Protocol to Assess and Standardize the Use of Mock Circulatory Loops for Ventricular Assist Device Testing

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1. Background and Objectives

1.1 Objective and Scope

> *Establish consensus standardized bench test methods and define the recommended baseline physiologic conditions to validate the use of mock circulatory loops (MCLs) as an effective and less burdensome tool for evaluating the hemodynamic performance of mechanical circulatory support (MCS) devices under clinically relevant heart failure (HF) patient conditions.*

The primary standard to evaluate MCS device safety and performance, ISO 14708-5 [7], currently lacks necessary details to be used as an effective regulatory and/or developmental tool. This study aims to gather data in support of developing consensus testing methods and patient conditions that can be included in the upcoming revision of the ISO 14708-5 standard. The protocol contained in this document is primarily intended for evaluating ventricular assist devices (VADs) and percutaneous transvalvular pumps. Labs with MCLs designed to evaluate other MCS technologies, such as total artificial hearts, will need to assess those devices differently but can still participate in the study. Please contact us (**Dr. Matthew Hirschhorn (matthew.hirschhorn@fda.hhs.gov)** or visit the study website) if you have other MCS technologies so we can discuss your participation.

1.2 Medical Need

Over 6 million Americans are currently living with congestive heart failure, with more than half of those dying within 5 years of diagnosis [1, 2]. One of the primary treatment options for advanced or end-stage heart failure (HF) is MCS device therapy, which involves the use of implantable, percutaneous, or extracorporeal mechanical pumps to replace or augment the function of the failing heart and maintain adequate blood perfusion to vital organs for temporary or long-term periods. With more than 22,000 VAD implantations in the U.S. [3], the reliance on these types of MCS devices has steadily increased due to a

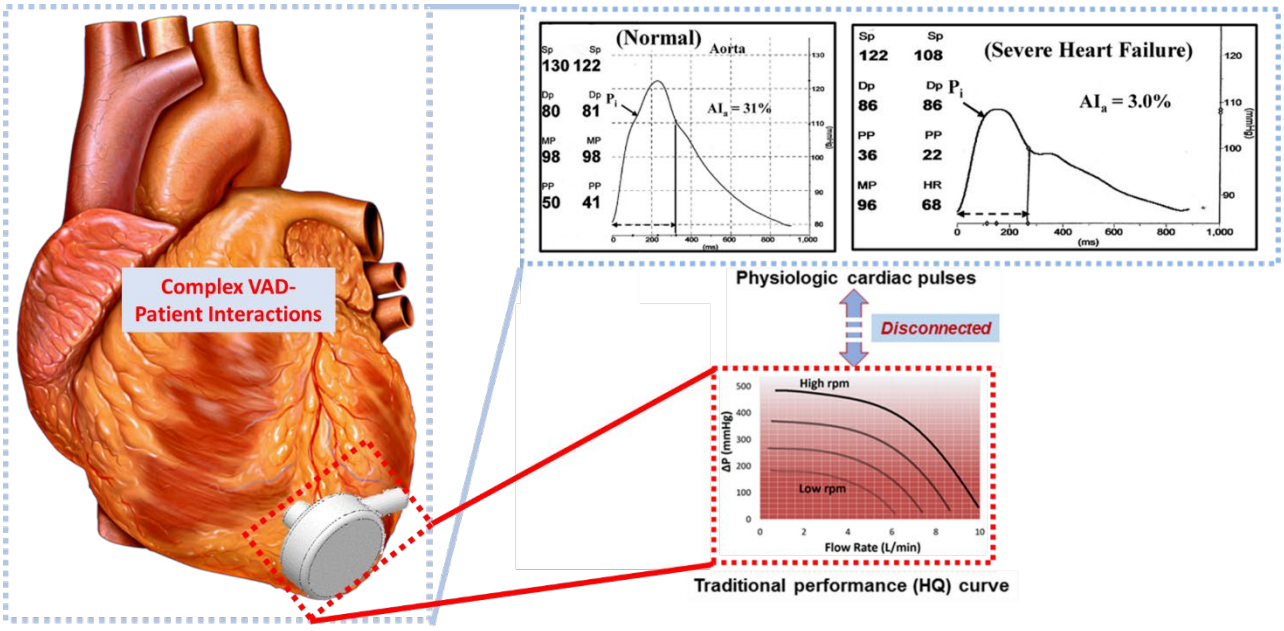

Figure 1: An image showing an implanted MCS device (i.e., ventricular assist device (VAD)) along with the knowledge gap in current in vitro testing.

