A Flow Measurement Guide
for Industry Bioengineers

MOCK CIRCULATORY LOOPS

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MOCK CIRCULATORY LOOPS

In Vitro Bench Simulation

As biomedical devices become ever more sophisticated, comprehensive testing and evaluation of a new cardiovascular device's function and performance is both necessary and mandatory before a device can be marketed and used clinically.

The preliminary step in biomedical device development is testing with an *in-vitro* mock circulatory loop (MCL). MCLs are mechanical representations of the human cardiovascular system and therefore, serve as a platform for testing the proof of concept of a device. Proof of principle is then demonstrated via *in-vivo* animal testing before proceeding with the clinical testing of the device itself.

Mock circulatory systems are comprised of tubing flow channels, compliance chambers, a pump or method to circulate reservoir liquid in a manner that mimics the arterial and/or venous circulatory system for the purpose of understanding the underlying mechanisms of blood flow, pressure and impedance. If well developed, circulatory models can be created for any arterial configuration to study cause and effect of blood flow and pressure/resistance changes in a physical system that can be monitored with flow and pressure sensors to characterize normal hemodynamics for basic science studies as well as compromised circulatory conditions such as heart failure, congenital heart flow defects, sheer stresses on vascular walls, vascular stenosis, etc. The real time monitoring of flow in the loop gives hands-on feedback to manipulations of the cardiovascular system without the need to sacrifice animal subjects.

Although bench-top testing via an MCL is not intended to and can not replace critical, but expensive *in vivo* trials, they are a way to test devices in a simulated physiological environment that imitates the human cardiovascular system at a lower cost. Robust MCL testing can then accelerate the design development process and is necessary in order to comply with Food and Drug Administration regulations before expensive animal and human trials can be undertaken.[1]

MCLs simulate pressure-flow responses as an analog of the human circulatory system in different physiological conditions. It has been suggested that an effective MCL should simulate at least three benchmark states in a healthy person: sleep, rest and mild physical activity.[2]

MCLs are used to test the proof of concept of biomedical devices across a spectrum of applications including artificial kidneys, lungs and other organs. However, some of their major applications are to test pumps, artificial heart valves, stents and ventricular assist devices.

Not only are MCLs used to test the proof of concept of novel devices, but they also are used as a "safe"and low-cost training platform for clinical students. Normal and abnormal conditions of cardiovascular hemodynamic function can be simulated with an MCL without having to use *in vivo* models. Pharmacologic agents can also be used with MCLs to test hemodynamic responses to a specific agent.

One might also be reminded that the use of MCLs also have an ethical value for they reduce the number of *in vivo* animal trials needed in the development of a new device.

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MCL Development History

Some of the earliest MCLs were simple pulse duplicators developed in the late 1960s and 1970s that simulated the function of the heart by simply generating pulsatile flow through a circulatory model. They were first used to test the development of artificial valves.[3,4] Other early mock vasculatures were used primarily to test, design, and validate the pumping performance of early ventricular assist devices (VADs) and artificial hearts.[5-10] In succeeding decades, ever more complex MCLs were continually being developed with more and more features to reproduce the systemic system such as vascular resistance, vessel compliance, as well as pulsatile flow.

University of Louisville MCLs

In 2003, Y. Liu from the Virginia Artificial heart Institute at the University of Virginia in Charlottesville, VA published his Master's thesis "Design of a Performance Test Loop for an Artificial Heart Pump" that provided a road map for those seeking to develop mock circulations to mimic actual physiological conditions.[8,11] Their MCL was a dual-loop design with a reservoir that simulated venous circulation.

Liu's model was followed by a mock circulatory loop developed by David Timms of Queensland University of Technology in Australia whose system mimicked several hemodynamic parameters including arterial compliance, pulmonary and systemic resistances, left and right atrial preloads, and left and right ventricular contraction.[1]

Presented first at the 2nd Joint EMBS-BMES Conference, October 23-26, 2002, in Houston, TX, the thesis was later published in ASAIO in 2004.[1]

University of Louisville MCL

Among the most widely cited mock circulatory loop that utilizes a four chamber design to evaluate left ventricle and ventricular assist device function is

Dr. G. Pantalos working on a mock circulatory loop.

that developed by George Pantalos, Steven Koenig, Kevin Gillars Guriprasad Giridharan at the Jewish Hospital Heart and Lung Institute, University of Louisville, Louisville, KY and Dan Ewert from the Department of Electrical and Computer Engineering, North Dakota State University, Fargo, SD. Also presented at the 2nd Joint EMBS-BMES Conference, October 23-26, 2002, in Houston, TX, the thesis was later published in ASAIO in 2004.[12,13]

