Mock Circulatory Loop (MCL) Simulations of the Target Test Conditions

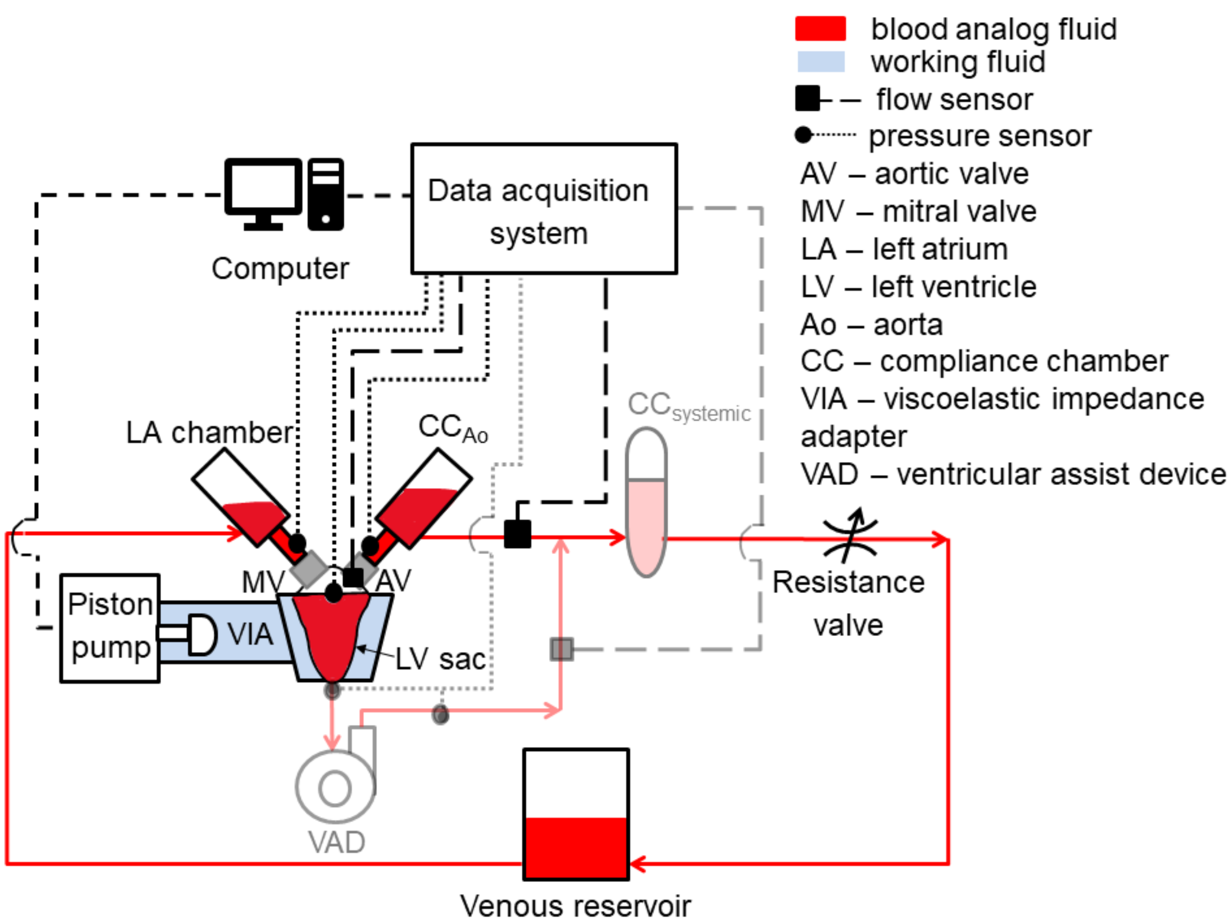
MCL Setup

Note: The test fluid used in the MCL is blood analog fluid (BAF). Please prepare the BAF by following detailed instructions outlined in the document, 'Preparation of Blood Analog Fluid (BAF)'. For preliminary or feasibility testing, De-ionized (DI) water may be used in place of BAF as the test fluid. While all test protocols in this document are written for BAF, they are also directly applicable to DI water, when used as the test fluid.

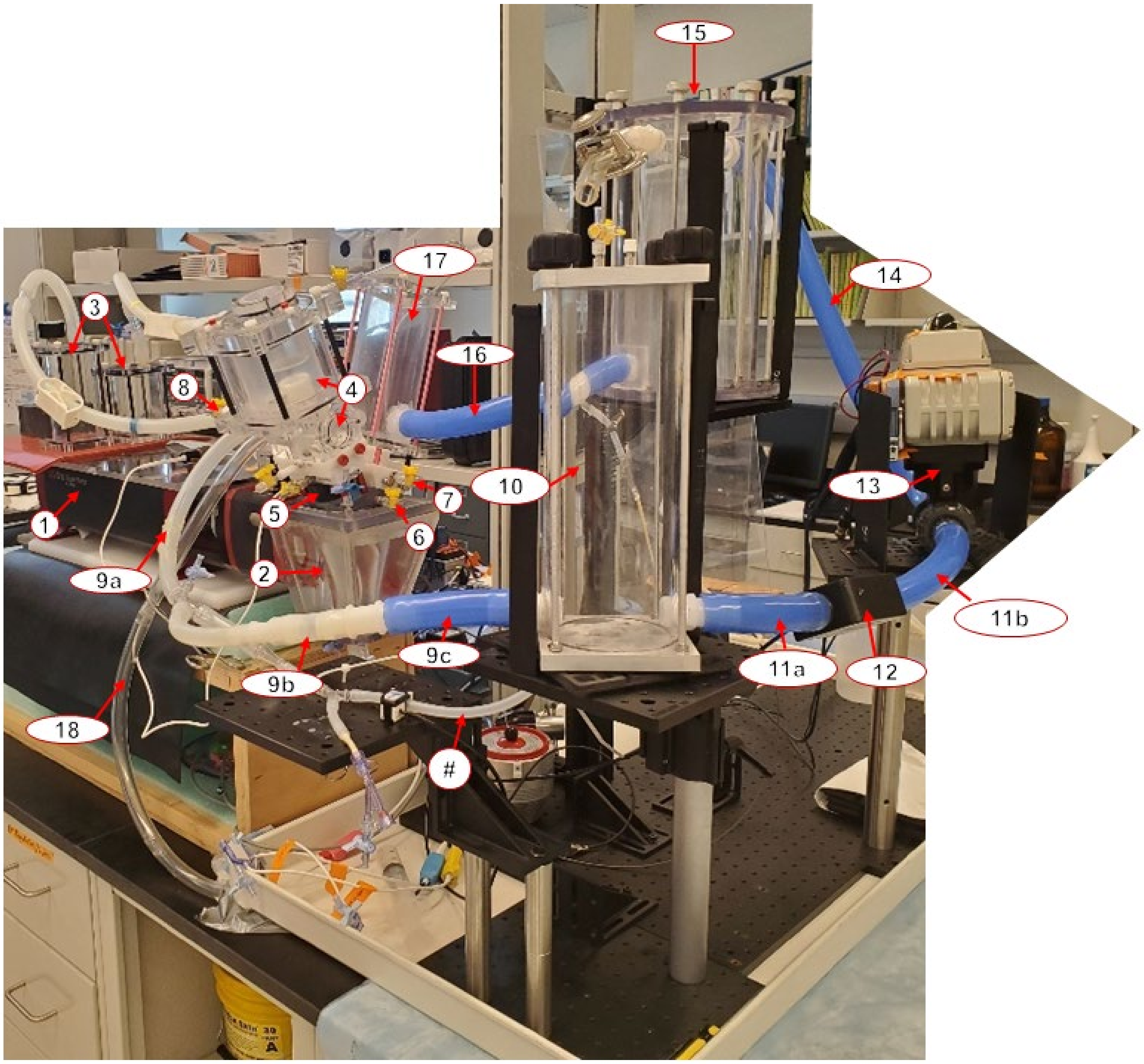
Note: Please ensure that all transducers/sensors/probes have been appropriately calibrated and their filter frequency response characterized by following detailed instructions outlined in the following documents: 'Pressure Transducer Calibration', 'Flow Sensor Calibration', and 'Filter Frequency Response Characterization'.