lengthy and growing heart transplant list, limited donor organ availability, and the prospect for improved quality of life in HF patients. Recent technological advancements and an increase in clinician confidence in placing MCS devices in less sick and special patient populations, such as in pediatric patients, has contribute to the expanded use of MCS devices [3]. With the increase in reliance on MCS devices to treat advanced HF, it is imperative to ensure that the devices are highly reliable and operate safely and effectively, in accordance with their prescribed performance specifications, to avoid major adverse clinical outcomes. Due to the inherently variable and pulsatile nature of the human cardiovascular system and the diverse HF etiologies [4], MCS devices are often subjected to varying and complex in vivo hemodynamic interactions when connected to the patient's failing heart. Due to the complex interactions between MCS devices and patients, it is difficult to accurately predict device performance prior to implantation. Complex cardiovascular hemodynamics and HF etiology warrant the need for better pre-market assessment of device-patient interactions under different HF conditions. To overcome the challenges, alleviate high risks and inconsistencies surrounding in vivo and clinical studies, and reduce device-related complications in the post-market stage, there is a compelling need for more meaningful non-clinical test methods to assess device safety and performance. Recent MCS device malfunctions have shown how serious device-related complications can impede otherwise promising MCS device technologies [5, 6]. Furthermore, next-generation MCS devices with advanced technological features will introduce new challenges for device manufacturers, healthcare providers, regulatory reviewers, and patients. Currently, regulatory bodies in the United States and internationally rely heavily on costly and time-consuming animal studies, clinical trials, and post-market studies to assess safety and effectiveness, since the true therapeutic benefits, functionality, and adverse events associated with these complex devices remain largely unknown until they are placed in humans [3]. This regulatory science knowledge gap presents an opportunity to address the predictive 'clinical performance' regulatory science priority by establishing less burdensome bench test methods to characterize complex device-patient interactions in a clinically relevant, reproducible, simulated-use environment during the pre-clinical assessment stages of the device's total product life cycle (TPLC).

1.3 Current in vitro Testing Standards

Although the ISO 14708-5 standard provides high-level guidelines for in vitro performance testing of MCS device systems for device manufacturers, it does not include specific details, standardized flow loop components, or quantifiable metrics for using an MCL as an evaluative tool.

1.4 Ongoing Needs

In the absence of reliable, consensus-developed test methods, device developers are limited to evaluating MCS devices under pressure and flow conditions using inconsistent, in-house protocols and in vivo studies in healthy animals. Thus, to better predict device functionality prior to clinical use and subject the device to a range of pathophysiologic conditions, the U.S. Food and Drug Administration (FDA) and the University of Twente developed this document so MCL users and experts from around the world can begin to develop consensus methods for using MCLs to assess MCS device performance under several HF conditions. The protocol aims to determine how MCLs can best be used as a pre-clinical regulatory tool for accelerating patient access to high-quality, innovative, safe, and effective MCS devices and create a more efficient and less burdensome regulatory decision-making process. The overall objective of the current project is to improve MCS device performance testing by developing well-defined, reproducible, consensus,

standardized bench test methods that evaluate the use of MCLs with simulated disease states and with VAD interaction. We hope to incorporate these updates into the upcoming ISO 14708-5 standard revisions. If you have comments or questions, please contact **Dr. Matthew Hirschhorn (matthew.hirschhorn@fda.hhs.gov)** or visit the study website.

2. MCL components

2.1 Overview

Historically, in an MCL, the human circulation is represented as a Windkessel model. The complexity and parts of the circulation represented are dependent on the intended use of the tool. Aortic root and downstream systemic arterial elasticity is recreated with a compliance chamber, which is often a pressurized container that takes advantage of the compressibility of air. The compliance can be adjusted by changing the air pressure in the chamber. Systemic resistance is generated by adjusting a tubing clamp. These benchtop hydraulic MCLs can become very advanced, with both the pulmonary and systemic circulations, even representing both cerebral and coronary vasculatures. Many autoregulatory mechanisms can also be represented, such as the baroreflex and Frank-Starling law. In recent years, a new class of MCL has been developed that links a lumped parameter model (LPM) with one or many hydraulic interfaces where the pressure and flow profile at the hydraulic interfaces is based on interaction of the physical model with the LPM.

2.2 MCL Minimum Requirements, Types and Descriptions:

To be able to utilize this protocol, interested labs should have an existing and functional MCL at the start of the study. Example baseline MCL components are listed in section 2.2.1 and 2.2.2. The approach and protocols in this document can be implemented in MCLs with a wide range of complexities. For this, labs should record and compile information about their MCL and any verification/validation work that has previously been completed to assess performance. Verification/validation of LPMs in hybrid MCLs is of particular interest.

