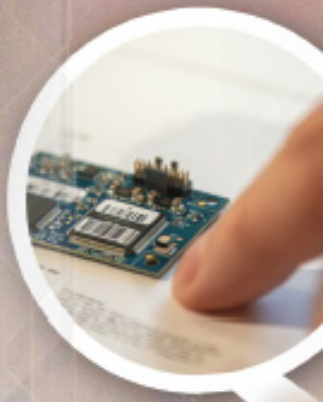
Harnessing Q

A Flow Measurement Guide for Industry Bioengineers



$$\text{flow}(Q) = \frac{\pi \Delta P r^4}{8nl}$$

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THE MEASURE OF BETTER RESULTS.

This handbook entitled Knowing Q (Flow) presents information for bioengineering students who are interested in the development of biomedical devices. Its content was developed by Transonic for the purpose of championing the importance of incorporating quantitative flow methodolgy into biomedical device manufacture.

Following a Table of Contents, Knowing Q offers an introductory forward that proceeds sections on cardiovascular physiology, flow dynamics and principles of flow measurement. Then chapters on biomedical device design and development, and on Knowing Q research and clinical applications that employ transit-time ultrasound and indicator dilution technologies follow. The second from the last chapter in the body of the handbook presents an outline for a pilot collaborative student / academic research program with Transonic while the final chapter gives an overview of Transonic flowsensing products. Finally, an annotated bibliography of relevant publications and an extensive glossary of technology and hemodynamic terms complete the handbook.

Cover photography by Kyle Re (www.kylerecreative.com)

Copies of this handbook may be ordered from Transonic Systems Inc.
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"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science, whatever the matter may be."

William Thomson, Lord Kelvin (1824-1907) Scottish physicist
"Electrical Units of Measurement," lecture (3 May 1883)

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Forward

From "Bench to Bedside"

Flow Is Life's Vital Sign

Blood flow enables life. It is life's vital sign. When blood flow is cut off or ceases, heart attacks and strokes occur. Life can end.

Yet, why is flow so often disregarded? Simply stated, devices and technologies to precisely measure blood flow were unavailable until the mid-twentieth century. In their stead, surrogate measurement modalities were introduced, became established and are still being used.

Pressure, used by the body to drive flow, is routinely used to assess hemodynamic function. But it does not always correlate with flow (see graphic on page 25). Pulses, visual and tactile, are felt and observed to assess blood pressure, but they do not provide adequate information about true flow. Angiography is used, but it shows anatomical structure, not quantitative function. Doppler technology is also a common measurement technique, but it measures the velocity, not volume, of flow. All are used as surrogates for flow. They do not provide quantitative true volume flow as measured precisely by Transonic devices. Volume flow is truly the quintessential "vital sign" of hemodynamic function.

Why Is Flow So Important?

Blood flow, defined as the volume of blood that passes a certain point in a vessel during a defined time frame, is crucial for proper metabolism. Blood delivers oxygen and nutrients to each cell in the body, then carries away the metabolic wastes. By measuring true blood flow, one is quantifying an essential medical parameter. Rather than relying on subjective impressions or qualitative images, real numbers provide functional information. Just as a pilot must learn to use instruments to fly safely, the engineer, researcher or clinician must rely on real quantitative data in order to arrive at accurate, objective conclusions.

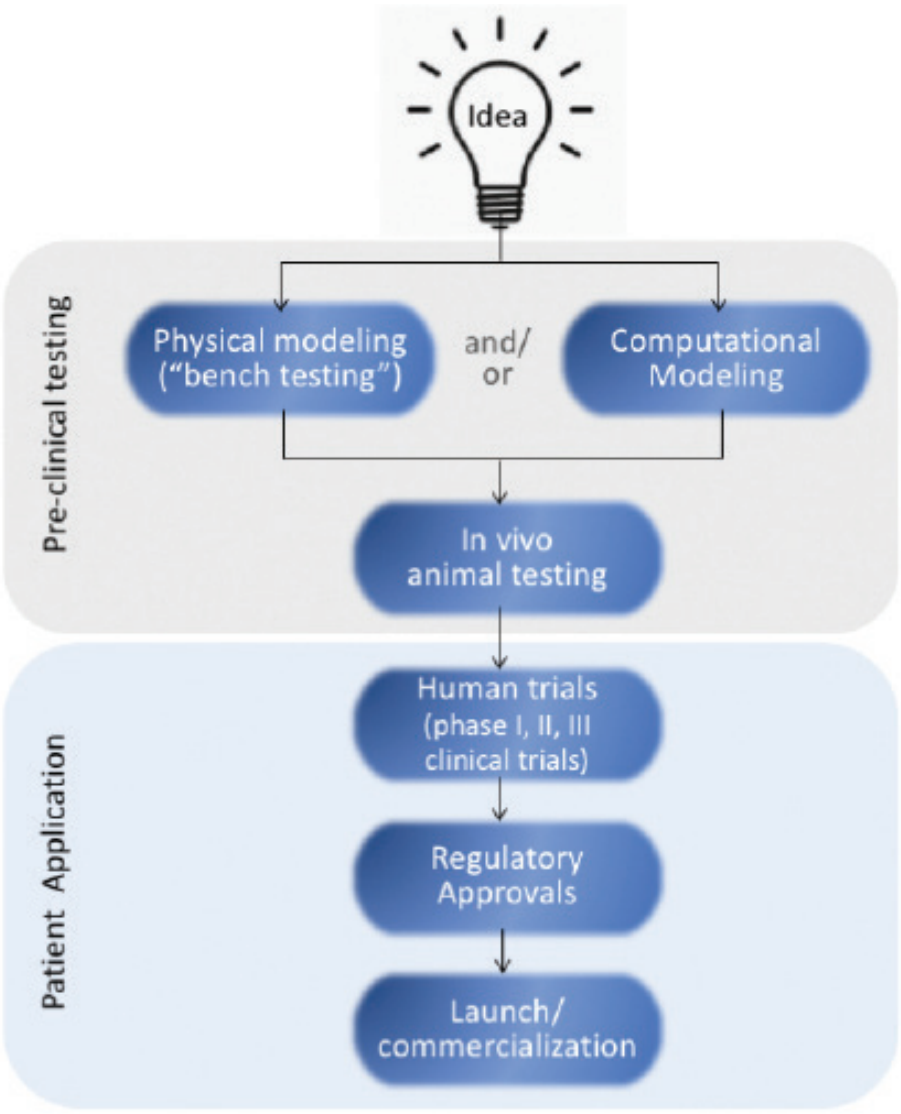
Transonic's Inspiration

Transonic's mission "To Advance Meaningful Measurements" has inspired, guided and propelled Transonic's growth from genesis 35 years ago to the present day where Transonic is globally recognized as a biomedical measurement company leader.

Purpose of Handbook

The intent of this booklet is to introduce bioengineers to the importance of flow (Q) and the measurement technologies offered used to measure flow. Transonic measurement technologies (transit-time ultrasound, indicator dilution, conductance, pressure and Laser Doppler) are used in a broad spectrum of applications and in the development of biomedical devices as it moves from bench-top scientific research to device development and pre-clinical validation to, ultimately, the manufacture of commercial products.

Typical Phases of Medical Device Development



B. Principles of Flow Measurement

Testing, verification and validation is key during each stage of medical device development. Measurement of blood flow by various methodologies is frequently used in combination with other hemodynamic parameters to test, validate and verify biomedical devices.

There are a myriad of methods, employed by biomedical engineers to measure hemodynamics and related parameters. This chapter will review flow measurements based on the following methodologies:

1. Ultrasound Principles
2. Indicator Dilution Principles
3. Electromagnetic Induction Principles
4. Principles of Radiography
5 Thermal Convection Principles

Many devices incorporate more than one of these principles in their device. One example is the Transonic HD03 Monitor that uses indicator dilution ultrasound technology, which couples ultrasonic principles with indicator dilution principles. Others are the Swan Ganz catheter that uses thermal principles with indicator dilution or Magnetic Resonance Imaging that couples electromagnetic principles with radiographic principles.

This section of the handbook will present brief overviews of each of these basic flow measurement principles together with some of the devices that use those principles.

Doppler Effect

In 1842, Johann Doppler of Salzburg, Austria described what has become known as the Doppler effect. It refers to the change in the frequency of sound waves that occurs due to motion of a sound source, a sound reflector, or a sound receiver. In biomedical instrumentation, the Doppler effect is used to confirm blood flow by detecting the change in frequency of ultrasound waves that occurs when sound is reflected from moving clumps of red blood cells (RBCs). .

Ultrasound: Doppler

To generate the Doppler effect, an oscillator generates a signal at several MHz to excite a piezoelectric transducer. The difference between the the original and shifted signals gives the Doppler frequency. A Doppler shift is the change in frequency between the ultrasound waves emitted by the transducer and the ultrasound waves returning to the transducer after reflection from moving ref blood cells (RBCs). The reflected sound frequency increases when the blood flow direction is toward the Doppler signal and decreases when the direction is away from the Doppler signal.

An increase in frequency (positive Doppler shift) is when the sound waves are compressed by encountering RBCs moving toward the sound source. A decrease in frequency is (negative Doppler shift) as the reflected sound waves are stretched by RBCs moving away from the sound source. The presence of a Doppler shift within a blood vessel confirms the presence of blood flow. The direction of the Doppler shift toward higher or lower frequency indicates the direction of blood flow.