1. Connect the components of the MCL per the schematic and diagram shown below.

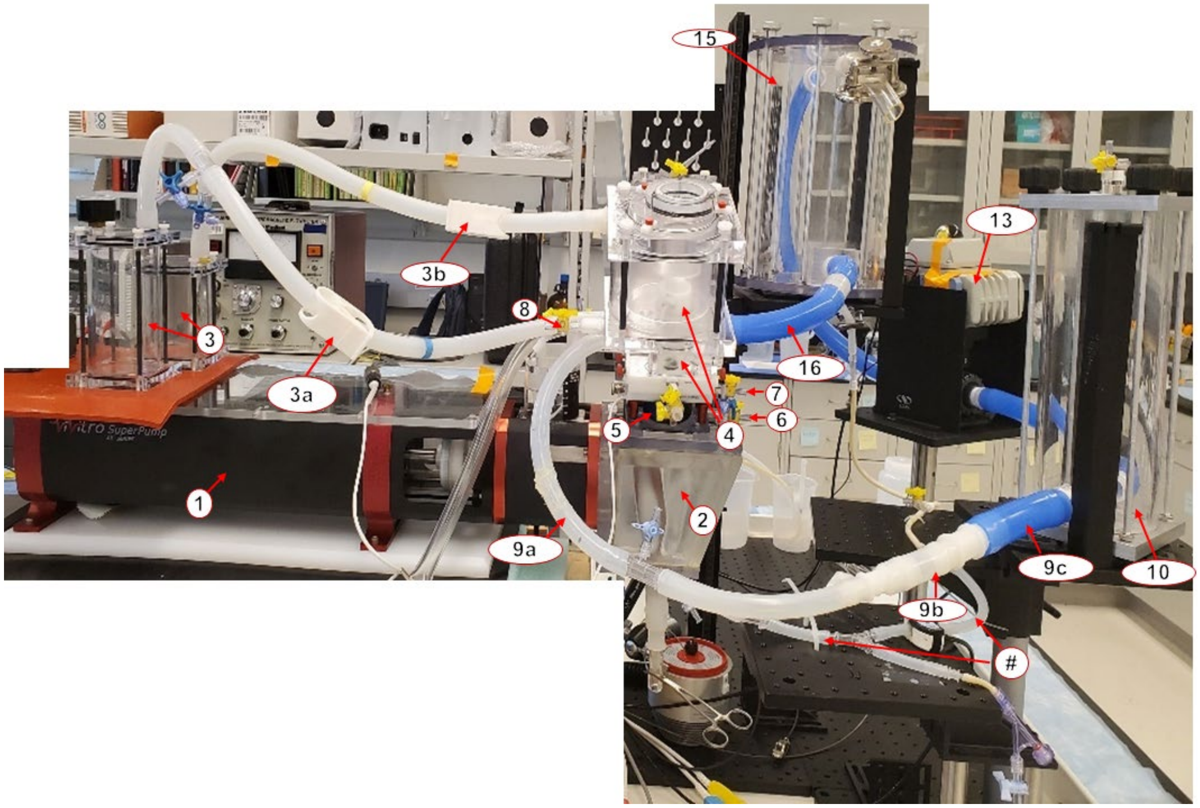
MCL Schematic and Diagram



MCL schematic



MCL diagram: Isometric view



MCL diagram: Side view

List of MCL Components:

Component No. *(please reference diagrams above)*	**Component Name & Description**
1	Piston pump [*SuperPump (AR Series), ViVitro Labs, Inc., Victoria, BC, Canada*] + Viscoelastic impedance adapter [*VIA, ViVitro Labs, Inc., Victoria, BC, Canada*]
2	Left ventricle (LV) chamber [*custom-built, acrylic*] + LV sac [*custom-built, 1 mm thick, SYLGARD 184 Silicone-50A, Dow Corning Corporation, Midland, MI*]
3	Aortic (Ao) root + Ascending Ao compliance chambers (CC) [*ViVitro Pulse Duplicator System, ViVitro Labs, Inc., Victoria, BC, Canada*]
3a	Ao root CC clamp [*ViVitro Pulse Duplicator System, ViVitro Labs, Inc., Victoria, BC, Canada*]

3b	Ascending Ao CC clamp [*ViVitro Pulse Duplicator System, ViVitro Labs, Inc., Victoria, BC, Canada*]
4	Ao root (bottom chamber) and Ascending Ao (top chamber) [*ViVitro Pulse Duplicator System, ViVitro Labs, Inc., Victoria, BC, Canada*]
5	Cardiac output (CO) flow probe [*EP688 (size 88 mm cir), Carolina Medical Electronics, East Bend, NC*] *Note: Since the EP688 flow probe (Carolina Medical Electronics) requires a conductive fluid, sodium chloride (NaCl) would need to be mixed with DI water, when used as the test fluid.*
6	LV pressure port + transducer [*Deltran 6069, Utah Medical Products, Inc., Midvale, Utah*] **Transducer not shown in diagram above*
7	Left atrium (LA) pressure port + transducer [*Deltran 6069, Utah Medical Products, Inc., Midvale, Utah*] **Transducer not shown in diagram above*
8	Ao pressure port + transducer [*Deltran 6069, Utah Medical Products, Inc., Midvale, Utah*] **Transducer not shown in diagram above*
9a	1/2” ID, 3/4” OD, 38 cm long tubing [*Silicone-50A, McMaster Carr, Elmhurst, IL*]
9b	3/4” ID, 1” OD, 7.5 cm long tubing [*Silicone-50A, McMaster Carr, Elmhurst, IL*]
9c	1” ID, 1 ¼” OD, 13 cm long tubing [*Silicone-50A, McMaster Carr, Elmhurst, IL*]
10	Systemic vascular CC [*custom-built, 4” ID, 28 cm height*]
11a	1” ID, 1 ¼” OD, 13 cm long tubing [*Silicone-50A, McMaster Carr, Elmhurst, IL*]
11b	1” ID, 1 ¼” OD, 15 cm long tubing [*Silicone-50A, McMaster Carr, Elmhurst, IL*]
12	Ao (or systemic) flow sensor [*ME-25PXN, Transonic Systems, Inc., Ithaca, NY*]
13	Systemic vascular resistance valve [Electric actuator ball valve, *Model 561857A, Valworx, Cornelius, NC*]
14	1” ID, 1 ¼” OD, 80 cm long tubing [*Silicone-50A, McMaster Carr, Elmhurst, IL*]
15	Venous return reservoir [*custom-built, 8” ID, 28 cm height*]
16	1” ID, 1 ¼” OD, 25 cm long tubing [*Silicone-50A, McMaster Carr, Elmhurst, IL*]

17	LA chamber [*ViVitro Pulse Duplicator System, ViVitro Labs, Inc., Victoria, BC, Canada*]
18	1/2" ID, 3/4" OD, 100 cm long LA chamber drain tubing [*Tygon, Qosina, Ronkonkoma, NY*]
# (optional)	Peripheral vascular circuit (*clamped off and not included within the scope of this RST*)

Note: For ViVitro components, please refer to the ViVitro Pulse Duplicator System user manual for detailed instructions related to setting up the pulse duplicator system.

Note: Uni-directional bi-leaflet mechanical valves [Regent™ Mechanical Heart Valve, Abbott Laboratories, Chicago, IL] are present in the aortic and mitral positions (not identified in the MCL diagram since they are hidden).