2.2.1 MCL with strictly hydraulic components

An example basic hydraulic MCL is represented in Figure 2A and consists of a pulsatile pump, method for systemic compliance and resistance, a fluid reservoir, and pressure and flow sensors. Because this loop is simple, the ability of the loop to reliably recreate cardiac rhythms is potentially limited. The inclusion of additional areas of compliance and resistance will increase both tunability and complexity. The MCL currently used at the FDA is shown in Figure 2B and has many components designed to improve the quality of the recreated cardiac rhythms. It also has a VAD model connected to the apex of the LV to study the effects of MCS devices on patients with HF.

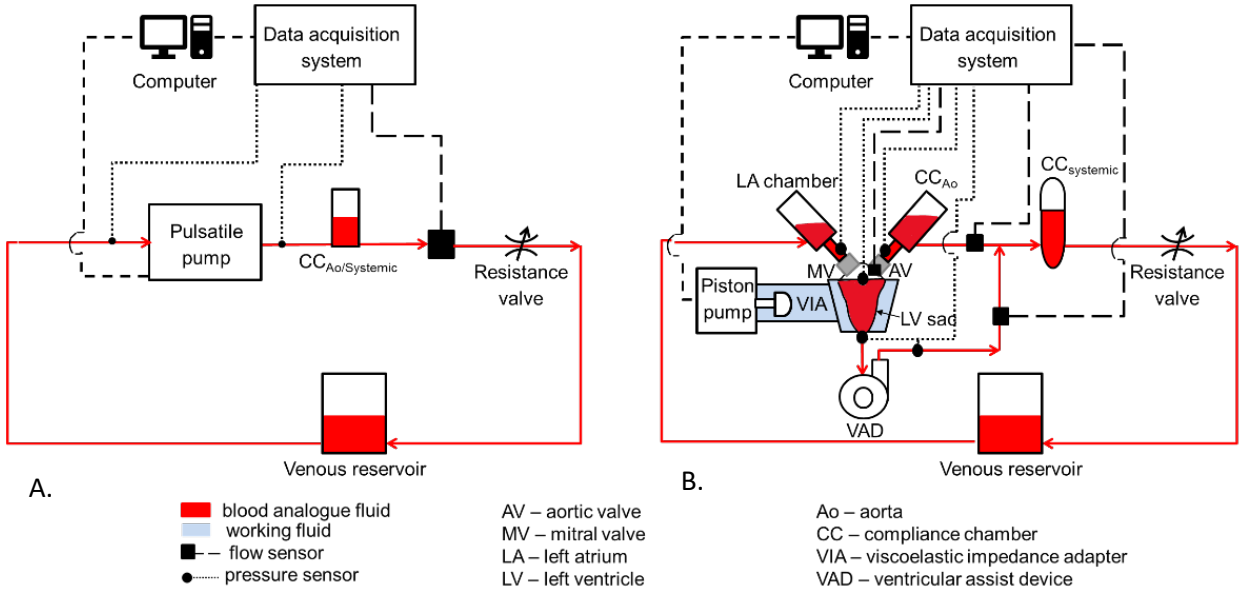

Figure 2 A) Basic MCL with standard components B) FDA MCL with components required to simulate different pathophysiologic conditions. More information about the MCL being used at the FDA can be found in the Regulatory Science Tool found here.

"Hybrid" MCL

There are also groups who will use this document that have developed hybrid MCLs which contain interfaces between a benchtop hydraulic circuit and a computational model, usually a LPM representative of human circulation. The hydraulic interfaces in the simulator are coupled to the LPM to create the specific pressures and flows prescribed by the LPM. The simulator also measures pressures and flows and provides that information to the LPM. As an example, Figure 3 is a graphic showing a hybrid MCL that is being used to study an LVAD. It was developed by Dr. Fresiello at University of Twente, one of the authors