Their work presented an *in vitro* mock circulatory system that produced physiologically equivalent flow, pressures, and volumes that mimicked the native cardiovascular system

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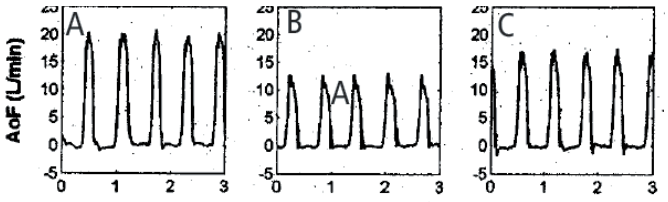
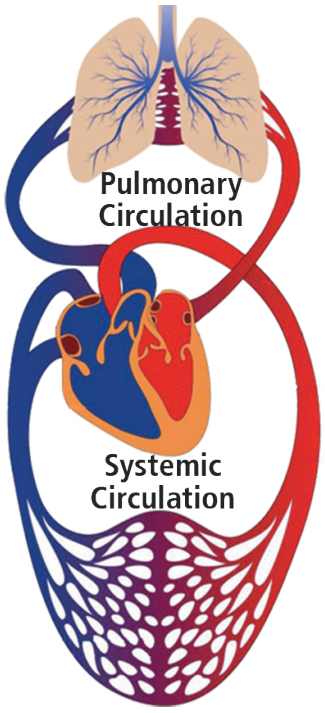


Flow waveforms from a adult left ventricle mock circulation loop during normal, failure and partial cardiac recovery test conditions at a heart rate of 100 beats per minute.[12,13]



Typical depiction that show the pulmonary (top) and systemic (bottom) circulations.

as they tested VAD and other cardiac device responses to a wide range of operating conditions, such as varying preloads, afterloads, heart rates, and clinical conditions (normal, failing, and recovering heart). Their mock circulatory system consisted of a mock systemic vasculature with aortic root or descending thoracic aorta outflow cannulation sites, and mock coronary vasculature with sensors to measure hemodynamic pressures flows, and volume.

One limitation of the University of Louisville MCL was that it only represented the systemic circulation (see figure on right) and did not include the pulmonary circulation that would allow testing during the simulation of both right ventricular and biventricular failure.

University of Queensland, Australia, MCL

Dr. Daniel Timms and his team from the University of Queensland, Brisbane, Australia have also been instrumental in furthering the development of MCLs. In 2005, they published two papers in Artificial Organs, "A Complete Mock Circulation Loop for the Evaluation of Left, Right, and Biventricular Assist Devices" and "Evaluation of left ventricular assist device performance and hydraulic force in a complete mock circulation loop."[1,14]

In the first paper they described the development of an MCL that replicated the necessary features of both the systemic and pulmonary circulatory systems, including pulsatile left and right ventricles coupled with vascular compliances and resistances.[1]

Their mock circulatory system was constructed as a loop containing heart and vascular components of the systemic and pulmonary circulations that were "assigned functional parameters obtained from the natural cardiovascular system to reproduce expected hemodynamic characteristics for each physiological condition."[14]

Natural simulation of the heart was achieved by creating a complete left and right mock heart composed of passive atrial and pneumatically actuated ventricular chambers. Clear PVC piping was used to construct open-to-atmosphere atria to replicate atrial compliance. This enabled the atrial chambers to change liquid volume in response to venous return, and

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hence pressure head was directly proportional to this liquid level.

The ratio of volume change to pressure head defines this value of compliance. A sufficient atrial/ ventricular pressure gradient was produced to passively fill each ventricle during the diastolic phase.

Rapid ventricular filling occurred through 40-mm diameter mitral/tricuspid brass swing check valves. These valves possessed sufficiently low forward resistance to flow while preventing liquid backflow during ventricular systole. The ventricular chambers were similar in construction to the atrial chambers, with the addition of an end cap that was tapped with a hose tailpiece to allow compressed air to be input during systole and vented during diastole.

Their mock circulatory system was able to simulate physiological pressures and perfusion throughout the cardiovascular network for resting normal and medically treated failing heart function. Both left or right ventricular heart functions could be independently tested and controlled.

The Frank-Starling response to all physiological conditions was observed in the developed rig, due to the recreation of passive filling ventricles. Easily variable vascular parameters enabled the system to recreate natural hemodynamics in each condition and the effects of medical treatment.