List of Tubing Connectors:

Tubing Component No. *(please reference MCL diagram and components list above)*	**Connector Type**
9a to 9b	1/2" x 3/4" straight reducer [*Nylon plastic, McMaster Carr, Elmhurst, IL*]
9b to 9c	3/4" x 1" straight reducer [*Nylon plastic, McMaster Carr, Elmhurst, IL*]

2. Make the appropriate electrical connections:

   ViVitro Pump and Pulse Duplicator System
   Note: Please refer to the ViVitro Pulse Duplicator System user manual for detailed instructions related to the system's electrical wiring diagram and electrical connections.

   a. Connect the piston pump to the Motor channel on the pump amplifier [ViVitro Labs, Inc., Victoria, BC, Canada].
   b. Connect the LV, LA, and Ao pressure transducers to the three input channels on the pressure amplifier module [Bus 21097, ViVitro Labs, Inc., Victoria, BC, Canada].

   Flow Probe/Sensor

   a. Connect the flow sensor(s) to the corresponding flowmeter module(s), as indicated in the table below.

Flowmeter	Flow probe/sensor
T402 (dual channel), Transonic Systems, Inc., Ithaca, NY	ME-25PXN
FM501, Carolina Medical Electronics, East Bend, NC	EP688 (size 88 mm cir)

Instrument Control and Data Acquisition

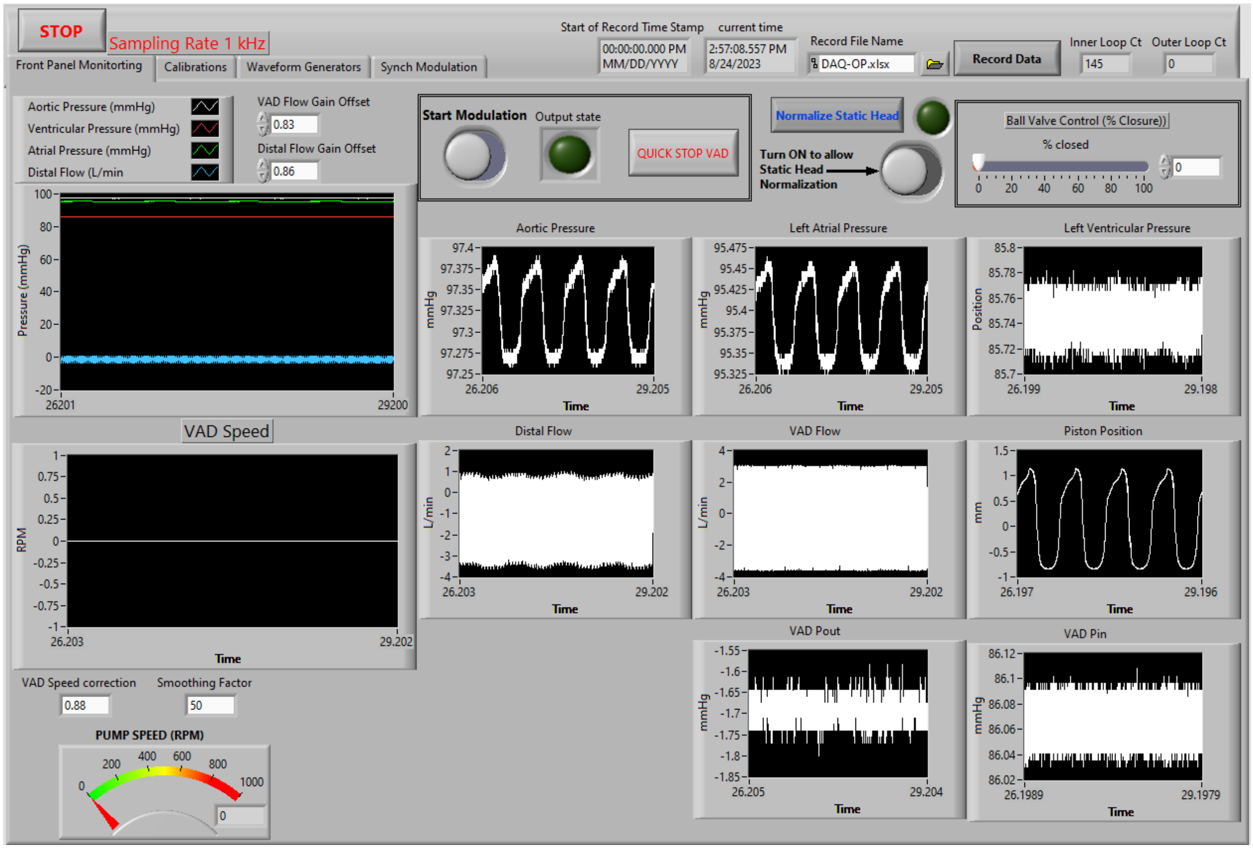
a. Connect the appropriate input/output channels on the instruments (i.e., pump amplifier, pressure transducer amplifier, flowmeter, electric actuator ball valve) to the appropriate channels on the analog input/output (AI/AO) modules of the data acquisition system [cDAQ-9174, National Instruments, Austin, TX] per the table below.

Instrument Channel	AI/AO Channel on cDAQ-9174
Pump amplifier – Waveform In	AO 1, NI-9264
Pump amplifier – Position	AI 0, NI-9205
Pressure transducer amplifier – Ao pressure channel	AI 1, NI-9205
Pressure transducer amplifier – LV pressure channel	AI 2, NI-9205
Pressure transducer amplifier – LA pressure channel	AI 3, NI-9205
T402 output channel	AI 4, NI-9205
FM501 output channel	AI 5, NI-9205
Electric actuator ball valve input channel	AO 0, NI-924

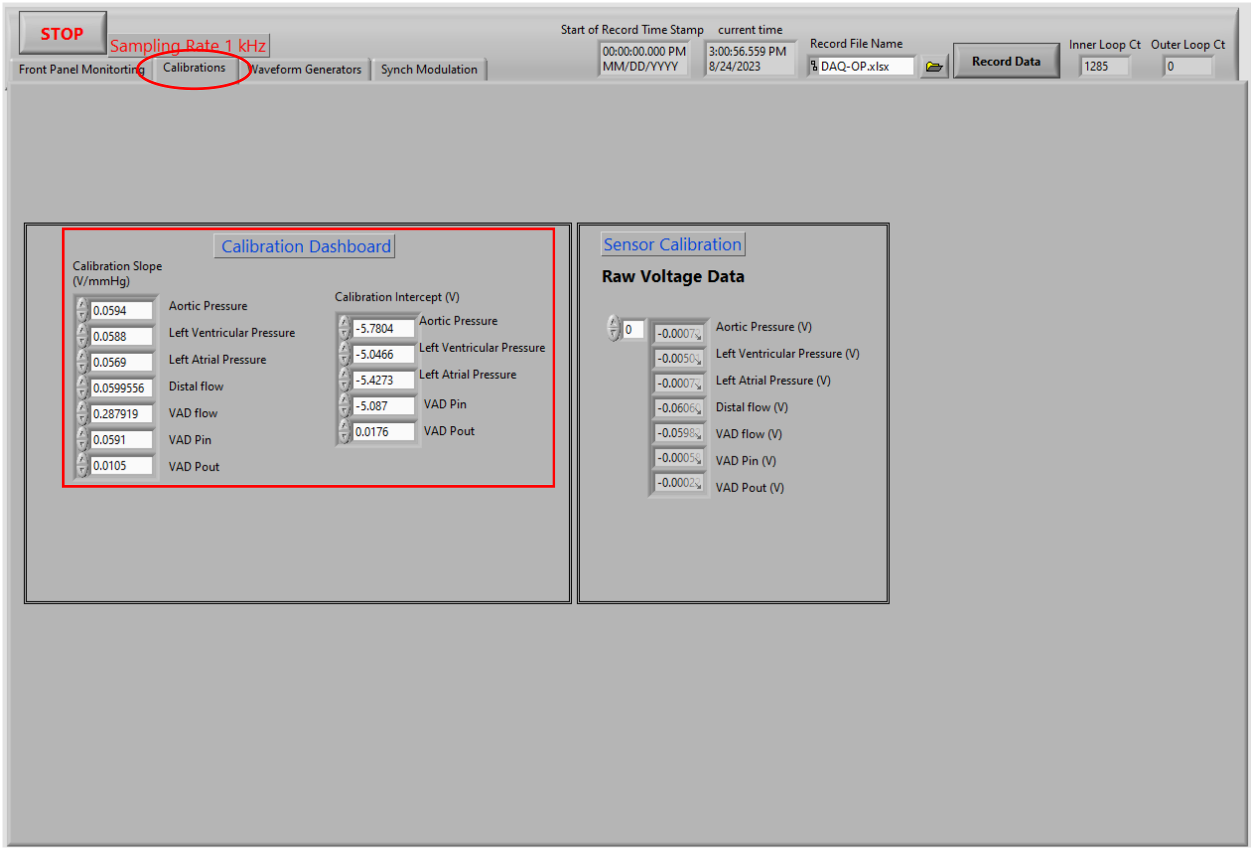
b. Connect the USB data cable from cDAQ-9174 to the MCL laptop.