The Doppler equation describes the relationship between the Doppler frequency shift (F) and the velocity (V) of the moving RBCs that produce the shift. In its simplest analog, a Doppler shift measures average velocity inside a tube or a blood vessel and volume is calculated from:

Volume = Integrated Velocity * (Tube) Area

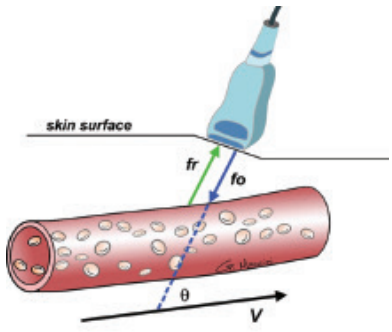


Fig C1: Doppler Principle

B. Principles of Flow Measurement cont.

Pen-tip Doppler Ultrasound

A pen-tip sensor is applied against the wall of a vessel exposed during surgery to "hear" how fast blood is moving (its velocity). Its measurement units are in KHz (sound pitch). Its primary measurement parameter is flow velocity. This Doppler shift falls in the audible range and produces a distinctive, synthetic, pulsating sound.

Pen-tip Doppler measurement is quick: < 1 min/test, < 3 min/surgery. Its advantages are its speed and its low cost, initially and per case. Its disadvantage is that it is a qualitative and not quantitative measurement. It cannot discern between mild to severe vessel occlusion. Doppler measures velocity, not volume flow and results are examiner angle dependent.

Duplex Doppler Ultrasonography

The Doppler effect is used in Duplex Doppler Ultrasonography to generate images of the movement of tissues and body fluids (usually blood), and their relative velocity to the probe. By calculating the frequency shift of a particular sample volume (for example, flow in an artery or a jet of blood flow over a heart valve) its speed and direction can be determined and visualized.

Color Doppler Ultrasonography

Color Doppler Ultrasonography or Color Flow Doppler presents velocity on a color scale. Color Doppler images are generally combined with grayscale (B-mode) images to display duplex ultrasonography images, allowing for simultaneous visualization of the anatomy of the area. Doppler data is displayed graphically using spectral Doppler, or as an image using color Doppler (directional Doppler) or power Doppler (non-directional Doppler).

Pulsed Wave Doppler

All modern ultrasound scanners use pulsed Doppler to measure velocity. Pulsed wave instruments transmit and receive series of pulses. The frequency shift of each pulse is ignored, however the relative phase changes of the pulses are calculated and used to obtain the frequency shift (since frequency is the rate of change of phase). The major advantage of pulsed wave Doppler (PW Doppler) over continuous wave (CW Doppler) is that distance information is obtained (time between transmitted and received pulses multiplied by sound velocity equals distance) and a gain correction is applied. The disadvantage of pulsed wave Doppler is that the measurements can suffer from aliasing or distortion of signals. The terms Doppler ultrasound and Doppler sonography have been accepted to apply to both pulsed and continuous wave Doppler systems, despite the different mechanisms by which the velocity is measured.

Doppler echocardiography is the use of Doppler ultrasonography to examine the heart. An echocardiogram can, within certain limits, produce an accurate assessment of the direction of blood flow and the velocity of blood and cardiac tissue at any arbitrary point using the Doppler effect. One of its limitations is that the ultrasound beam should be as parallel to the blood flow as possible so requires an experienced operator.

An esophageal Doppler monitor measures blood flow velocity in the descending aorta from a small probe inserted into the esophagus under sedation. This measurement, when combined with an estimate/measurement of the cross-sectional area of the descending aorta, allows calculation of various hemodynamic variables including cardiac output.

Laser Doppler

Laser Doppler technology measures regional perfusion within a tissue at a capillary level by emitting a low intensity beam of monochromatic light (instead of sound) from a laser diode to illuminate the tissue under study. The laser beam is guided from the monitor through a fiber optic cable to a probe which is positioned carefully over the area of interest.

There the laser beam is scattered by reflective components within the tissue. A portion of the light is reflected back, via the Probe's receiving fiber optic light guide, onto a photo detector inside a monitor. Generally, this received light

B. Principles of Flow Measurement cont.

has been reflected many times by stationary structures within the tissue as well as by one or more moving particles (mainly red blood cells) within the tissue. Through the Doppler effect these moving particles change some of the received light signal's frequency and the received signal spectrum is processed within the monitor. Measurements are qualitative, not quantitative. The initial cost for this technology is low as is the cost per measurement.

Ultrasound: Transit-time

Transit-time ultrasound technology also falls under the broad range of Doppler measurements because it records velocity shifts as ultrasound passes through the vessel or tube under investigation to derive volume flow.

Ultrasound refers to high frequency sound waves that are outside of auditory range. Ultrasound velocity depends on the acoustic properties of the liquid being measured and its temperature. Transit time is the length of time it takes for ultrasound waves to pass through the material being measured.

Transit Time = Distance / Velocity

Knowing the time of travel over a given distance allows velocity calculation. The primary measurement parameter in transit-time ultrasound is volume flow. All ultrasound waves begin at the same frequency and velocity. As the ultrasound waves travel downstream or with the flow within the vessel or tube, its velocity increases. As ultrasound waves travel upstream or against the flow, its velocity decreases. Faster flow produces a greater change in ultrasound wave speed. One ray of the ultrasonic beam undergoes a phase shift in transit time proportional to the average velocity of the liquid times the known path length over which this velocity is encountered.

A Flowmeter subtracts the average downstream transit times from the average upstream transit times. This difference is directly proportional to Volume Flow. Transit-time Flowsensors are

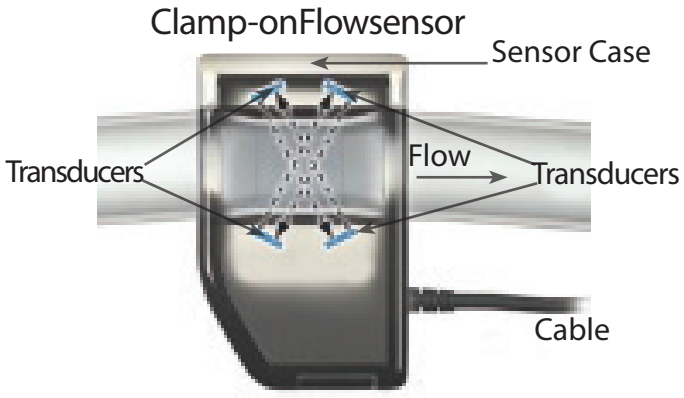


Fig. C2: X-style Flowsensor configuration

calibrated based on known liquid properties and temperature conditions. Calibration supplies the flow Gain constant (k) which transforms the proportional signal to true volume flow.

Differential TT x k_{gain} = Volume Flow

Contrary to Doppler measurements of velocity, transit-time ultrasound offers a functional quantitative assessment of volume flow. Measurement units are milliliters or liters per minute and are independent of vessel diameter estimations. Also, transit-time ultrasound measurements are not dependent on particulate matter in the fluid media and, therefore, can measure liquids other than blood. This is convenient for device prototyping in R & D where flow measurements testing can be performed with a suitable blood analog. Water with various concentrations of glycerin to minic the viscosity of blood can be measured with transit-time flowsensors making it the method of choice for testing blood pumps and heart assist devices.

Transit-time Ultrasound in Biomedicine

Transit-time ultrasound technology (TTU) was refined for biomedical use by Cornelis (Cor) Drost who, as a senior research associate under Dr. Alan Dobson, Professor of Physiology at NYS College of Veterinary Science at Cornell University in Ithaca, NY, figured out how to measure the amount of blood flowing through vessels/tubing without influencing the liquid flow itself.

B. Principles of Flow Measurement cont.

Transit-time ultrasound (TTU) is a direct, real-time measurement of pulsatile and mean volume flow, both intraoperatively and extracorporeally. Perivascular Flowprobes measure volume flow of blood intraoperatively to test anastomotic quality during coronary artery bypass grafting (CABG) surgery, cerebrovascular and liver transplant surgeries. It is also used to measure delivered blood flow during extracorporeal procedures such as hemodialysis and extracorporeal membrane oxygenation (ECMO) with sensors that clamp around the outside of the tubing (Fig. C2). TTU also has innumerable applications for research in many animal species and on the bench.

Indicator Dilution

Indicator dilution is based on the principle that the total uptake of a substance by an organ is the product of the amount of blood flowing through the organ and the difference between the arterial and venous concentrations of that substance. When the uptake is known, then the flow can be calculated.

Indicators

Any readily mixable substance can be used as an indicator. Its concentration in the blood is sensed by various methods (ultrasound, thermal) to measure blood flow. Administration of an indicator depends upon a determination of whether the system is open or closed. If the circulation system is considered open, it is assumed that the fluid is not recirculated. Therefore, the indicator is administered at a constant infusion rate, i.e., the Fick Method. With a closed loop system in which the indicator is recirculated, the indicator is administered as a bolus, i.e. isotonic saline with hemodialysis ultrasound dilution system.

Common indicators include:

- Saline: Isotonic saline is considered an ideal innocuous indicator solution when used with ultrasound sensors to measure the acoustic velocity of the protein concentration of blood. Alternately, in thermal dilution technology, the change in temperature of saline administered can be sensed by thermisters that measure blood flow (See Swan Ganz in sidebar). Also, RheoCath Flow Catheters and an Endovascular Flowmeter measure flow during angioplasty using thermisters situated within the proximal and distal ends of antegrade or retrograde catheters to detect the change in temperature of saline as it passes through the catheter.
- Indocyanine dye used in an isotonic

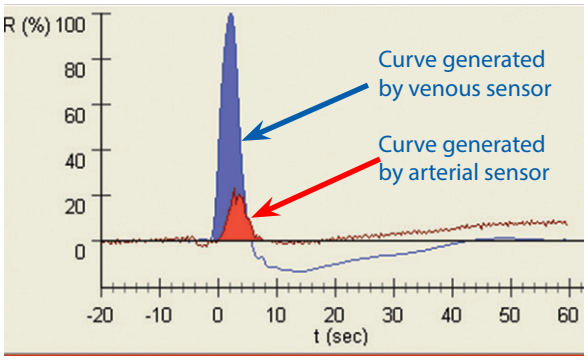


Fig. C3: Bell-shaped saline indicator dilution curve.