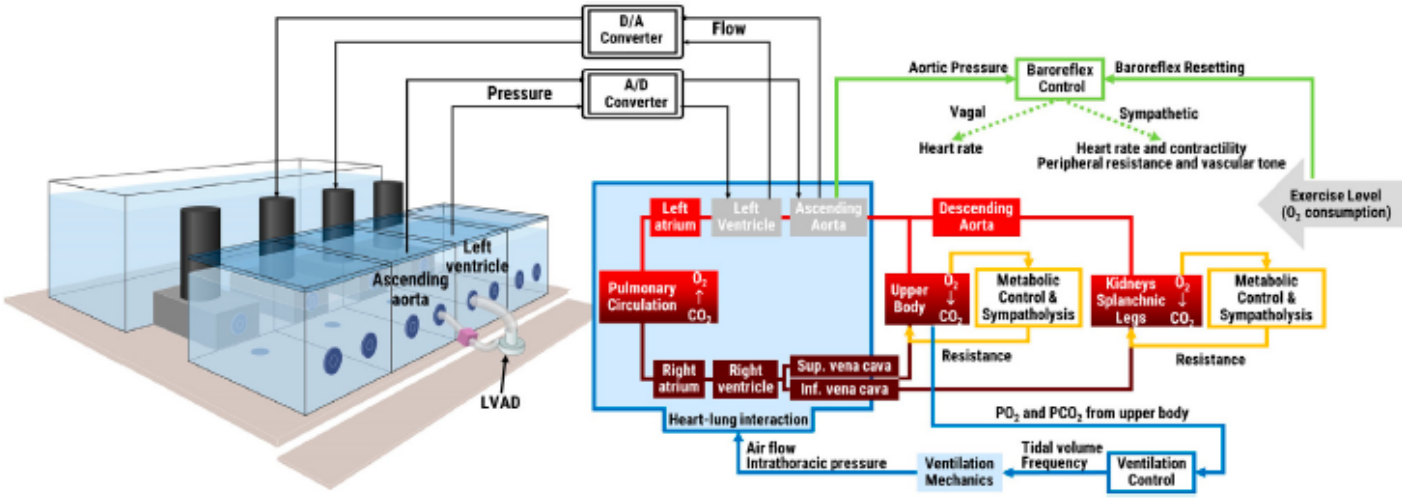

Figure 2 : Example Hybrid MCL testing an LVAD with a physical benchtop left heart model and an in silico LPM to represent the rest of the body. [Fresiello et al, 2022, Frontiers in Physiology]

of this document. When sharing information and results from hybrid MCLs, a record of all verification/validation work that has been completed on the LPM should be provided. Hybrid MCLs depend on the validity of the LPM and coupling algorithms, and these areas will need to be considered when discussing results.

2.2.2 Other Potential MCL Features:

If a participant's loop has additional complexities or capabilities, they should be included and explored as part of the study. The specifics of what simulated conditions each group chooses to assess will depend on their loop and will be determined individually. Wherever possible, studies will be designed such that results from different groups can be directly compared where similar or shared components exist, such as use of commercially available piston pumps, pulse duplicators or rotary pumps. Other features that could be included are given in the list below and is not inclusive of all possibilities.

1. VAD model
2. Closed loop with both left/right heart represented
3. Physiologic aorta and/or other anatomy
4. Frank-Starling response mechanism
5. Ability to measure: LV end diastolic/end systolic left ventricular volumes, systemic vascular resistance, ejection fraction, aortic flow rate, and VAD flow rate
6. Suction model
7. Respiration model/mechanical ventilation
8. Baroreflex model
9. Coronary circulation
10. Cerebral circulation
11. Heart rhythm disturbances
12. Valve disease and valvular regurgitation

3. Experimental Simulated Patient Conditions

3.1 Proposed pathophysiologic conditions with corresponding cardiac hemodynamic indices.

Healthy and Pathophysiologic Patient Conditions

Test Condition	HR (bpm)	CO (L/min)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	mPAP (mmHg)	Wedge (mmHg)	RAP (mmHg)	LVEF (%)	LVESV ml	LVEDV ml	SVR mmHg min/L	PVR mmHg min/L
Healthy adult, rest	70	5.0	120	80	93	15	10	6	55	58	130	1.04	0.06
Healthy, 7y/o rest	100	2.8	106	70	82	15	10	6	55	23	51	1.63	0.11
Cardiogenic shock: SCAI Level C/D/E Stable	100	3.5	80	50	60	28	20	12	25	105	140	0.82	0.14
Cardiogenic shock: SCAI Level C/D/E On Admission, Critical	100	2.1	80	50	60	28	20	12	15	119	140	1.37	0.23
HF with preserved EF NYHA II-IV	90	4.5	130	95	107	36	24	12	57	38	88	1.27	0.16
HF with reduced EF NYHA II-IV	72	4.5	112	65	81	23	16	9	29	153	216	0.96	0.09

VAD Simulated Conditions and Tests

Test Condition	HR	Total CO (L/min)	VAD Flow (L/min)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	mPAP (mmHg)	Wedge (mmHg)	RAP (mmHg)	LVEF (%)	LVESV ml	LVEDV ml	SVR mmHg s/ml	PVR mmHg s/ml
VAD Baseline HF	80	3.8	0.0	98	60	73	31	21	10	19	203	250	0.99	0.16
VAD Patient, Exercise*	117	7.3	6.1	Depends on VAD used		98	32	22	13		154	186	0.70	0.08
VAD Running, Partial Support	80	5.0	2.5	Follow VAD Assessment Instructions in Section 5.5.3									0.99	0.16
VAD Running, Full Support	80	5.0	5.0										0.99	0.16
Assessment of Preload and Afterload on VAD performance	Follow Static and Dynamic HQ Curve Protocols in Section 5.5.2													
Suction Detection	80	Follow Suction Protocol in Section 5.5.4											0.99	0.16
VAD Running, Artificial Pulse	80	Follow Pulse Pressure Protocol in Section 5.5.5											0.99	0.16

*The hemodynamic profile depends on the LVAD used, the values reported in the table are only an example for a rotary LVAD similar to the HVAD.