MCL Initialization

3. Fill ultra-purified DI water (~ 1.5 L) in the LV chamber surrounding the LV sac, and in the VIA following the instructions in the ViVitro Pulse Duplicator System user manual. Ensure that the LV sac is in the neutral position. Set the Source Compliance and Output Compliance volumes in the VIA to 60 mL and 20 mL, respectively.
4. Power ON all equipment.
5. Set the Waveform Source on the pump amplifier to External.
6. Open and Run the LabVIEW VI (or Virtual Instrument) that executes the custom MCL software (snapshot graphical user interface (GUI) shown below).

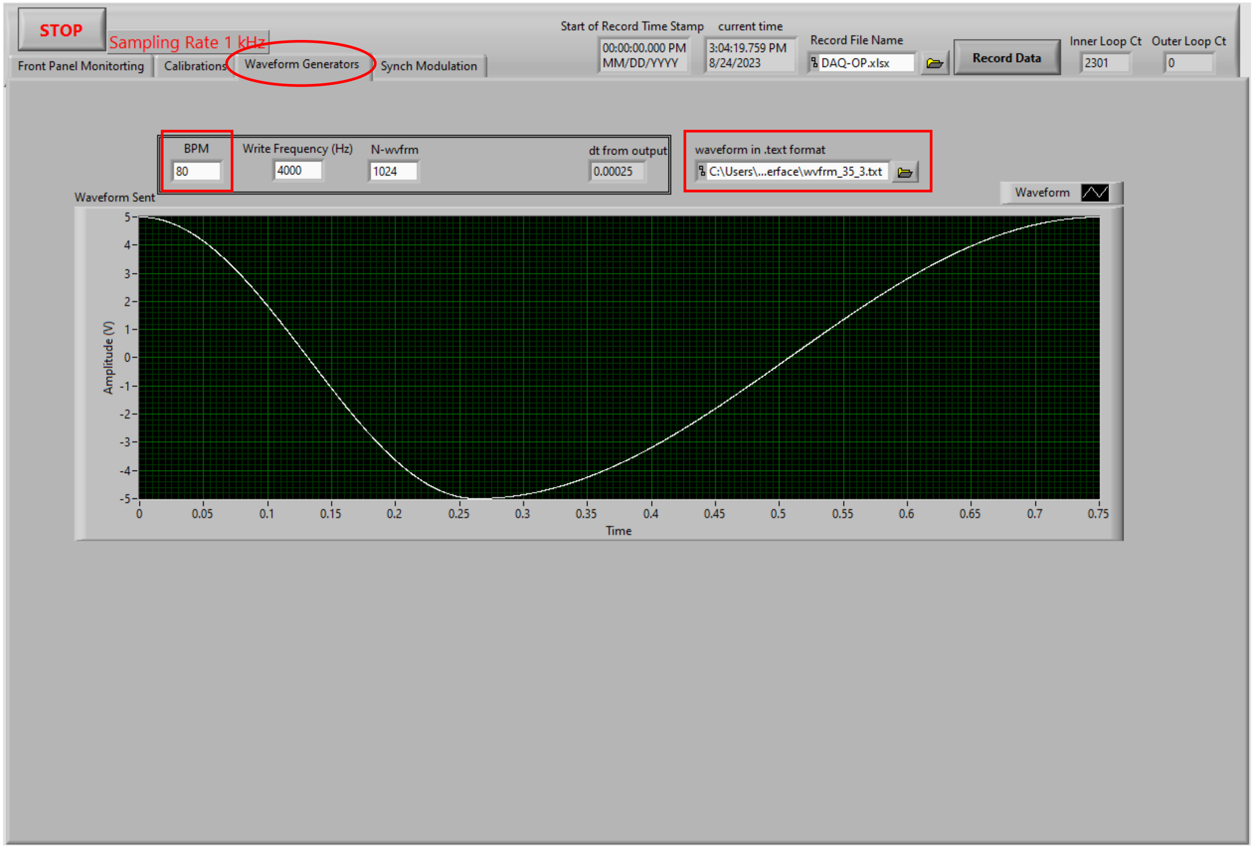


a. Select the Calibrations tab and apply the sensor/transducer Calibration Slope and Calibration Intercept such that the MCL software displays the pressure in mmHg and flow rate in L/min. Please refer to the documents, 'Pressure Transducer Calibration' and 'Flow Sensor Calibration'.
<u>Note</u>: The MCL software has been developed with the goal of evaluating ventricular assist devices (VADs) within the MCL, which is the reason for the nomenclatures, 'Distal flow' and 'VAD flow'. The MCL is designed to incorporate a maximum of 2 flow sensors at any given time of testing. Thus, in the absence of a VAD connected to the MCL, the 'VAD flow' AI channel is used to record cardiac output (CO) using the EP688 flow probe. 'Distal flow' represents the aortic (Ao) or systemic flow recorded by the ME-25PXN flow sensor.
<u>Note</u>: Please ensure that the VAD Flow Gain Offset and Distal Flow Gain Offset (in the Front Panel Monitoring tab) are set to 0.00.