Indicator Dilution Development

Three scientists introduced, expanded and refined indicator dilution technique. In 1824, E. Hering, a professor in the Royal Veterinary School in Stuttgart, Germany first introduced the indicator dilution method for measuring a hemodynamic property by injecting K ferrocyanide into a jugular vein on 14 horses and sampling the indicator from other parts of the vascular system.

Nearly seventy-five years later, in 1897, G. N. Stewart, a professor/researcher, then at Western Reserve University in Cleveland, Ohio suggested that indicator dilution could be used to measure blood flow. Stewart's formula was evolutionary because it used the area under a bell-shaped indicator output concentration curve to calculate flow.

From the late 1920's through the 1940's William F. Hamilton, with his many colleagues, first in Louisville, KY and then in Georgia expanded this concept. Hamilton used the Hering–Stewart technique with a dye as the indicator. In 1928 he published a paper in which he resurrected Stewart's formula. Hamilton refined Stewart's formula to arrive at the classic Stewart-Hamilton equations for measuring blood flow with indicator dilution.

B. Principles of Flow Measurement cont.

Ultrasound Indicator Dilution

In the early 1990s Nikolai Krivitski, DSc, PhD, who had recently immigrated to the US from Russia, incorporated saline indicator dilution measurements into a hemodialysis treatment by marrying transit-time ultrasound technology with saline indicator dilution technology. This combination allowed for the measurement of recirculation, vascular access flow and cardiac output during hemodialysis that gave immediate feedback on the status of the patient.

He later used thermal dilution principles to measure flow in the vascular access during angioplasty.

solution is another indicator. A known quantity concentration of nontoxic, indocyanine green dye is injected into the pulmonary artery. The blood/dye solution is sampled at a constant rate from a systemic artery (such as the brachial, radial, or femoral artery). The concentration of the dye is measured over time by a densitometer that records a dye concentration curve over time. The amount of dye injected is divided by the area under the curve to yield a measure of cardiac output.

- Microspheres are round microparticles that are often used as tracers in medical devices. Fluorescent microspheres are particles that emit distinctive colors when illuminated by UV light and offer additional sensitivity for observation through the use of microscopes, lasers, and other analytical methods. Examples include microcirculation and biological research, imaging, and flow cytometry. Fluorescent microspheres can be excited and detected by a wide range of methods and are useful as experimental particles for acoustical and optical analytical systems.
- Lithium Chloride salt solution is detected by a lithium sensor. Lithium salts have a narrow therapeutic-to-toxic blood level threshold so that Lithium salt doses must be carefully recorded. Its use is contraindicated for patients undergoing lithium therapy or patients who weigh less than 40 kg.
- Oxygen (O_2) Indicator: With direct Fick CO determinations, the amount of oxygen extracted in the respiratory cycle is measured from inspired and expired gas as the "total oxygen consumption." Oxygen consumption (mVO_2) is measured with indirect calorimetry.

$$Q = mV_{O2}/Ca_{O2} - Cv_{O2}$$

Accurate cardiac output derived via the direct Fick method is dependent upon the patient being in a steady hemodynamic and metabolic state with a stable respiratory rate, heart rate, oxygen consumption, and respiratory exchange ratio. Direct Fick cardiac output measurements are time consuming, require multiple personnel meticulously carrying out the technique in specialized environments, and produce a discrete one time only cardiac output measurement. Therefore, its use is limited.

Indirect Fick CO measurements use a sample of mixed venous blood drawn from the pulmonary artery. However, rather than using direct measurement of total oxygen consumption and arterial blood oxygen, the indirect Fick uses pulse oximetry devices to derive the arterial oxygen content. Less cumbersome than direct Fick, indirect Fick can be performed at the patient's bedside by specially trained personnel and can be used in sequence.

Adolf Fick

In the mid 19th century, the German physician Adolf Eugen Fick (1829–1901) hypothesized that cardiac output (C)) could be estimated if the arterio-mixed venous oxygen content difference and systemic oxygen consumption are known. Fick's principle later formed the basis of Stewart's indicator-dilution technology.

B. Principles of Flow Measurement cont.

FLOW MEASUREMENT COMPARISON OF FEATURES TABLE			
FIELD OF USE	TRANSONICTTFM	DOPPLER-TRANSCUTANEOUS	MICROSPHERES
Measures arterial blood flow	Yes	Yes	Yes
Measures venous blood flow	Yes	No	Sometimes
Measuresorganflowdistribution	No	No	Yes
Measures flow in small vessels	Yes	Yes?	Yes?
Measures flow through tubing	Yes	n/A	N/A
Measuresprimingsolutionflow	Yes	No	N/A
Measures flow in humans	Yes	Yes	No
For long-term observations	High	Excellent	Medium
For acute observations	High	High	High
Parameter(s) measured	Volume Flow	Flow velocity	Voliume Flow
Temporal resolution	Excellent	Good	None
EASE OF USE			
Degree of Surgery required	Significant	None	Minor
Ease of Data Collection	Minimal	Moderate	Difficult
Labor to derive Volume Flow	Simple	Simple:vesselgeometry/angle,flowprofile measurements	Dissectioncomputercalculations
Pre-calibrated Flowprobes	Yes	No	N/A
RISK TO SUBJECT			
Animal sacrifice required	Low	No	Yes
Trauma to vessel	Low	None	Radioactive/capillary blockage
Risk of electrical leakage	Low	No	None
INVIVO/INSITUACCURACY			
Interferencewithhemodynamics	Small	Minimal	Minimal
In vivo Accuracy	± 10%	40% (±20%)	±5%
Accuracywithinsitucalibration	± 2%	N/A	±5%
Repeatability	± 2%	±20% (±20%)	±5%
Zero errors	Low/constant	Low variable	±5%
Linearity	± 2%	Non-linear calibration at zero and high velocities/vesseldiameterandflowprofile dependent	±5%
Predictability(benchcalibration)	± 10%	Vesseldiameter.flowprofiledependent	N/A
COST			
Initial acquisition cost	Moderate	Moderate	High
Repetitivecostpermeasurement	Low	Low	Medium

al sacrifice required Measures organ flow distribution Measures arterial blood flow

B. Principles of Flow Measurement cont.

FLOW MEASUREMENT COMPARISON OF FEATURES TABLE				
FIELD OF USE	FICK/PAL	ELECTROMAGNETIC	DOPPLER-INTRAOPERATIVE	THERMAL DYE DILUTION
Measures arterial blood flow	Yes	Yes	Yes	Yes
Measures venous blood flow	Yes	No	No	No
Measuresorganflowdistribution	No	No	Sometimes	No
Measures flow in small vessels	No (?)	No	Yes	No?
Measures flow through tubing	N/A	No	Yes	N/A
Measuresprimingsolutionflow	N/A	Sometimes	No	N/A
Measures flow in humans	No	Yes	Yes	Yes
For long-term observations	Medium	Low	Medium	Medium
For acute observations	High	High	High	High
Parameter(s) measured	Volume Flow	Volume Flow	Flow velocity	Volume Flow
Temporal resolution	No	Excellent	Good	None
EASE OF USE				
Degree of Surgery required	Minor	Significant	Significant	Minor
Ease of Data Collection	Medium	Simple	Simple	Catherization
Labor to derive Volume Flow	Chemistry; ComputerCalc.	Hematocrit/zeromeasurement	Vessel geometry/angle, flowprofilemeasurements	Calculations (automatic)
Pre-calibrated Flowprobes	No	No	No	N/A
RISK TO SUBJECT				
Animal sacrifice required	No	No	No	Yes
Trauma to vessel	Moderate	Constricts/heats/endothelial damage	Small	Small
Risk of electrical leakage	None	Yes	No	None
IN VIVO/IN SITU ACCURACY				
Interferencewithhemodynamics	Small	HeatResponse/pressuregradient distortion,stenoticflowartifacts	Small	Heat Response
In vivo Accuracy	±10%	± 20%(?)	± 20%(?)	±20%
Accuracywithinsitucalibration	±10%	± 10%(?)	± 10%(?)	±10%
Repeatability	±10%	± 10%(?)	± 10%(?)	±10%
Zero errors	Large	Large/variable	Low variable	Large
Linearity	±10%	± 20%(?)		±5%
Predictability(benchcalibration)	N/A	± 20%(?)	Vesseldiameter/flowprofile dependent	N/A
COST				
Initial acquisition cost	High	Moderate	Moderate	Medium
Repetitivecostpermeasurement	Low	Low	Low	Low

B. Principles of Flow Measurement cont.

ElectromagneticInductionPrinciples

Electromagnetic blood flowmeters are based on Faraday's laws of electromagnetic induction: if an electrical current conductor (blood) moves through a magnetic field, an electromotive force is induced in the conductor that can be measured. With an electromagnetic flowmeter, an electromagnet is positioned so the magnetic field is perpendicular to the direction of the flow. A set of electrodes are placed across the blood vessel mutually perpendicular to both the magnetic field and the direction of flow. Blood flowing through the magnetic field carries a current that will indicate the direction of flow; the magnitude of the induced electromagnetic field will be proportional to the volume and velocity of the blood flow. An electromagnetic flowmeter picks up and converts these signals to voltages to measure volume flow in blood vessels; or liquid flow in tubes provided the flow media is conductive. Electromagnetic flowprobe sensitivity is greatest in the area of the vessel closest to the electrode and thus they require a const ricti ve fit on the vessel to make measurements.