Since the development and presentation of these early MCLs, MCLs have continued to be refined for various testing purposes and are now rooted as a necessary step in device development and testing.

Guidance Standards

Another critical step in the performance validations and safety analyses of device development is adherence to the guidance and regulatory documents that evaluate medical devices *in vitro*. Three documents that are used for safety assessment are ISO documents 5840, 5198, and 14708-5. Understanding the contents and requirements of these documents is crucial when designing the mock circulatory loops that will be utilized for these certifications. Then, by executing these ISO certifications many of the requirements outlined in the U.S. Food and Drug Administration (FDA) draft guidance are supported.

ISO 5840

The ISO 5840 document governs the safety assessment of cardiac valves where safety evaluation is crucial due to the high cycle life expectancy of the device and the forces exerted during their use. The application of the testing methods from ISO 5840 not only serve as regulatory compliance, but also as guidance for the conditions used by researchers. The document prescribes *in vitro* experiments and *in vivo* animal trials that work to replicate the target operating conditions in humans. Non-rigid heart valves require use of compliant chambers to replicate the mounting tissue's structural deformation that might affect the regurgitation of the valve.

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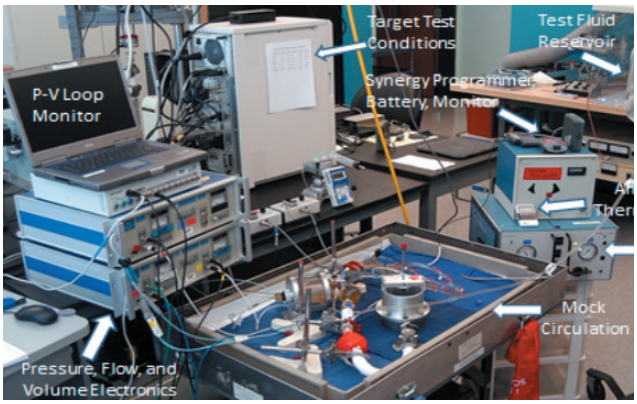
ISO 5198 and ISO 14708-5[1]

Ventricular assist devices and total artificial hearts have complex, multifaceted systems that operate the device. Two ISO guidance documents, ISO 5198 and ISO 14708-5, assist in certifying VAD performance and pumping safety. ISO 5198 details the appropriate means of characterizing performance in all pumps, regardless of application.

It also forms the basis for the methods and testing outlined in ISO 14708-5, which details the evaluation schema for a cardiovascular circulatory support pump. The 14708-5 document is specific to circulatory support devices, and is the fifth in a series of documents that describe safety for a wide range of implantable medical devices. It details a set of physiological conditions for the assessment of a left ventricular assist device. ISO 14971 describes risk management techniques applied to medical devices, and serves as a guidance on product life cycle safety determination. It is cited by many of the experimental standards as a means of identifying, or categorizing failures.

1Taylor CE, *"Moderization of the Mock Circulatory Loop: Advanced Physical Modeling, High Performance Hardware, and Incorporation of Anatomical Models,"* 2013 PhD Thesis, Virginia Commonwealth University, Richmond VA.



A LVAD mock circulatory loop presented by Pantalos *et al at ASAIO 2018.* Countesy of Geroge Pantalos, PhD

Current MCL Use

Mock circulatory loops have established themselves to be a mainstay in device testing. To that end, Timms *et al* presented a compact MCL design in 2010 along with a computer mathematical simulation with a variety of physical loop characteristics, such as pneumatic drive parameters, to create pressure and flow, and pipe dimensions to replicate the resistance, compliance, and liquid inertia of the native cardiovascular system. Their five-element MCL reproduced the physiological hemodynamics of a healthy and failing heart by altering ventricle contractility, vascular resistance/compliance, heart rate, and vascular volume. Cardiovascular hemodynamic pressures (arterial, venous, atrial, ventricular), flows (systemic, bronchial, pulmonary), and volumes (ventricular, stroke) were analyzed in real time. The effects of interpatient anatomical variability, such as septal defects and valvular disease, were also assessed.