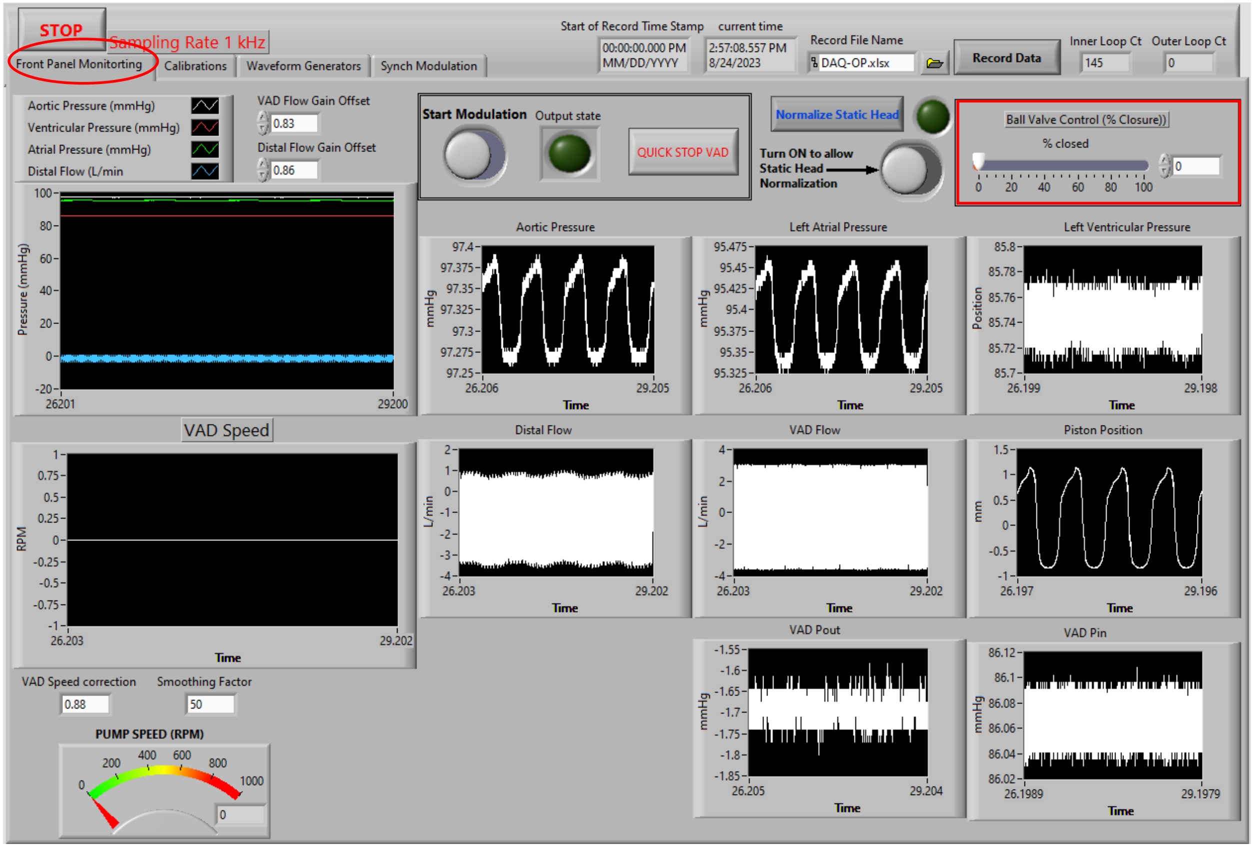


b. Select the Waveform Generators tab and enter the target heart rate (i.e., pump beat rate) in the BPM (beats per minute) box. Ensure that the ‘wvfrm_35_3.txt’ file is selected as the ‘waveform in .text format’. This corresponds to a 35% systole cycle, which is used as the default cycle for all test conditions.

Note: Set the heart rate corresponding to the first condition being tested. Definitions of Recommended Test Conditions can be found in D’Souza et al., JBME, 2023.



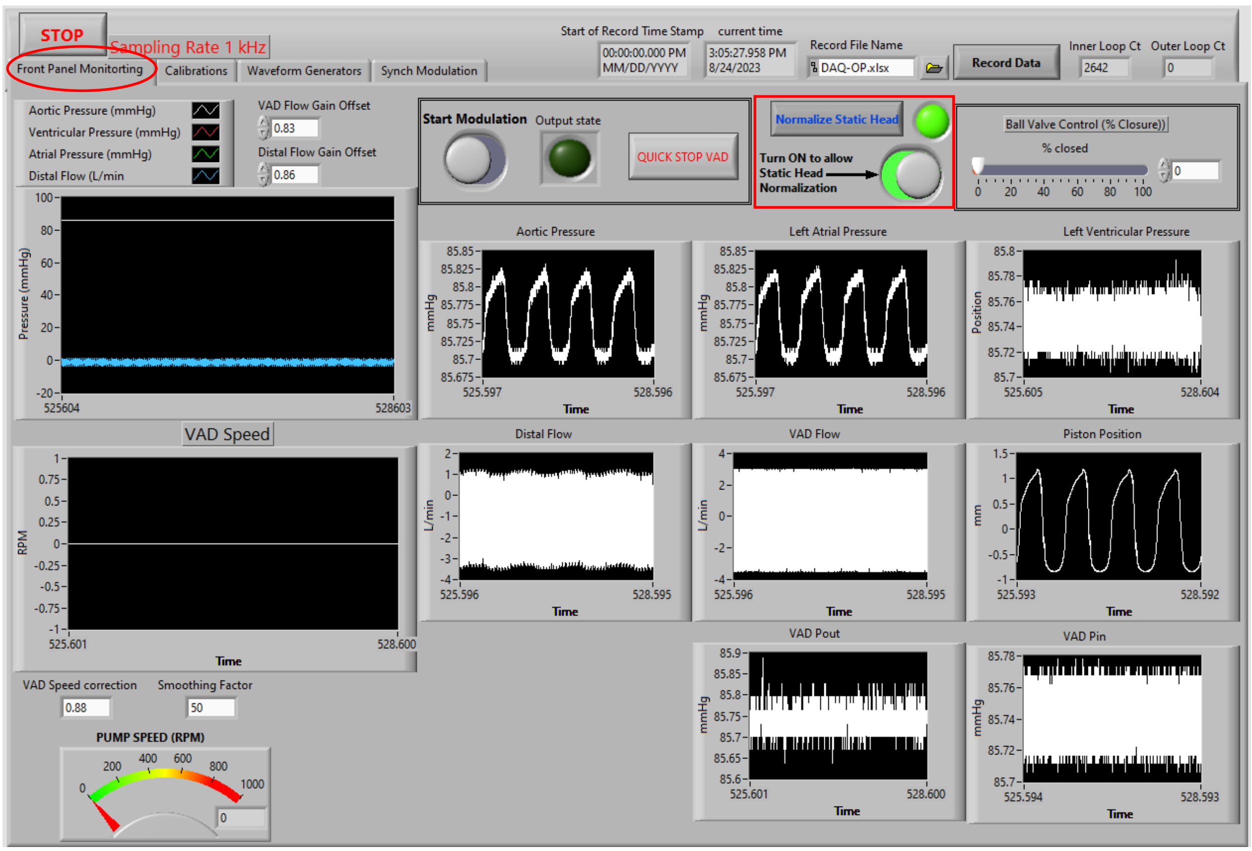
c. Select the Front Panel Monitoring tab and set the Ball Valve Control (% Closure) to 90% closed. This is to ensure that the systemic vascular CC first fills completely with BAF.



7. Ensure the ascending Ao and Ao root CC clamps are in the fully clamped/closed position.
8. Ensure the 3-way stopcock at top of the systemic vascular CC is open to air.
9. Ensure the LA chamber drain tubing is fully clamped using forceps.
10. Identify the catheter line connected to a 3-way stopcock at the top of the Ao root/ascending Ao chamber. Place the open end of the catheter line into the LA chamber. Open the stopcock to vent air from the inside of the ascending Ao. Please refer to the Air Bubble Removal section in the ViVitro Pulse Duplicator System User Manual.
11. Slowly start to pour BAF into the LA chamber until the LV sac is completely filled and fluid starts to enter the ascending Ao and loop tubing. Keep adding BAF to the LA chamber such that the chamber is always fluid-filled.
12. Slowly start to increase the pump gain using the Amplitude knob on the pump amplifier to start circulating BAF in the loop.
13. BAF will start to fill in the systemic vascular CC. Once the systemic vascular CC is completely filled with BAF, close the 3-way stopcock at top of the systemic vascular CC to atmosphere.
14. Immediately set the Ball Valve Control (% Closure) to 0% closed to allow BAF to recirculate back to the LA chamber.
15. During steps 11 – 13, BAF will start to fill the ascending Ao chamber (inner volume of the annular region). Allow the ascending Ao chamber to completely fill with BAF. Close the catheter line stopcock when all air in the ascending Ao chamber has been displaced by BAF.