Electromagnetic probes were used to measure flow during surgery, but their use was limited by the difficulty in maintaining constant contact with the vessel or by causing constriction of the vessel. Their flow sensitivity was also affected by the conductive properties of the vessel wall and ambient noise in the surgery suite.

Bioimpedance Cardiography

Bioimpedance (thoracic) cardiography (BCG) involves the placement of voltage sensing and current transmitting electrodes on the chest or via left ventricle conductance catheter. The patient's chest may be regarded as a conductor whose impedance is altered by changes in blood volume and velocity with each heartbeat. Stoke volume is calculated from an equation involving baseline and maximum rate of change in impedance, ventricular ejection time, and thoracic segment length.

PV Loop Conductance

Pressure volume (PV) technology uses conductance of the blood to measure ventricular volume during the cardiac cycle, plotting the dynamic relationship between pressure and volume to assess cardiac function . A conductance & pressure sensor catheter placed in the ventricle generate PV Loops to derive the following parameters: End-Diastolic Pressu re and Volume, End-Systolic Pressure and Volume, Heart Rat e, Cardiac Output, Stroke Volume, Ejection Fract ion , Min and M ax dP/dt (derivative of pressure), Min and Max dV/dt (derivative of volume) , contractility and elastance; essential to understanding hemodynamics and cardiac function .

Deriving ventricular volume from a Conductance Catheter is based on Ohm's Law: Voltage (V) = Current (I) X Resistance (R) V = IR Conductance (G) rather than resistance is the parameter of interest. Since conductance is the inverse of resistance, Ohm's Law can be rewritten as:

Voltage = Current/Conductance V = I/G

Conductance Catheters are comprised of both excitation electrodes and recording electrodes. The excitation electrodes (most distal and proximal electrodes on the Catheter) generate an electrical field inside the heart from the aortic valve to the apex. This field is generated as a result of an alternating current being applied (at a constant magnitude) between these 2 outermost electrodes. The inner recording electrodes measure voltage change which is proportional to a change in resistance.

The electrical field cannot be restricted to just the blood volume and must pass through some of the cardiac muscle. This means that the measured conductance value is actually a combination of blood conductance and muscle or parallel conductance .

Admittance PV technology provides an additional "Phase" signal to isolate the parallel muscle conductance component to more accurately report volume.

B. Principles of Flow Measurement cont.

Currently, this technology is mostly available for research purposes where it has been used in both animal and clinical studies of cardiac function .

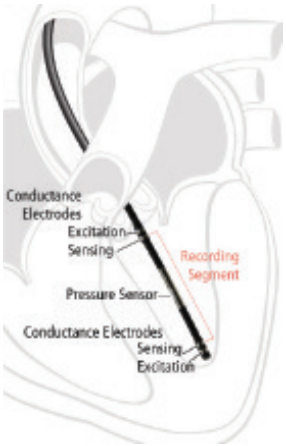


Fig. C4: Diagram of conductance catheter inserted into the heart.

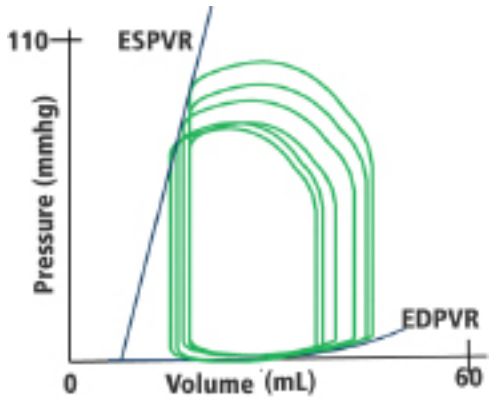


Fig. C5: Representative PV Loop

Magnetic Resonance Imaging (MRI)

A MRI or NMR scanner uses three powerful magnets to polarize and excite hydrogen nuclei of water molecules in human tissue. A a detectable signal is produced which is spatially encoded to generate images of the body. MRI uses three electromagnetic fields to create three fields: a strong static magnetic field to polarize the hydrogen nuclei; gradient fields that can be modified to vary in space and time for spatial encoding; and a spatially homogeneous radio-frequency (RF) field for manipulation of the hydrogen nuclei to produce measurable signals, collected through an RF antenna.

Magnetic Resonance Imaging

In tIn 1971 Paul Lauterbur at Stony Brook University in New York applied magnetic field gradients in all three dimensions and a back-projection technique to create the first nuclear magnetic resonance (NMR) images. His work was followed in the late 1970s, with physicist Peter Mansfield, who further developed MRI techniques for which they were awarded the Nobel Prize for Physiology and Medicine in 2003.

Radiographic (X-Ray) Principles

X-rays and fluoroscopy are used widely for medical imaging. X-rays are often used to determine the type and extent of a fracture as well as for detecting pathological changes in the lungs. They can also be used with radio-opaque contrast media such as barium to visualize the structure of the stomach and intestines. Fluoroscopy employs a constant input of low dose x-rays to produce real-time images of internal structures. Contrast media, such as barium, iodine, and air are used to visualize internal organs as they work. Fluoroscopy is also used in image-guided procedures such as angioplasty when constant feedback during a procedure is required. An image receptor is required to convert the radiation into an image after it has passed through the area of interest.

Intraoperative Angiography

Angiography or arteriography (derived from the Greek words for 'vessel' and ' to record') is a medical technique in which still or moving images are taken to visualize the blood filled areas of the body including veins or arteries and the chambers of the heart. This is traditionally done by injecting a radio-opaque contrast agent into the blood vessel and imaging with X-ray based techniques such as fluoroscopy. Blood circulation patterns can be made locally visible by the injection of a contrast medium like an isolated organic compound into the blood vessel. Sequential photographic or video recording of X-ray

images of the contrast medium can be used to detect obstruction and blood flow rate in the artery. This technique is call video or cine angiography.

The advantage of intraoperative angiography is that it provides a visual (anatomic) image of the area under study. Its disadvantages are that it is time consuming (20-30 min), requires a team, is technically demanding, invasive and can possibly produce systemic side effects. Intraoperative images can also have questionable quality. Angiography shows anatomy, so it is not a quantitative measurement.

Thermal Convection Principles

A hot wire in a flowing liquid medium can be used to measure various properties of flow. The rate at which the wire cools is proportional to the flow rate of the liquid. The energy required to maintain the temperature of the hot wire is proportional to the velocity of the flowing liquid.

There are two ways that this works. In one, a thermistor is kept at constant temperature with a servo controller. The energy required to keep the temperature constant is directly proportional to the velocity of the liquid. In another method, a heater is placed in the flowing liquid. Two transducers, one to measure the upstream temperature and another to measure the downstream temperature are used. The difference between the two temperatures is directly proportional to the velocity of the blood flow. Some thermodilution pulmonary artery catheters use a heated filament to produce the temperature gradient necessary to determine blood flow by thermodilution in the vessel. The heated filament is used in frequent repetition to provide a measurement of "continuous cardiac cutput (CCO)".

Summary

A biomedical device that can be used to provide accurate assessment in the medical market is invaluable. It may either confirm a clinical impression or alert the practitioner to a potential problem. Desirable characteristics for any hemodynamic monitoring device are precision, accuracy, reproducibility, fast response, operator independency, continuous and ease of use.

Device development entails a long, arduous process that requires detailed planning and meticulous execution. Bioengineers must take into consideration the ultimate purpose of the device, its components, and make sure that its design meets medical, environmental and economic requirements. Rigorous testing of any biomedical device that will be used with a patient is mandatory before release to market.

Swan Ganz Catheter

The Swan Ganz (SG) or Pulmonary Artery Catheter (PAC) uses an inflated balloon tip that acts as a 'sail' to float the distal catheter tip through the vena cava, right atria and ventricle into the pulmonary artery.

The catheter can measure pressure, cardiac output by thermodilution and other parameters. It takes about an hour to place a PAC performed by a skilled physician. PAC is commonly used in cardiothoracic surgery or in surgery patients with high cardiac risk. A poor location of the catheter will result in poor measurements or damage to surrounding tissue.

A Swan Ganz may utilize several different measurement modalities for assessing hemodynamics. Most PAC devices will usually contain both a pressure and a thermodilution modality. PACs may also include fiberoptic oxygen sensors and pacing electrodes.

A thermodilution PAC uses either iced injectate for intermittent or bolus CO or a heated filament to produce the temperature gradient (thermal convection) necessary to determine blood flow by thermodilution in the vessel. The heated filament is used in frequent repetitive measurements to provide a Continuous Cardiac Output (CCO). For years the PAC was the most common invasive cardiodynamic measurement. Despite the information provided by the PAC its disadvantages outweigh its advantages. They are:

- Temperature as an indicator may be lost in the lungs producing a questionable measurement.
- Results rely on a precise catheter position.
- Invasive procedure with specific skills required.
- Use in low weight pediatrics is restricted due to small vessel size and high degree of invasiveness.