Table 1

These indices have been identified through engagement with clinicians, real-world clinical evidence, and published reports. HR: Heart Rate, CO: Cardiac Output, SAP: Systolic Arterial Pressure, DAP: Diastolic Arterial Pressure, MAP: Mean Arterial Pressure, mPAP: Mean Pulmonary Arterial Pressure, RAP: Right Atrial Pressure, LVEF: Left Ventricular Ejection Fraction, SVR: systemic vascular resistance, PVR: pulmonary vascular resistance, LVESV: left ventricular end-systolic volume, LVEDV: left ventricular end diastolic volume.

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3.2 MCL Specific Experimental Conditions

The physiologic and pathophysiologic conditions outlined in the top section of Table 1 should all be recreated based on the capabilities of individual circuits. This will largely be based on the complexity of the loop. Not all metrics will be able to be measured and recorded by every lab. When prioritizing metrics to match, reference the following tiers from high to low priority:

1. HR, CO, SAP, DAP, MAP
2. mPAP, Wedge, RAP
3. LVEF, LVESV, LVEDV

In the table, SVR and PVR are derived quantities from the other metrics. The listed LVESV and LVEDV represent one way the metrics could be achieved. Based on the capabilities of the MCL being used, additional testing should be completed, as outlined in Section 5.5 and defined in the second section of Table 1. For MCLs with the ability to add a VAD, the device should be tested in a simulated severe heart failure patient in both full and partial assist modes and with the VAD connected but not running. As the capabilities of each MCL allow, if a VAD model is being used, it should also be assessed by creating static and dynamic pressure-flow curves. As MCL capabilities allow, labs can assess suction and artificial pulsatility. If a participating group has multiple available VAD models, study organizers will help select the most appropriate model to be used for testing. Groups may also submit data for multiple VAD pumps if time and resources allow. Please note that direct comparison of different VADs and their capabilities is outside the scope and will not be completed. The goal of this study is to evaluate the capability of different MCLs to simulate and assess VAD hemodynamic outcomes. It is recognized that different technologies aim to serve different populations and conditions and direct comparison is inappropriate. Additionally, limits on maximum pump flow rate and other perceived limits should not prevent participation.

4. Data and Information Handling and Processing

4.1 Study Initiation

Each lab utilizing this protocol should compile and record:

1. Complete list of MCL components, along with their dimensions and materials, including descriptions of all tubing, compliant and resistive elements, physiologic geometric or material models.
2. Complete list of all sensors used, including information on instrument calibration. This should include both sensor calibration curves and records of current calibration. and specific models.
3. Complete description of data collection methodology, including the data acquisition board make and model. Information about analog and digital filters should be included in description.
4. Schematic drawing of the finalized MCL circuit and photos of the actual MCL with components labeled.
5. For hybrid MCLs, a representation of the LPM as a circuit diagram, including governing equations where appropriate, should be included.
6. Although groups will be expected to follow the protocol outlined in Section 5, labs should provide an overview of the loop specific procedure followed to achieve the simulated patient conditions. This will include descriptions of how parameters such as systemic compliance and resistance, stroke volume, cardiac output and heart rate are set. Study organizers want to understand in detail how the different conditions are achieved in each participating loop. ,
7. For groups with an existing VAD in the circuit, participant labs will also record a description of the VAD used and its configuration in the MCL, particularly if the VAD model is a commercially available product. Report material, dimension (internal diameter and length) of the tubes and connectors used to link the VAD to the MCL.
8. Include photo documentation about the set up to evaluate possible curvature of the tubes, position of the flowmeter and position of the pressure sensors in the MCL. Setups should ideally be standardized across groups that are using the same VAD model (likely a commercially marketed device) and will need to be coordinated between groups. Connecting groups for these discussions can be organized by contacting **Dr. Matthew Hirschhorn (matthew.hirschhorn@fda.hhs.gov)** or visiting the **study website.**