16. During this time, ensure that the loop is completely free of air bubbles. Bleed the pressure transducers (using a syringe) till no air exists in the connectors and around the pressure transducer sensor. The MCL is now completely filled.
17. Turn down the Amplitude knob on the pump amplifier till the pump stops (0% gain).
18. Set the desired settings (e.g., low pass filter, pulsatile frequency response, probe factor, gain) on the pressure amplifier and flowmeter modules per the instrument's User Manual and the sensor calibration outputs.
19. Wait ~ 5-10 minutes till the pressure values stabilize. In the MCL software, select the Front Panel Monitoring tab and Toggle On the 'Turn ON to allow Static Head Normalization' button. Then select Normalize Static Head. Both static head selections will be illuminated with a green light.

    Please refer to the ViVitro Pulse Duplicator System User Manual for information related to static head correction of the pressure transducers.



The MCL is now initialized and ready for testing.

MCL Testing

<u>Note</u>: Please refer to Recommended Test Conditions in D'Souza et al., JBME, 2023 for detailed information and exact definitions of target test conditions which can be reproducibly simulated in the MCL.

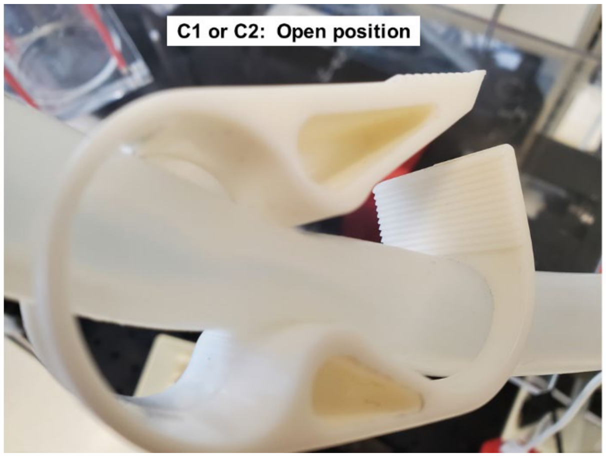
20. The following MCL Control Table provides set controls for the MCL inputs in order to reproducibly simulate the recommended test conditions.

MCL Control Table

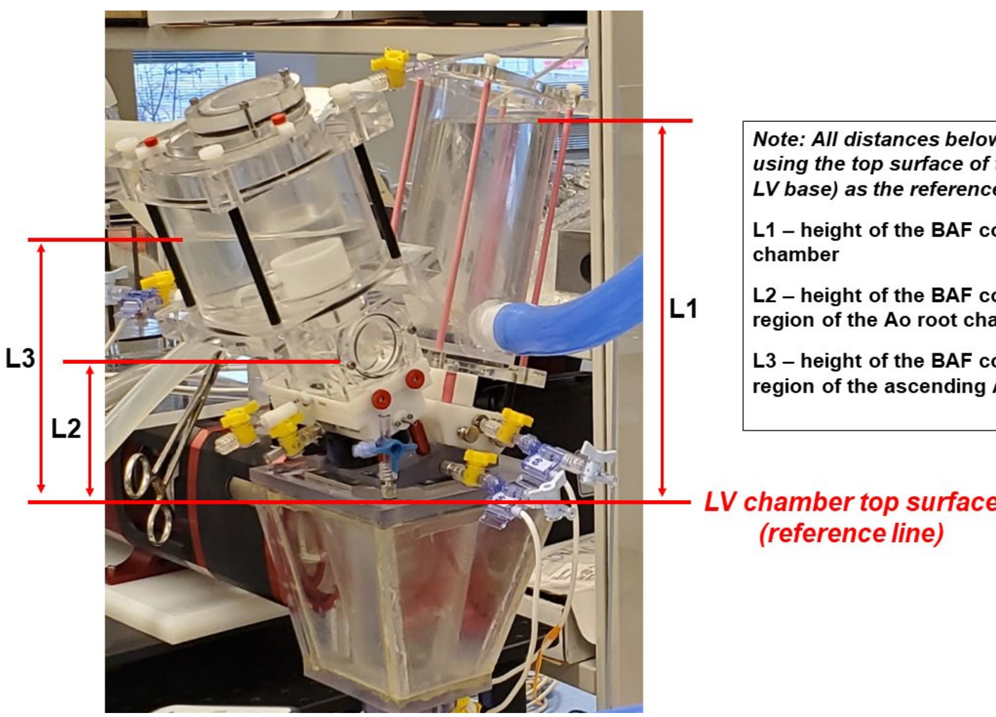
Test condition	Piston pump settings: Beat rate [BPM]	Piston pump settings: Gain [%]	LA chamber BAF level L1 [cm]	Ao root CC BAF level L2 [cm]	Ascending Ao CC BAF level L3 [cm]	Systemic vascular CC BAF level L4 [cm]	Ao root CC clamp position C1	Ascending Ao CC clamp position C2	Ball Valve Control [% Closure]
Cardiogenic shock	110	27.8	21	10	17	full	2	1	61
LV hypertrophy secondary to hypertension	72	58.3	22	9	16.5	full	1	1	63
Coronary artery disease	70	55.8	11.5	9	16.5	22	open	open	55
Healthy adult at rest	70	57.2	11.5	8	16.5	22	1	open	59
Healthy adult during exercise	120	85	13	8	16.5	23.5	2	1	45

Repeat the following steps 21-30 for each of the five recommended test conditions.

21. In the MCL software
    a. Select the Waveform Generators tab and enter the target heart rate (i.e., pump beat rate) in the BPM (beats per minute) box based on the MCL Control Table.
    b. Select the Front Panel Monitoring tab and set the Ball Valve Control (% Closure) based on the MCL Control Table.
22. Set C1 and C2 to the Open (or unclamped) position.



23. Using a syringe, adjust the air volumes in the Ao root CC and ascending Ao CC (via the 3-way stopcock on the CC tubing) till target levels L2 and L3 (specified in the MCL Control Table) are achieved.



Note: All distances below are measured using the top surface of the LV chamber (i.e., LV base) as the reference line (0 cm).

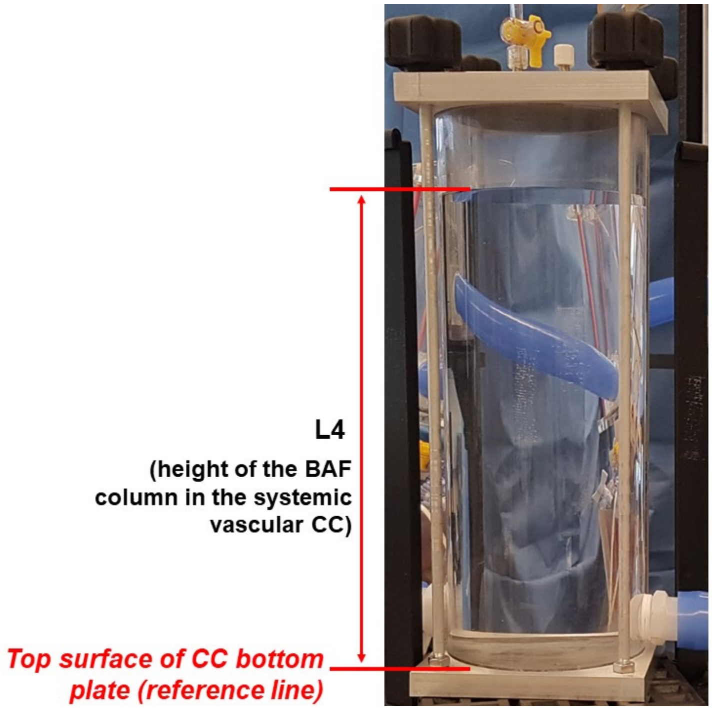
L1 – height of the BAF column in the LA chamber