C. Medical Device Design & Development

Introduction

Biomedical devices or instrumentation refers to a set of instruments and/or equipment used to measure one or more characteristics of a biophysical system. Clinicians use such instrumentation in the diagnosis and treatment of disease, while researchers use biomedical instrumentation in vivo or in vitro research studies. Important factors to consider when developing a biomedical device include:

- Parameter(s) of interest
- Targeted organ or organ system
- Method of measurement (direct or indirect; invasive or noninvasive)
- Level of patient or subject contact
- Sensor technology and potential impacts on living tissues or organs
- Biocompatibility of all materials
- Real-time, meaningful display of data

Signal Characteristics

Medical devices use a variety of signals to extract information. They can be as simple as a wrist pulse or as complex as ultrasonic waves from an internal soft tissue. Common types of biological signals are described in Table D1. Understanding how these signals are received, processed, and transmitted is crucial to designing a device that is accurate and precise. The following signal properties must be examined in order to determine how well a device will perform.

- Range – The amplitude and frequency of input over which the device is expected to operate.
- Resolution – The minimal variation that can be read accurately by the device.
- Sensitivity – The smallest range of a variable and parameter that can be measured by the instrument (ratio of output signal magnitude to input signal magnitude). In electronic systems, sensitivity is referred to as gain; in mechanical devices, sensitivity is referred to as amplitude.
- Linearity – A constant gain over an entire range of measurements.
- Hysteresis – When an instrument produces unequal output for the same input during increasing and decreasing trends. This can produce misleading errors.
- Flat Frequency Response – When the sensitivity or gain of the instrument is equal for the entire operating range of frequencies. A usual requirement is that the frequency of input signal should not exceed 60% of the natural frequency of the measuring instrument.
- Accuracy – The ability to obtain a measurement value close to the true value.
- Signal to Noise Ratio – The ratio of the output magnitude of the instrument to the underlying noise level. For ideal measurements, this is infinity.
- Reproducibility – The ability for a device to obtain consistent results when measurements are repeated.

Approaches to Device Development

Medical devices are being developed at an increasingly rapid pace. In The Innovator's Prescription, Clayton Christensen recounts an administrator in one of the major Boston-area teaching hospitals remarking that "for us that 70 percent of the patients in his hospital today would have been in the intensive care unit 30 years ago, and that 70 percent of the patients in his ICU today would likely have been dead 30 years ago." New medical devices are constantly re-shaping the way healthcare is provided. This section of Knowing Q provides an overview of how these new product ideas get their start.

C. Medical Device Design & Development cont.

The genesis of a new medical device is typically either technology-driven or market-driven, as explained below:

- Technology-driven development. The mindset of advancing what is believed to be relevant technology without a clear vision for the eventual or practical use of that technology. This is a supply-based perspective - - "if we build it, customers will discover the value."
- Market-driven development. The mindset of developing devices that meet a clearly defined set of customer needs and/or solve specific customer pain points. This is a demand-based perspective, i.e. "the market will buy what the market needs."

There are pros and cons to each of these mindsets. One obvious advantage to designing a device and its features around customer needs is that these products tend to meld with established workflows for patient care. As such they can be more readily integrated by facilities and accepted by end-users who may be reluctant to change the way they work. A disadvantage of this approach can be that it results in incremental improvements to the same bedrock technologies, rather than spurring true breakthroughs. Further, a buyer or enduser may not be able to articulate that they have a need for something new until they have actually seen or experienced it. It may actually take putting a prototype in their hands before they truly see the benefits.

Countless numbers of successful medical devices have arisen from both approaches and there is no one "right" approach. Start-up and early-stage device companies often spring from new scientific or technological discoveries that have the potential for healthcare application. Conversely, established medical device companies, who are frequently more risk averse and depend on a steady stream of new product releases, tend to favor need-based, market driven approaches.

It is also very possible for new product development processes to incorporate a mix of both approaches. Within medical device companies, R&D departments can be given

Table D1. Common Biological Signals.

Type of Signal	Description	Examples
Bioelectric	An electric potential produced by a biological function	Signals produced by nerve or muscle cells
Biomechanical	Sound waves produced or transmitted by a biological function	Flow of blood in an artery
Biochemical	Mechanical functions such as motion, displacement, pressure, or fluid dynamics in a biological system	Blood pressure; Volume expansion of the lungs
Bio-optic	Visual properties of a biological system	Blood hemoglobin concentration based on color
Bioimpedance	Measurement of how electric current passes through the body	Galvanic skin resistance; Respiratory rate measurements

C. Medical Device Design & Development cont.

Table D2. Medical Device Development Process

Steps in Medical Device Development Process			
1. Concept Development & Market Analysis	a) Identify Market Need	b) Execute Proof of Concept Studies	c) Define Regulatory Status
2. Prototype Development & Feasibility Testings	a) Define Device Requirements	b) Complete Preliminary design	c) Build and Test Prototypes
3. Design Verification & Validation Testing	a) Identify Design Changes	b) Define & Execute Test Cases	c) Complete Verification Protocols
4. Final Design Validation, Transfer to Production	a) Develop Product Work Instructions	b) Complete Pilot Production Run	c) Validate Production Process
5. Product Approved, Full Market Launch	a) Obtain Regulatory Approval	b) Begin Full Scale Production	c) Initiate Sales to Customers

the leeway to develop technology within a loosely structured framework to see what might be possible. These are often referred to as innovation labs. At the same time, the product development teams (e.g. Product Managers and Project Engineers) can focus on market-driven approaches and providing solutions that address specific customer needs.

Medical Device Development

The product development process for medical devices is long, strenuous, and meticulous. The guidelines enforced by government regulatory bodies must be strictly adhered to in order to ensure each device that is approved for market is safe, functional, and beneficial to patients. Figure D1 shows the five main steps for successful medical device development and product launch.

Concept Development & Market Analysis

Before engineers can begin designing or manufacturing a device, they must understand what the product will be used for. Identifying a market need is essential for successful device commercialization; it makes little sense to design and build something if no one is ever going to buy it! Thorough market research and analysis before prototype development can shape an initial idea into a complete vision for a product, how it will be used, and who will use it.

MEDICAL DEVICE MARKET RESEARCH

Because engineers, through their training, may not have had much exposure to market research, this provides a brief overview of the methodologies commonly utilized by medical device companies. These methods can be used both early in the product life cycle to identify needs, and during future stages of development to prioritize specific features.

C. Medical Device Design & Development cont.

1. Quantitative Research Methods
   a. Analytics. For most developed countries, a wealth of data exists on patient demographics, diagnoses, procedure volumes, reimbursement, and outcomes. This data can be mined to spot macro and micro trends and needs in the marketplace.
   b. Customer Feedback. A variety of mechanisms exist to get direct feedback from potential customers including closed-ended surveys, correlational research, and comparative research. One commonly used example of comparative research is conjoint analysis, which helps identify customers' relative priorities and price-value perceptions.

2. Qualitative Research Methods
   a. Open-ended Customer Feedback. These methods include focus groups and 1-on-1 interviews. While discussions can be guided, the potential customer is free to elaborate as they choose. This can be valuable in early market research to capture the customer mindset and big picture priorities. A company's sales reps or distributors can also be surveyed as they should be closely familiar with the needs of their customers.
   b. Observational Research. Simply observing doctors, nurses and other clinicians doing their jobs in their natural environment can reveal valuable pieces of information including tendencies, time consuming activities, and other things they might not even be aware of when responding to a survey or interview question.

While conducting market research, it is critical to maintain objectivity and not become emotionally enamored to a project. Always avoid the pitfall of seeking out information that justifies a product development project for the sake of keeping a project alive. To avoid this pitfall, many medical device companies use outside market research companies for all or some of their research needs.

Prototype Development, Feasibility Testing

Once the concept development is complete, specific requirements for the device can be defined. These requirements specify the required function of the device, the user-interface, the size and shape, and any design constraints. This allows engineers to begin making decisions about how they are going to design and build the device. Then, they can develop proof-of-concept prototypes to test their idea and attempt to obtain accurate and repeatable measurements. Testing in this phase is typically done in a simulated, laboratory environment. Finally, the design history file (DHF) is created in this phase to store all files regarding the device's development and testing. Proper documentation and organization are essential for successful medical device development.

Design, Verification & Validation Testing

After the core technology is proven to be functional through feasibility testing, more design work is done to address the rest of the device requirements. In this phase, engineers design and build a true prototype of what they envision the device to be. This allows for rigorous verification and validation testing of the prototype device to

C. Medical Device Design & Development cont.

make sure that it satisfies all the requirements, provides accurate measurements, and is safe for the user. If applicable, animal trials are used to assess device performance.

Final Design Validation, Transfer to Production

The device's design is finalized once it has passed all initial verification and validation testing. If applicable, clinical trials are performed in this phase to assess how the device will function in the intended use environment. Additionally, most companies are ready to submit their design and completed design history file to the regulatory body or bodies in the region which they plan to market and sell their product. A summary of the main global regulatory bodies can be found in Table 2 below. The company now must prepare their device to enter production which involves defining and validating their production and quality processes. These must confirm with ISO 13485, the medical device life cycle quality management standard.

Example Home Hemodialysis Monitor

Concept Development for a Home Hemodialysis Monitor	
Use Cases: s Patients with kidney disease requiring regular extracorporeal blood cleansing, for whom home treatment eliminates economic and lifestyle barriers associated with treatment at dialysis clinics and hospitals.	
Market Considerations	What other home dialysis solutions are on the market (e.g. peritoneal dialysis) and what needs do they fail to satisfy?
Economic Considerations	How does the price compare to other home treatments and what are the cost savings are compared to treatment at a clinic?
Environmental Considerations	What types of conditions should be considered for use of the device in the home (e.g. temperature, internet access, power, etc.)? How is waste fluid handled? How will the device be cleaned and maintained?