The objective of this study is to describe the developmental stages of the compact MCL and demonstrate its value as a research tool for the accelerated development of cardiovascular devices.[19]

In 2019, mock circulatory loops have been used to test a variety of devices (stents, cannulae, intra-aortic balloon pump, VADs, artificial hearts) and conditions. These include valvular regurgitation in a biventricular device,[21] in the Cleveland Clinic's continuous-flow total artificial heart,[22] Dacron aortic graft behaviour,[23]

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cardiac output estimation during transvalvular left ventricular assistance.[24]

In addition they have been used to test a mock printed pump that mimics left ventricle motion,[25] to compare two centrifugal LVADs,[26] to evaluate an intraventricular balloon pump,[27] for machine implementation for left ventricle modeling and control,[28] testing of pulsatile pressure in the HeartWare HVAD,[29] analysis of a stent graft design for thoracic aortic aneurysm,[30] and venous return in rotary VADs.[31]

Also, in 2019, MCLs have been used to test a computational modeling framework for device testing,[32] a controller for dual rotary VADs,[33] levitated centrifugal blood pump's[34] the effect on a LVAD inflow cannula angle,[35] iron dextran infusion in a VAD patient,[36] a tipless inflow cannula design with the EVAHEART LVAD[37] and pressure and flow properties of extracorporeal membrane oxygenation (ECMO) drainage cannulae.[38]

In many of these models Transonic Flowsensors are integral to the model in order to measure volume flow. For instance, in the EVAHEART LVAD model, 10PXL and 20PXL flowsensors were placed at several locations of the assembly to measure flow. The model was immersed in a water-filled tank and attached to a Windkessel model of the circulation and a blood analog was circulated throughout the system.[37] Pressure transducers along with the Flowsensors recorded LV pressure (LVP), aortic root pressure (AoP), LVAD flow rate (QLVAD), and distal aortic flow rate (Q total). Baseline measurements simulated a Pre LVAD heart failure patient followed by measurements with the LVAD support.

Various Specialized Models

Pulse Duplicators & Heart Valve Testing:

Some flow loop models are configured to specifically duplicate a pulse with the same characteristics of a human heart beat. These pump devices produce a flow wave pattern to test performance of replacement aortic and mitral heart valves under the hydrodynamic flow conditions found in the heart and adhering to stringent FDA Guidelines for regurgitant fraction (low leakage values), effective orifice area and mean transvalvular pressure gradient.

With the increase in valve replacement therapy, there are several new valve options. The valves undergo testing in specialized labs at the major medical device suppliers (St. Jude, Edwards, Medtronic, Abbott, etc.) High resolution instantaneous flow measurement is required to characterize valve function in the pulse duplicator.

Ventricular Assist Device (VAD) & Pump Testing

A VAD or bypass pump's purpose is to augment, relieve or replace the human heart pumping action for short or extended periods of time to deliver oxygenated blood flow to the systemic circulation. Any such device, from its design conception, must be tested and measured to ensure that the pump is delivering the required flow. Flowsen-

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sors are used at all phases of the device development from design, validation, and also in LCT (Life Cycle Testing) where Flowsensors independently measure pump outputs 24/7 to monitor pump performance. Performance data is supplied to the FDA annually.

Flow Phantoms (Liquid Dynamics/Physics Labs)

Flow Phantoms are specialized circulatory models used to test and validate ultrasound imaging systems that monitor flow profile and velocity to study shear stresses on the vessel walls and stenosis. They are typically set up to use liquids that can model the acoustic properties as well as the physical properties of blood such as viscosity. While Doppler imaging systems give information on flow profile and velocity, volume tubing Flowsensors provide validation for the volume flow component. Microspheres or nanoparticles may be added to the solution to provide refractive index to the solution to monitor flow profile by laser light or Doppler ultrasound. Viscosity is often achieved by mixing specified concentrations of glycerine (typically 35 – 55%) to water. Some solutions also include concentrations of salt.

Bioreactors, Cell Culture & Regenerative Medicine

Bioreactors are environmental vessels or fermentation chambers used to mix cell media and nutrients at optimal doses to grow biologic material: virus vaccines, biologic pharmaceuticals, tissue engineered vascular grafts (TEVG) and other cell therapies. Conditions are optimized for cell growth and survival, so any dosing or flow transport is done at specific flow rates to guard against shear damage.

Isolated Perfused Organ Research & Langendorff Heart Preparations

This is a staple application of the research cardiovascular laboratory. One of the best methods to study organ perfusion or cardiac function is to isolate the organ and maintain the living tissue in a chamber where it can be studied without the complications of hormonal changes or maintenance of the rest of the body. Pressure and Flow are monitored via catheterization of the heart chambers. Langendorff and working heart preps allow study of myocardial circulation in mice and rats that cannot otherwise be measured directly.

Organ Perfusion Devices

R & D development of organ perfusion chambers for transplant also use Transonic tubing flowsensors. These devices require circulation of nutrient perfusates at cold temperatures to preserve tissues after harvest and during transport before transplant.

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