L2 – height of the BAF column in the annular region of the Ao root chamber

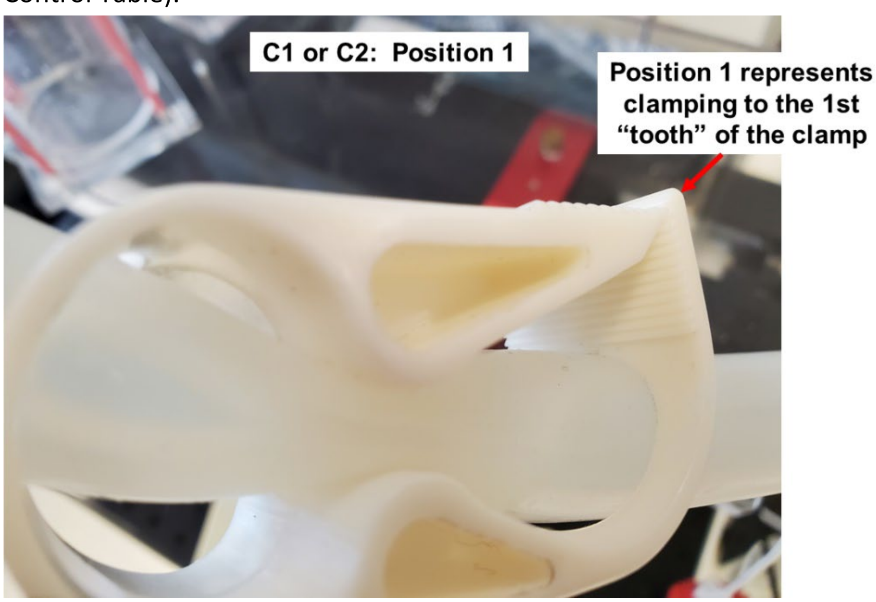
L3 – height of the BAF column in the annular region of the ascending Ao chamber

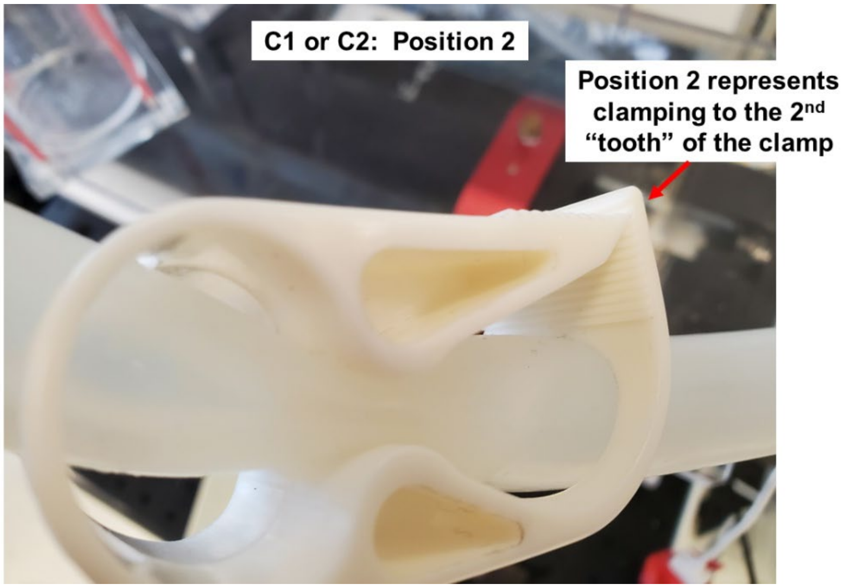
24. Set C1 and C2 to the fully clamped/closed position. This is done to avoid sudden changes in target levels L2 and L3 due to pressure changes in the system as the piston pump gain is increased.
25. Fill BAF in the LA chamber until target level L1 (specified in the MCL Control Table) is achieved.

26. Using a syringe, adjust the air volume in the systemic vascular CC (via the 3-way stopcock at the top of the CC) until target level L4 (specified in the MCL Control Table) is achieved.



27. Slowly start to increase the pump gain using the Amplitude knob on the pump amplifier until the target gain (specified in the MCL Control Table) is achieved.
    a. While increasing the pump gain, ensure that the LA chamber is always fluid-filled by adding more BAF, if necessary. Once the target pump gain is achieved, add or remove an appropriate volume of BAF to/from the LA chamber to achieve target level L1.
    b. After reaching 50% of the target gain, set C1 and C2 to the target positions (specified in the MCL Control Table).





After setting C1 and C2, levels L2 and L3 may vary from the target values due to pressure changes in the circulating BAF. If necessary, use a syringe to adjust the air volumes in the Ao root CC and ascending Ao CC (via the 3-way stopcock on the CC tubing) until target levels L2 and L3 are achieved. Further adjustment of air volume in the CCs may be necessary once the target pump gain is achieved to maintain target levels L2 and L3.

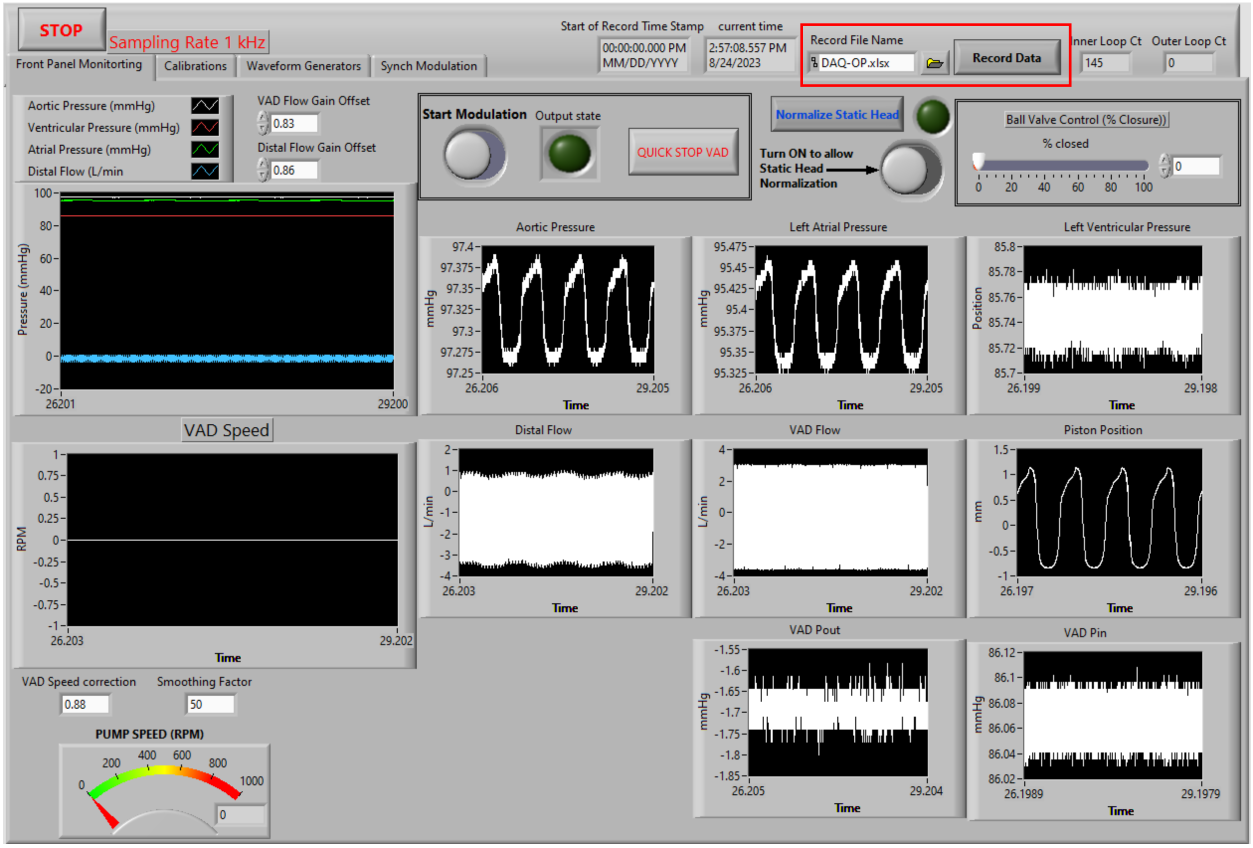
<u>Note</u>: Due to pulsatile flow and compressible air in the CC, levels L2 and L3 will vary between an upper and lower level (within ~ ± 0.5 cm of target levels L2 and L3).