Table D3a. Identifying the use cases is critical to understanding how the device will be used and what functionality it should have. Additionally, the market, economic, and environmental consideration will help define the market and regulatory strategies for the device.

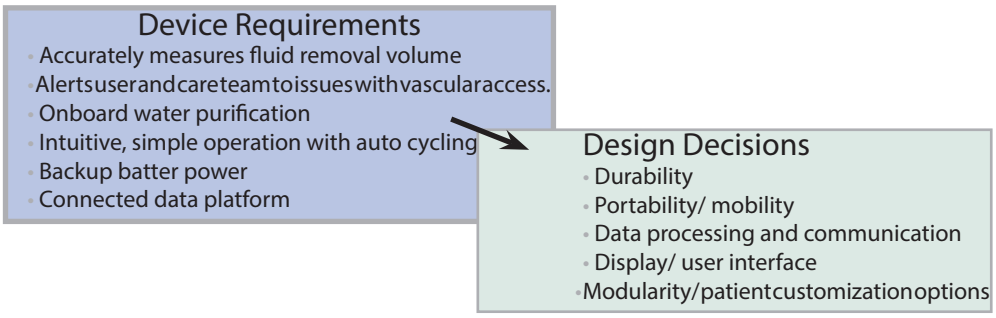


Fig. D1. Graphic shows the defined device requirements for a home hemodialysis system based on the market analysis performed in the concept development phase. For example, it was identified that this device may be used by someone in the home who needs to monitor their blood pressure regularly. This person could be elderly, weak or disabled. Therefore, several of the requirements emphasize this device must be lightweight and easy to use. This will help engineers make decisions such as which material to use, how the device will be powered, etc.

C. Medical Device Design & Development cont.

Table D3. Agencies in major countries who are responsible for device development.

Medical Device Regulatory Authorities in Major Countries		
Country	**Authority**	**Description**
Australia	Therapeutic Goods Administration (TGA)	Agency responsible for regulating the supply, import, export, manufacturing and advertising of therapeutic goods.
Canada	Health Canada	Reviews medical devices to assess their safety, effectiveness, and quality.
China	National Medical Products Administration (NMPA)	The Chinese agency for regulating drugs and medical devices (formerly the China Food and Drug Administration or CFDA).
Europe	European Commission Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs	The Medical Devices Unit provides detailed on-line information about the legal framework for access to the European market as well as trade relations in the medical devices sector within the European Union.
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	The Japanese government agency in charge of reviewing drugs and medical devices, overseeing post-market safety, and providing relief for adverse health effects.
Russia	Russian Ministry of Health	Agency that regulates all medical devices under Resolution 1416.
South Korea	Ministry of Food and Drug Safety	Agency responsible for ensuring the safety and efficiency of foods, pharmaceuticals, medical devices and cosmetics.
United States	U.S. Food and Drug Administration of US Dept of Health and Human Services	Responsible for the safety regulation of most types of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products, and cosmetics.

References:
1. https://www.fda.gov/medical-devices/cdrh-international-programs/international-medical-device-regulators-forum-imdrf;
2. https://www.regdesk.co/resourcelibrary/
3. https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/global-regulatory-authority-websites
4. https://www.raps.org/regulatory-focus™/news-articles/2015/4/
5. wikipedia.org

Product Approved, Full Product Launch

Once the device's regulatory submission is approved, full production can begin. The company must offer appropriate training and sales support for their device, if applicable. Post market surveillance, process improvements, and maintaining ISO 13485 standards are ongoing tasks that the company will be responsible for while their device is on the market.

Weighing the Cost Benefit of a New Biomedical Device

The cost of healthcare in many parts of the world is rising at an unsustainable pace. Device manufacturers and health care facilities and governments are increasingly looking to justify any increase in device costs with improvements in clinical or financial outcomes. As Terri Wells notes in Medical Device Marketing, "Window-dressing product changes with insubstantial benefits and higher prices are quickly losing ground" in the marketplace.

C. Medical Device Design & Development cont.

Fortunately, there are ever increasing opportunities to accomplish both innovation and cost reduction. Clearly, technology is providing unprecedented opportunity to innovate, with advancements in areas such as micro processing, sensing technology, molecular biology, and cell generation. At the same time, technologies such as predictive analytics and telecommunication are allowing for care to become more standardized and practiced in lower cost settings by lower cost staff. Surgeries once delivered in the OR can be provided in Ambulatory Surgery Centers. Dialysis has migrated from the hospital, to clinics, and is now poised to enter the patient's home. Chronic conditions can be managed with inter-connected ambulatory devices. As stated in The Innovator's Prescription, the medical device industry "must play a pivotal role in the disruptive transformation of health care, because they supply the technological enablers that allow lower cost venues of care, and lower cost caregivers, to do more and more remarkable things."

Fig. D2. ISO13485 Quality Management System. Reference: https://www.process.st/iso-13485/

D. Applications

Transonic advances liquid flow measurement innovations from early R&D research, through device development and pre-clinical validation to production of standard-of-care biomedical devices.

Gold Standard Life Science Flow Solutions

- Non-invasive tubing flow & vascular measurements for pre-clinical studies in a broad spectrum of applications
- Pressure volume (PV) measurements define cardiac function in pre-clinical studies
- Implantable telemetry for flow, pressure

Extensive Experience in Medical Device Product Design & Development

- Advanced R & D capabilities
- High experienced flow measurement engineering team
- Extensive knowledge of healthcare regulation & FDA approvals

World Class Manufacturing Capabilities

- ISO-certified manufacturing facility, Ithaca, NY
- A highly skilled workforce with state-of-the art asutomation
- Rigorous compliance to quality control standards

Scientific Research

▽

Device Development

▽

Pre-clinical Validation

▽

Full-scale Prodcution

D. Applications cont.

Research Applications - Mock Circulatory Loops (MCL)

Mock Circulatory Loop (MCL)

The preliminary step in cardiovascular device development is testing with an in vitro mock circulatory loop (MCL). MCLs are mechanical representations of the human cardiovascular system and are comprised of tubing flow channels, compliance chambers, a pump or method to circulate reservoir blood analog liquid in a manner that mimics the arterial and/or venous circulatory system for the purpose of understanding blood flow, pressure and impedance. If well developed, the MCL can be created for any arterial configuration to study cause and effect of blood flow and pressure resistance changes in a physical model that can be monitored with flow and pressure transducers 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.

If well designed, the real time monitoring of flow and pressure in the MCL gives hands-on feedback to manipulations of the cardiovascular system and serves as a platform for testing proof of concept of a therapeutic device. This can accelerate device development by allowing bioengineers to obtain data on device performance and adjust their design, as necessary, before proceeding to animal trials. This leads to safer testing in both animal and human subjects.

MCLs are mainly used to test cardiovascular devices such as pumps, artificial heart valves, stents and ventricular assist devices. However, they can also be used to test prototypes across a spectrum of applications including artificial kidneys, lungs and other organs. Not only are MCLs used to test novel devices, but they also are used as a safe and low-cost training platform for clinical students. Normal and abnormal

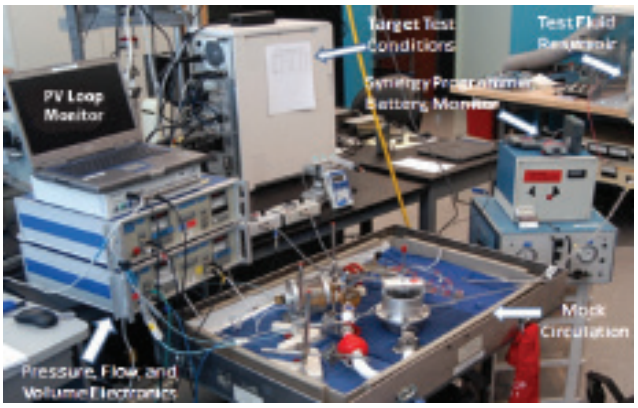


Fig.E1:ALVADmockcirculatoryloop.Photo:GeorgePantalosMD

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.

In 2019, MCLs have been used to test: a computational modeling framework for device testing, a controller for dual rotary VADs, levitated centrifugal blood pumps, the effect on a LVAD inflow cannula angle, iron dextran infusion in a VAD patient, a tipless inflow cannula design with the EVAHEART LVAD, and pressure and flow properties of extracorporeal membrane oxygenation (ECMO) drainage cannulae.

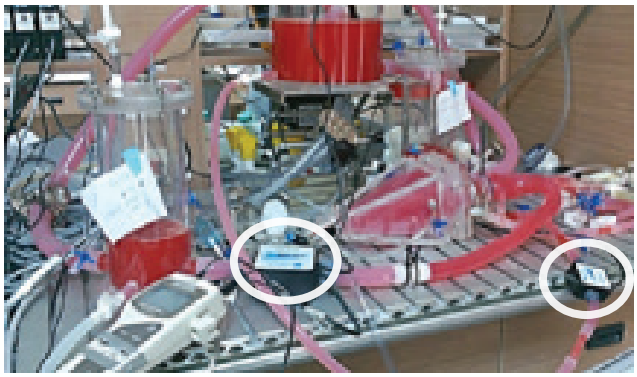


Fig. E2: Mock Circulatory Loop Model for simulating cardiovasculardynamicsonthebench.Inlinesensors are circled. Photo credit: Dr. Chi-Hsiao Yeh, Chief for Dept. of Surgery in CGMH, Keelung, Taiwan

D. Applications cont.

Research Applications - Mock Circulatory Loops (MCL)

Transonic Solutions

Transonic flow sensing technology is used in MCL models to measure volume flow through the circuit. Transit-time ultrasound measurements give researchers a value in mL or L/min for the flow volume moving through the circuit. This allows them to report quantitative data on device performance which is required when authoring formal reports, academic papers, regulatory submissions, and more. Transonic Inline and Clamp-on Tubing Flowsensors can be used with most blood analogs (various glycerine/water concentrations) that are used to characterize pump or device performance under various viscosity conditions. These flow media may contain nanoparticles or microbeads that are used to image flow profiles to study pump shear concurrently with output performance. Transonic Flowsensors also measure flow over a wide dynamic range to fully resolve characteristic flow waveforms from a pulsatile pump.