4.2 Data Collection Scheme

4.2.1 Approach

Systems and equipment used for data acquisition, manipulation, display, and storage should be documented. Data acquisition methods and equipment used should also be specified (e.g., real time, triggering methods, sampling rate, filters, amplification). If any data manipulation (e.g., averaging, smoothing) is performed prior to display and storage of final information, this should be clearly explained, including the algorithms used and documenting evidence of system consistency. Characteristics for the display shall be documented (e.g., accuracy, precision, and error). [Adapted from ISO 14708-5:2020; Clause 6.6.2.4.4.3 Data handling]

Time-dependent waveforms should be collected for each modeled physiologic or simulated use condition. For data consistency, it is recommended that reported time-dependent waveforms begin at the start of systole when ventricular pressure begins to increase. Waveforms should be reported with full sampling resolution (i.e., 1000 data points per second if recording at recommended 1 kHz sampling frequency). A minimum of 10 cardiac cycles should be reported. As discussed in Section 3.2.2, data collection will need to be longer for measurement of many transient compensatory processes. Submitting only ensemble averaging of waveforms obtained from many cycles into a composite averaged waveform is not preferred. Instead, all data should be submitted to assess variability and transient effects beat to beat. Labs can produce composite waveforms with error bands for submission, but the raw, unaveraged data is the primary submission requirement.

4.2.2 Minimum Requirements

Data should be collected with a minimum sampling frequency of 1 kHz and all data should be collected for at least 10 seconds. If a sensor and/or data acquisition module in an existing MCL cannot achieve a sampling frequency of 1 kHz, the lab will report the sampling frequency achieved. Many experimental setups and tests will require a longer collection period than 10 seconds. This likely applies when modeling short term transient effects, such as respiratory rate, that only compensate and resolve over a longer time period.

4.3 List of Collected Data

4.3.1 Baseline Collected Output Parameters

The following parameters, at minimum, should be collected for all experimental conditions tested.

- Cardiac output from left ventricle (L/min)
- Left ventricular pressure (mmHg)
- Left atrial pressure (mmHg)
- Aortic pressure (mmHg)
- Cardiac cycle time (ms)

4.3.2 Other Measured Parameters and Results

If the MCL being used has the capability, the following parameters and results should also be reported, if applicable.

1. Flow loop temperature (°C)
2. LV end diastolic/end systolic ventricular volumes (mL)
3. Systemic vascular resistance (dynes.sec/cm^5)
4. Pulmonary vascular resistance (Wood units)
5. Pulmonary arterial pressure
6. Right atrial pressure
7. Right ventricular pressure
8. Ejection fraction, if a physiologic/geometric LV is present.

9. Aortic flow rate (L/min)
10. VAD flow rate (L/min)
11. VAD inlet/outlet pressures (mmHg)
12. VAD internal air sac pressure, if using pneumatic VAD (mmHg)
13. VAD motor current, voltage, and power (A, V or W)
14. VAD rotational speed (RPM)
15. VAD cycle time and/or pulse rate (ms or pulse/min)
16. VAD steady-flow and dynamic HQ curves
17. Mock ventricle material and geometric properties sufficient to characterize the ventricle. Material properties could include material type, stiffness, and elasticity. Geometric descriptions could include ventricular volume, and ventricular length/diameter throughout cardiac cycle.

5 Proposed Methods

5.1 Transducers

All transducers used for the measurement of system parameters shall be specified in the study protocol or test procedure. Transducers shall be capable of measuring time-dependent waveforms. Multiple cycles will be recorded to produce representative waveforms and any cycle-to-cycle variation can be measured. All transducer characteristics, including amplifier devices (e.g., range, resolution, error, frequency response), shall be given. [Adapted from ISO 14708-5:2020; Clause 6.6.2.4.4.1 Transducers]

5.2 Blood Analog Solution

The relevant properties of fluids used to simulate human blood shall be described. Test fluids can be Newtonian (blood analog). Characteristics of the fluid and its composition shall be given. The recommended blood analog solution should start with a 60%/40% w/w water/glycerol at 22°C, which is then adjusted to 3.5 ± 0.1 cP at the MCL specific temperature, as measured by a calibrated viscometer or rheometer. Also, include a measurement of the density of the solution. Justification for necessary blood-matching trade-offs shall be given (e.g., viscosity, temperature, salinity, and pH). [Adapted from ISO 14708-5:2020; Clause 6.6.2.4.3 Blood analogue fluid]

5.3 Calibration

Calibration schedules and calibration methods used for all transducers are required, as well as evidence that the transducers have been calibrated before use. [Adapted from ISO 14708-5:2020; Clause 6.6.2.4.4.1 Transducers]