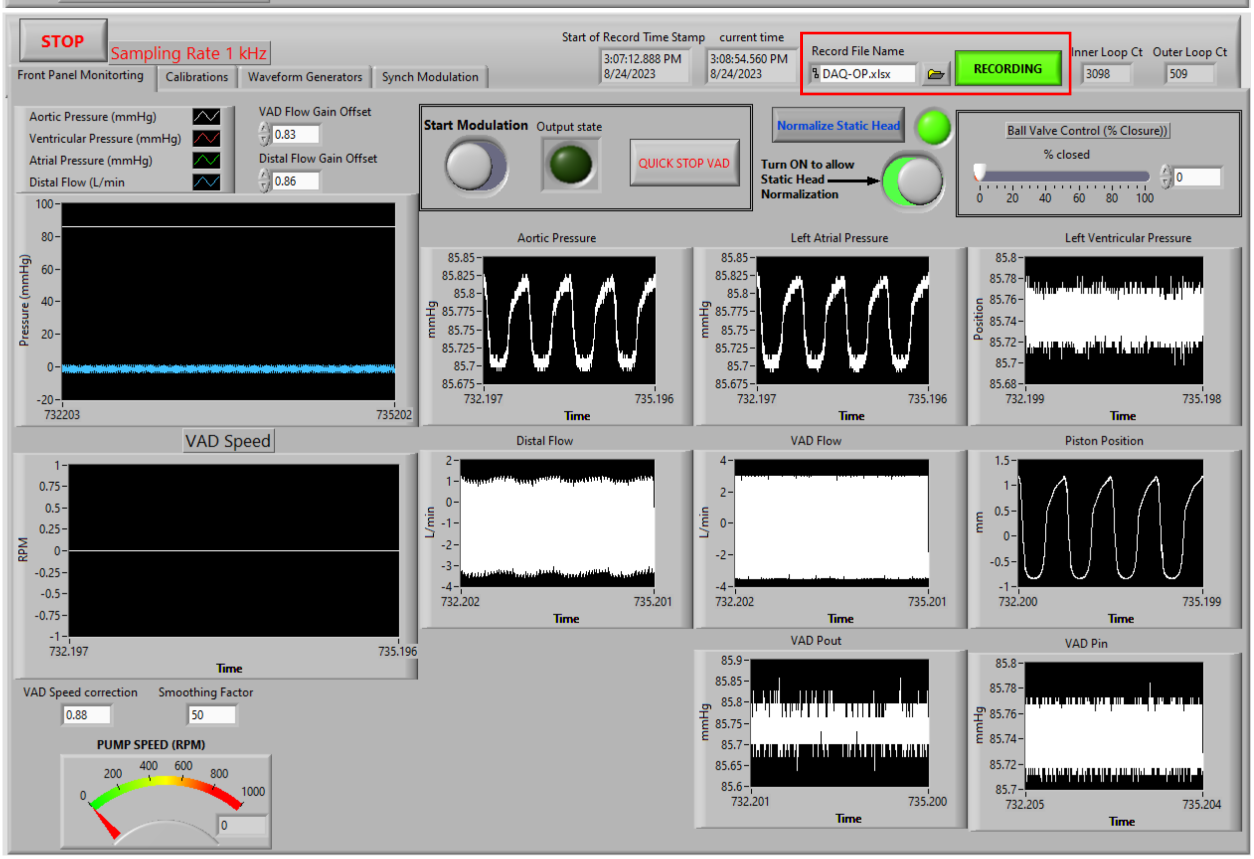
<u>Note</u>: Upon setting C1 and C2, in the event where the BAF pressure is lower than the air pressure in the CC, air may enter through the Ao root chamber get entrapped in the ascending Ao chamber. In this scenario, execute steps 10 and 15.

c. Once the target pump gain is achieved, ensure target level L4 is maintained by executing step 26.

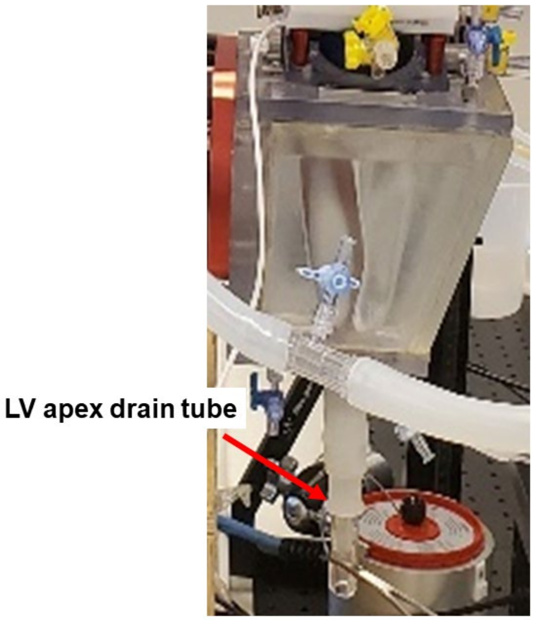
   <u>Note</u>: Due to pulsatile flow and compressible air in the CC, level L4 will vary between an upper and lower level (within ~ ± 0.5 cm of target level L4).

28. Confirm that the target hemodynamic (pressure, flow rate or CO) waveforms are achieved by visualizing the continuous instantaneous data monitoring on the MCL software (Front Panel Monitoring tab).
29. Wait for 1-2 minutes to ensure stabilization of the simulated test condition. Record 60 seconds of data by selecting Record Data in the MCL software (Note: A green illuminated Recording tab will appear when the software is recording data). Select an appropriate file name and path under Record file Name to save the Excel (.xlsx) data file. At the end of 60 seconds, select the green illuminated Recording tab to stop recording. Note: An Excel (.xlsx) file with time series pressure and flow rate/CO data will be saved in the location defined by the file path.
    Please refer to the snapshots below.


STOP
Sampling Rate 1 kHz
Front Panel Monitoring
Calibrations
Waveform Generators
Synch Modulation
Start of Record Time Stamp
current time
Record File Name
DAQ-OP.xlsx
Record Data
Inner Loop Ct
Outer Loop Ct
Start Modulation
Output state
QUICK STOP VAD
Normalize Static Head
Turn ON to allow Static Head Normalization
Ball Valve Control (% Closure)
% closed
Aortic Pressure
Left Atrial Pressure
Left Ventricular Pressure
VAD Speed
Distal Flow
VAD Flow
Piston Position
VAD Pout
VAD Pin
VAD Speed correction
Smoothing Factor
PUMP SPEED (RPM)


STOP
Sampling Rate 1 kHz
Record File Name
DAQ-OP.xlsx
RECORDING
Normalize Static Head
Turn ON to allow Static Head Normalization
PUMP SPEED (RPM)

30. To begin the MCL shutdown process, first set the ascending Ao and Ao root CC clamps to the fully clamped/closed position. Slowly turn down the Amplitude knob on the pump amplifier till the pump stops (0% gain). Caution: While decreasing the pump gain, the BAF level in the LA chamber will start to rise. To avoid overflow of BAF, unclamp the forceps on the LA chamber drain tubing to gradually drain BAF from the LA chamber while decreasing the pump gain to 0%.
31. Drain the residual BAF in the loop by disconnecting tubing and by unclamping the drain tube located at the LV apex (i.e., bottom of the LV chamber and sac, per image below).



32. Stop the LabVIEW VI that executes the custom MCL software.
33. Power OFF all equipment.