg, 1995).

62 Weiss, W. J. *et al.* Permanent circulatory support systems at the Pennsylvania State University. *IEEE Transactions on Biomedical Engineering* 37, 138-145, (1990).

63 Doi, K. *et al.* In Vivo Studies of the MagScrew Total Artificial Heart in Calves. *ASAIO Journal* 48 (2002).

64 Schenk, S., Weber, S., Smith, W. A. & Fukamachi, K. MagScrew Total Artificial Heart. *The Annals of Thoracic Surgery* 81, 2338-2339, (2006).

65 Laumen, M. *et al.* A Novel Total Artificial Heart for Destination Therapy: In-Vitro and In-Vivo Study. *Biomedizinische Technik* 58, 000010151520134373, (2013).

66 Pelletier, B. *et al.* System overview of the fully implantable destination therapy-- ReinHeart-total artificial heart. *European Journal of Cardio-Thoracic Surgery* 41, 80-86, (2014).

67 Cuenca-Navalon, E., Laumen, M., Finocchiaro, T. & Steinseifer, U. Estimation of Filling and Afterload Conditions by Pump Intrinsic Parameters in a Pulsatile Total Artificial Heart. *Artificial Organs* 40, 638-644, (2016).

68 Schmitz, S. *et al.* Prototype Development of an Implantable Compliance Chamber for a Total Artificial Heart. *Artificial Organs* 41, 122-129, (2017).