5.4 MCL Basic Operation

1. Calibrate all pressure and flow sensors and provide the calibration curves.
2. Make blood analog solutions from 60%/40% w/w water/glycerol at 22°C. Adjust to 3.5 ± 0.1 cP, as measured by a viscometer. Document process and equipment used.
3. Recreate the metrics defined in Table 1 for each experimental condition. This should be done by adjusting the stroke volume, heart rate, fluid volumes, and the compliance and resistance components in the system.
4. Record all relevant metrics pertaining to creation of waveforms. These include HR, stroke volume, VAD speed (if a VAD is present in the circuit) and numeric indications of level of compliance/resistance. (i.e., % opening of pinch valves, volume of air added to or air pressure in compliance chambers, fluid levels of different reservoirs, total volume of fluid in circuit.)
5. Record at least 60 seconds of data for each condition, allowing 60+ cardiac cycles of data to be collected. The sampling rate should be a minimum of 1 kHz. Collect synchronized time-dependent pressure, flow, and other data, as determined by the specific experimental setup. At a minimum, aortic pressure, left ventricular pressure, left atrial pressure, and left ventricular cardiac output (or aortic flow rate) should be recorded.

5.5 VAD Performance Assessment

5.5.1 VAD Connection and Cannulation Scheme

The method by which the VAD is connected to the MCL should be photographed and reported. When devising a cannulation scheme, the method should try to mimic human physiology and device use as closely as possible. For most durable VADs, the ventricle should be cannulated at the apex and flow created by the VAD should return to the ascending aorta. Tubing and connector diameters and lengths should be measured and reported. The recommended sizes for the HMIII outflow graft are: diameter 14 mm and length 22 cm.

5.5.2 Creation of HQ curves

Both steady and dynamic pressure-flow (HQ) curves should also be created in each MCL for the VAD model utilized in the study.

5.5.2.1 Basic Steps to Create Steady Flow HQ Curves

To create steady flow HQ curves:

If your system allows you to set the preload and afterload:

1. Impose a constant differential pressure across the VAD (outlet-inlet pressure), remove any pulsatility in the mock loop, activate the VAD at a fixed speed with artificial pulse (or similar features) off.
2. Starting from a differential pressure of -20 mmHg (inlet pressure > outlet pressure), increase the differential pressure with steps of 20 mmHg, until the VAD flow measured is 0 L/min. From this working point, increase the differential pressure of further 20 mmHg and then 40 mmHg so to measure also the backflow through the VAD. Measure VAD flow at each differential pressure level of the tested range in steady state conditions.
3. From the maximal differential pressure reached, reduce the differential pressure back to -20 mmHg with steps of 20 mmHg. Measure VAD flow at each differential pressure in steady state conditions.
4. Repeat the protocol for different VAD speeds across the entire operating range. For HMIII we recommend to execute the protocol for 4400-5400-6400 rpm.

If you change the circuit resistance to modulate flow:

1. Activate the VAD at a fixed speed with artificial pulse (or similar features) off.
2. Remove any pulsatility in the mock loop. Increase circuit resistance using a Hoffman clamp or similar until there is backflow of -0.2 L/min. Record pressure at the VAD inlet and outlet.
3. Reduce circuit resistance until there is 0.0 L/min flow. Record VAD inlet and outlet pressures.
4. Reduce the circuit resistance to obtain increase in VAD flow in steps of 0.2 L/min. Record VAD inlet and outlet at each step until the pump has achieved its maximum flow and clamp is no longer adding resistance to circuit.

5. From this condition, increase the resistance of the circuit back to baseline value in same steps as point 2-4. Record pressure at the VAD inlet and outlet at each step.
6. Repeat the protocol for different VAD speeds across the entire operating range.

5.5.2.2 Basic Steps to create Dynamic HQ curves

To create dynamic HQ curves:

1. Establish the *VAD Baseline HF* from Table 1, Section 3.1. Activate the VAD at a fixed speed and set any speed pulsatility mode off (e.g. artificial puse, lavare cycle). Measure the VAD flow, LV and aortic pressure waveforms.
2. Increase the systemic peripheral resistance until a backflow in the VAD is observed. Collect data.
3. Repeat steps 1-2 for different VAD speeds across the entire operating range.
4. Establish *VAD providing partial support* condition, Section 5.5.3 and repeat steps 1-3.

5.5.3 Assessing Effect of VAD Support in Heart Failure States:

VADs should be assessed, as a baseline, in the MCL at a constant rotational speed resulting in both full and partial support. The circuit should also be run with the VAD connected but not running. Data collection refers to pressures, flow rates and other data recording as described in Sections 4.2, 4.3 and 5.4

- VAD connected but not running.
    1. Establish the *VAD Baseline HF* from Table 1, Section 3.1. With VAD connected and clamped, collect data according to Section 4.3.
    2. Leave VAD connected and not running, unclamp tubing. Collect data.