Transonic Tubing Flowsensors are available in multiple sizes to fit virtually all common laboratory tubing and can be calibrated for up to four distinct operating conditions (fluid type, temperature) to allow for increased system flexibility. Onboard flow gain adjustment allows the bioengineer to recalibrate the sensor on-site for alternate conditions and increased precision.

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 "pulse duplicator" pump devices produce a systolic wave pattern with up to 30 L/min peaks and diastolic flow to zero showing valve closure to test performance of replacement aortic and mitral heart valves under the hydrodynamic flow conditions found in the heart reproduced on the bench. The FDA has stringent test requirements for heart valves including regurgitant fraction (low leakage values < 200 ml/min), 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 (examples: St. Jude, Edwards, Medtronic, Abbott). High resolution instantaneous flow measurement synchronous with pressure waves are required to characterize valve function in the pulse duplicator throughout the cardiac cycle.

Transonic Inline Tubing Flowsensors are well designed for this purpose and are now integrated into some of the commercially available pulse duplicator test devices on the market including systems from BDC Laboratories (USA), Lifetec Group (Netherlands), Medical Implant Test Lab (USA). Transonic's high fidelity, low and stable zero offset specifications together with the modern pulse duplicators utilizing wave form analysis software with video capture and playback are now able to reproduce these dynamics and document valve performance criteria and leaflet kinematics.

VAD (Ventricular Assist Device) & Pump Testing:

The purpose of a VAD or bypass pump is to augment, relieve or replace the human heart's pumping action for short or extended periods 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. Transonic plays a well established role in this market with its Tubing Flowsensors used at all phases of the device development including design, validation, and also in LCT (Life Cycle Testing) where Transonic Flowsensors independently measure pump outputs 24/7 to monitor pump performance. Performance data is supplied to the FDA annually.

D. Applications cont.

Research Applications - Specialized Models

Flow Phantoms (Fluid Dynamics/Physics Labs):

These 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, Transonic 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 glycerin (typically 35 – 55%) to water. Some solutions also include concentrations of salt. All these additives can have an effect on the timing of ultrasound signals and sensor calibration must be performed with the actual fluid to ensure the most accurate calibration.

Bioreactors, Cell Culture & Regenerative Medicine:

Bioreactors are simply environmental soup-pots 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 to the cells. TEVGs are an emerging technology that use biologic materials (collagen, gelatin, elastin or fibrin) or synthesized material from Poly glycolic acid (PGA), poly lactic acid (PLA), or poly glycerol sebacate (PGS) to form biodegradable scaffolding or extracellular structural matrix onto which cells are seeded and provided growth factors or other stimulation to grow living replacement arteries and veins. Research in this area seeks to provide an alternative to synthetic vascular graft prosthetics based on polyethylene terephthalate (Dacron®) and polytetrafluoroethylene (e-PTFE®) grafts used widely in revascularization surgeries, coronary bypass graft (CABG) surgery, and peripheral artery disease. These nonbiological grafts suffer from poor patency and thrombosis in small diameters and do not grow with the recipient, so use in pediatric applications is severely limited.

Regenerative Medicine is in its infancy using in vitro laboratory techniques to discover and develop a recipe that can "produce biocompatible implants with the ability to repair, remodel, grow and regenerate."[1]

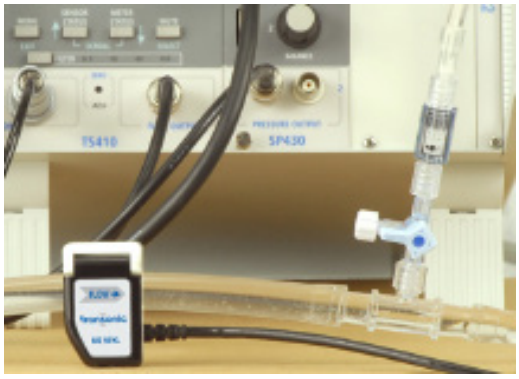


Fig. E3: Mock Circulation Loop: Transonic ME9PXL Clamp-on Tubing Flowsensor with an Inline Transpac IV Pressure Sensor tapped off a stopcock to measure pressure and flow simultaneously in a tubing loop.

Flow measurement plays a pivotal role in the development technique, testing and efficacy of the end product.

1Matsuzaki Y, John K, Toshihiro Shoji T, Toshiharu Shinoka T, "The Evolution of Tissue Engineered Vascular Graft Technologies: From Preclinical Trials to Advancing Patient Care," Appl Sci (Basel). 2019 Apr; 9(7): 1274.

D. Applications cont.

Research Applications - Preclinical *In Vivo* Trials

Preclinical Trials

Device engineering and testing on the bench with tubing MCLs are among the preliminary steps toward development of athe ascending aorta of a pigse in human patients. Bench models can be controlled and tweaked with little oversight, risk and regulatory consequence. Devices destined for clinical use may require in vivo testing and validation using a suitable animal model. These studies are reviewed by an Institutional Animal Care and Use Committee (IACUC), a local working group that research facilities, either university-based or contracted research organization (CRO), must appoint in accordance with the Animal Welfare Act (AWA) and PHS Policy on Humane Care and Use of Laboratory Animals. Preclinical animal trials for medical device testing may be intraoperative only and short-term, or long-term to allow implantation of a device to study and validate its efficacy and effectiveness in live conditions that are much less controlled.

Animal studies allow investigators to benchmark the direct targets of a medical device, in addition to their functional operation without endangering human lives. Through the use of Flowprobes, pressure sensors, ECG and other instrumentation, measurements can be made to access the effect of a device on cardiac output, organ blood flow, peripheral circulation, vascular resistance and a host of other indicators that would determine whether a device is safe for use and effective.

Transonic Solution

Flowprobes may be implanted on the outlet graft of a VAD to validate whether pump blood flow output is accurate and delivers blood flow volumes as specified. In addition, Flowprobes can also be implanted around peripheral vessels to ensure that the blood flow delivery to the rest of the body is adequate. Perivascular Flowprobes can evaluate heart valve replacement therapies and stent deployment protocols.

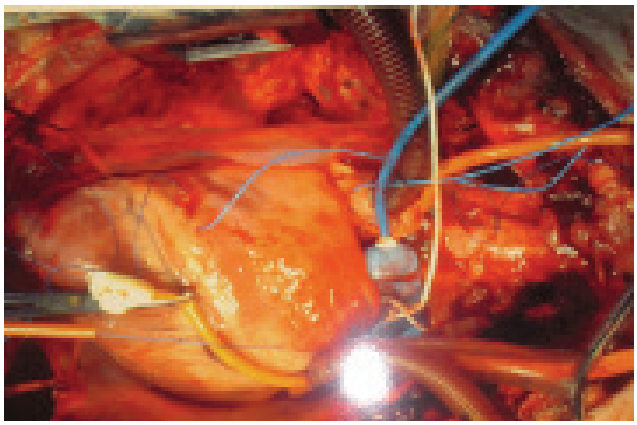


Fig. E4: Transonic PAUCOnfidence Flowprobe implanted on a the ascending aorta of a pig during a pre-clinical in vivo trial at Columbia Presbyterian Hospital in NYC.

Transonic Perivascular Flowprobes are available in sizes from 0.5 mm to 36 mm diameter for arteries/veins and have been used in acute intraoperative and chronic implantation studies from weeks to years in a variety of animal models including bovine artificial heart and heart assist models, porcine heart failure models, as well as in rodent discovery studies.

E. Applications

Research Application - Silicone Vascular Models

Silicone Vascular Models

With the proliferation of 3D printing techniques and complex MRI recordings of true to life vascular configurations from patient data, a new kind of vascular model has emerged. Silicone vascular models can now be made with anatomical accuracy. Coupled with a pulse duplicator and measurement sensors, the MCL can now be utilized for new kinds of study that investigate device interactions with simulated vessel structures such as catheterization techniques and intravascular devices that deploy stents or valves.

Anatomical vascular models also provide new opportunities to train surgeons and medical staff with low risk methods without the ethical dilemma of animal sacrifice. All of this is possible as long as the devices and measurement tools can provide appropriate physiological simulation and feedback.

Transonic Solution

An interesting conundrum of the anatomical vascular model is the fact that most tubing sensors are modeled after MCL (Mock Circulatory Loop) construction where economy of tubing is less important. Clamp-on and Inline Flowsensors are big, bulky and require a minimum length of straight tubing to fully develop a laminar flow. This is not appropriate for the anatomical model. Instead, Transonic Perivascular Flowprobes fit the simulated vessels like those native vessels for which they were designed. Low profile probes can slip around short or close anatomical structures. There are some nuances to make the acoustic coupling work but that is the nature of research and bioengineering design. By understanding tools and technology, the research bioengineer can adapt the tool to fill the need. Custom Transonic PAU-Series Perivascular Flowprobes can provide the same dynamic range for pulsatile flow measurement in a limited space environment on thin walled silicone tubing, as they would be used on living tissue structures.