- To assess a VAD providing full support:
    1. Establish *VAD Baseline HF* from Table 1, Section 3.1. Collect data according to Section 4.3.
    2. Turn on the VAD and increase the VAD speed until the total cardiac output is 5.0 L/min Set any VAD speed pulsatility mode off (e.g. artificial puse, lavare cycle).. Collect data.
    3. Increase the VAD speed, if necessary, until the AV is not opening. Collect data.
    4. Optional step for simulators with control mechanisms: activate the control mechanisms (e.g. baroreflex, metabolic controls) and collect data.
- To assess a VAD providing partial VAD support:
    1. Establish *VAD Baseline HF* from Table 1, Section 3.1. Collect data according to Section 4.3.
    2. Turn on the VAD and increase the VAD speed until average VAD flow is 2.5 L/min. Set any VAD speed pulsatility mode off (e.g. artificial puse, lavare cycle). The AV should be opening during systole. Total cardiac output should be adjusted to 5.0 L/min by tuning the left ventricular contractility or equivalent parameter in the MCL. Collect data.
    3. If needed, decrease VAD speed until the AV is opening.
- Optional step for simulators with control mechanisms: activate the control mechanisms (e.g. baroreflex, metabolic controls) and collect data. To assess a VAD providing support during exercise:
    1. Establish *VAD Patient, Exercise* from Table 1, Section 3.1.

2. Set the VAD speed to the same level as in the *VAD providing full support* test.
3. Collect data according to Section 4.3.
4. Optional step for simulators with control mechanisms: establish the *VAD Baseline HF* from Table 1, Section 3.1. Then activate the control mechanisms (e.g. baroreflex, metabolic controls) and input exercise condition equivalent to 80 Watts. Collect data.

5.5.4 Suction protocol

To assess the conditions under which a VAD will likely produce a suction event:

1. Place an additional pressure sensor at the tip of the VAD inflow. Describe the element used to reproduce suction (e.g., collapsible tube, pinch valve).
2. Establish *VAD providing full support* condition, Section 5.5.3 with the same VAD speed level. Collect the VAD flow, VAD speed and current (if available), pressure in the left ventricular chamber, in the aortic chamber and at the tip of the VAD inflow cannula.
3. Reduce the preload of the left ventricle in steps of -50 mL until intermittent suction is observed. This can be done by reducing total blood volume in the MCL or an equivalent parameter. Collect data.
4. Reduce the preload of the left ventricle further in steps of -50 mL until suction is observed every heartbeat. Collect data.
5. Increase the total blood volume back to baseline.
6. Repeat steps 3 and 4 and collect data again.
7. Establish *VAD providing partial* support condition, Section 5.5.3 with same VAD speed level. Repeat the protocol.
8. For this test it is optional to activate the ventilation model.

5.5.5 Pulse pressure protocol (for VADs with speed changes, i.e., artificial pulse)

To assess the pulse pressure created while a VAD is in use, particularly due to pump speed changes.

1. Establish *VAD providing full support* condition, Section 5.5.3 with the VAD off and clamped. From this condition, set the aortic compliance to 1.0 mL/mmHg and the systemic arterial resistance to 1.0 mmHg/ml/s. Record data.
2. Reduce the contractility of the LV to 0 mmHg/ml (so no contraction occurs). Unclamp and activate the VAD at the same speed level used for the VAD providing full support condition, Section 5.5.3. Activate the VAD pulse modality and record data/
3. Increase the contractility of the LV back to baseline value.
4. Activate the VAD pulse pressure modality and record data. If the change of VAD speed is synchronized with the heartbeat then extend the recording for 60 seconds. If the change of VAD speed is not synchronized with the heartbeat then prolong the recording considering the heart beat and the frequency of the pump speed change:
   a) HR → period length A
   b) VAD speed change frequency → period length B
   c) Total duration of the recording = 5 * lowest common multiple (A,B)

d) In case the duration of the recording is too long, HR can be changed to better match the frequency of the VAD speed change.

5. For this test it is recommended to switch off the ventilation and the baroreflex models and keep heart rate and heart contractility constant.
6. Suggestion: Check whether the resistance and compliance settings are correct. We recommend groups analyze the diastolic aortic pressure decay from the test with the VAD off at point 1). This verification is optional and results should not be submitted.

5.6 Repeatability Assessment

Repeatability of results should be demonstrated. It is recommended data should be collected for healthy adult baseline physiologic conditions three times, with a system reset between each trial. All sets of data should be submitted for assessment of repeatability.

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