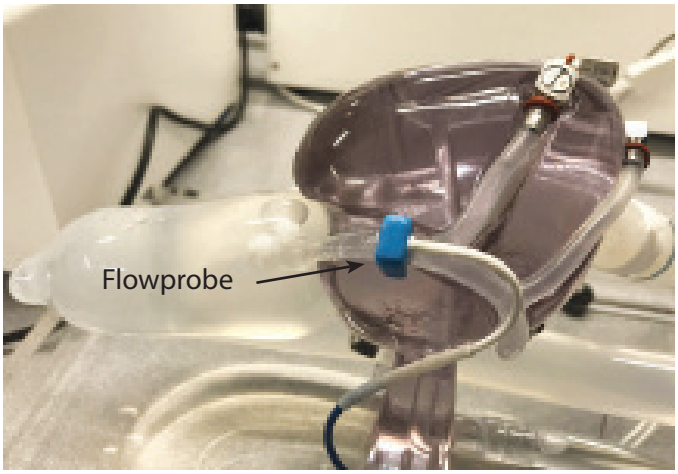


Fig. E5: New anatomically correct models of the cardiovascular system made from silicone are becoming increasingly applicable for various flow dynamics studies where pumps can be integrated to supply true pulsatile flows generated from actual physiological data. The above photo shows a Transonic Perivascular FLowprobe measuring flow in the Right Coronary Artery (RCA) of a simulated heart model from BDC Laboratories.

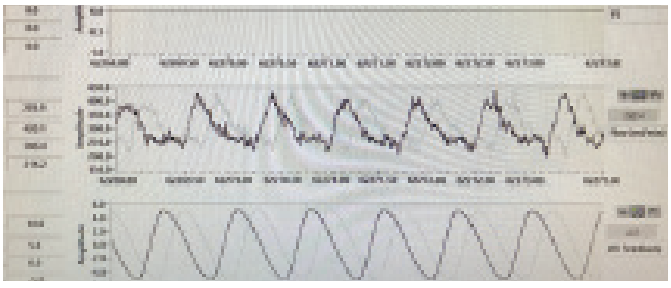


Fig. E6: Right Coronary Artery (RCA) flow (top trace) and pressure (bottom trace) in a silicone simulated heart model.

E. Applications cont.

Research Application - Early Stage Artificial Organ Research

Artificial Organ Research

The development of functional, affordable, and safe artificial organs has been a popular topic in medical research for many years. As of March 2020, 112,000 individuals were on the waiting list for an organ in the United States alone, and each day 20 people die waiting for a transplant. The potential impact of commercially available artificial organs is substantial; this would eliminate the need for donor hearts, lungs, livers, and kidneys and would dramatically decrease the time that an individual must wait for a life-saving organ transplant. Additionally, artificial organs may decrease overall medical costs because patients would no longer need to rely on bridge-to-transplant treatments (e.g. dialysis, ventricular assist device circulatory support, ECMO) for extended periods of time while they are waiting on a transplant.

Despite all the benefits that artificial organs offer, there is still a great deal of risk in using such devices and it is crucial that they are tested extensively before they are used clinically in humans. Mock circulatory loops are an invaluable tool to test artificial organs in vitro since they can closely mimic the human circulatory system and can identify potential problems with the artificial organ during bench testing. Once benchtop testing has been successfully completed, animal trials are performed to test the use of the artificial organs in vivo. Data collection during benchtop and animal testing is absolutely critical; accurate and reliable data must show device success before the artificial organ may be eligible for clinical trials in humans.

Transonic Solution

Transonic was conceived 35 years ago with a mission to "advance meaningful measurements" in medical research. Today, Transonic's Flowmeters and Flowsensors are used in a multitude of applications to quantify blood flow and other important flow parameters. This is especially prevalent in new devices such as artificial organs including artificial lungs, artificial hearts and artificial wombs. In all cases, Transonic technology helped researchers assess the efficacy of the device under test by providing accurate, quantitative measurements, which has brought these devices one step closer to clinical use.

https://www.organdonor.gov/statistics-stories/statistics.html

American Society for Artificial Internal Organs (ASAIO)

ASAIO is an organization of individuals and groups that are interested in artificial internal organs and their development. It supports research into artificial internal organs, publishes a peer-reviewed ASAIO Journal six times a year and holds an annual meeting that attracts industry, researchers and government officials.

ASAIO offers a venue for young investigators to start building their careers; it is home for seasoned visionaries and entrepreneurs; and a crossroads where science, engineering, industry, regulatory & clinical practice intersect.

At ASAIO, young and senior investigators have a unique opportunity to present new innovations that may portend future medical technologies that challenge today's conventional and current clinical treatment paradigms. Since its founding in 1955 the Society has been and continues to be an engine for promoting and facilitating innovation in medical and biological technologies.

D. Applications cont.

Clinical Application - Mechanical Circulatory Support

Introduction

The fist-sized human heart is an incredibly precise pump. To be exact it is two pumps separated by a wall down the middle and encased in a single sheath of muscle. Each side has two chambers, a receiving tank atrium and a ventricle pump. The right side sends blood gently to the lungs, while the left side pump propels five quarts of oxygen-rich blood per minute throughout the body. The heart beats 2.5 billion times in a 70-year-old person's life.

Although the two pumps within the heart must exert significantly different forces, their synchronous beat ensures that blood flow is smooth and continuous. When blood flow no longer is smooth and continuous, heart failure ensues and the heart's action must be augmented. Mechanical circulatory support (MCS) is one strategy used to help a failing heart pump.

The need for mechanical circulatory support for heart failure is daunting. There are an estimated 5.7 million Americans with heart failure. That number is expected to increase to over eight million by 2030[1]. Of these, nearly one million have end-stage heart failure and are no longer responsive to maximal medical therapy.

The ultimate and ideal goal for these patients is to receive a heart transplant, but in actuality only 2-4% will receive a new heart. Many will die waiting for a transplant. In the interim, many of these patients depend on a variety of mechanical circulatory support devices to improve their cardiac outflow, hemodynamics, and tissue perfusion.

A host of mechanical circulatory support devices are now available. Temporary devices include the intraarotic balloon pump and the bypass pump, both used during cardiothoracic surgery, ECMO systems for more extended heart and/or pulmonary bypass, and percutaneous ventricular assist devices (pVADs). Longer term solutions for heart failure include implantable VADs and total artificial hearts first pioneered at the University of Utah.

All these devices attempt to augment, replace or restore the function of the body's most essential pump, the heart. They pump blood flow. Therefore, their flows must be accurate and verified. Tubing flow measurements with Transonic's highly accurate Tubing Sensors fill this need.

The following pages will address four mechanical circulatory support devices and modalities: the heart bypass pump, extracorporeal membrane oxygenation (ECMO), temporary and permanent ventricular assist devices (VADs) and the artificial heart.

Reference

[1]*Ergle K et al, Ochsner J 2016; 16: 243-249.*

D. Applications cont.

Clinical Application - MCS CP Bypass

MCS: Cardiopulmonary Bypass Pumps

A cardiopulmonary bypass (CPB) pump, often referred to as a heart lung machine, temporarily takes over the function of the heart and lungs during surgery. This enables the surgeon to operate in a bloodless surgical field. The CPB pump was first used by Dr. John H. Gibbon, its developer, in 1953 during successful open heart surgery. Now used during coronary artery bypass grafting (CABG), heart and lung transplantation, and numerous other cardiothoracic surgeries, the heart lung machine has become a fixture in any modern operating room.

Fig.E7:PerfusionistoperatingCPBypassPump.

Transonic Solution

The true volume flow through a CPB pump can be measured using Transonic's gold standard transit time ultrasound technology. Transonic's system uses a clamp-on tubing Flowsensor and can provide noninvasive, sterile measurements without any contact with the fluid or interruption of tubing. It has a stable and low zero offset, and calibration can be adjusted on site. Air bubbles as small as 20% of the tubing inner diameter can also be detected using transit time ultrasound. Bubble detection algorithms can be integrated into the heart lung machine to create an alarm or stop the pump when bubbles are identified in the tubing circuit. The data obtained from the Transonic system can help perfusionists and other clinicians optimize flow, detect early warning signs of adverse events, and improve patient outcomes.

D. Applications cont.

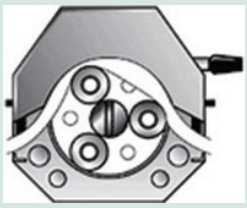
The Need for Mechanical Blood Pumps

The heart is the ultimate blood pump, but in many procedures such as cardiopulmonary bypass (CPB), hemodialysis, and extracorporeal membrane oxygenation (ECMO), mechanical pumps are necessary to maintain adequate blood flow throughout the external tubing circuit and the body. Two major risks of pumping blood through a mechanical device are thrombosis (clots) due to contact with the foreign material of the pump and hemolysis (destruction of red blood cells) by running the pump at high speeds. Therefore, it is critical that pumps for medical applications are designed and operated to minimize these risks.

Types of Blood Pumps

Roller (Peristalic) Pumps

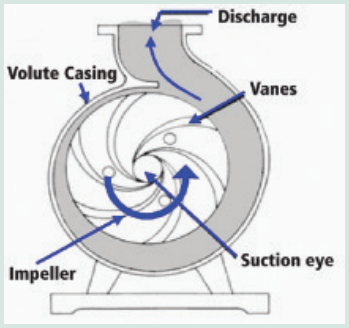
Roller (peristalic) pumps operate by positive displacement. A moving roller compresses the tubing and pushes blood through the circuit. This action is similar to how the gastrointestinal tract moves food through the body. Single roller pumps can produce pulsatile flow while double roller pumps produce a more continuous flow profile. Roller pumps are used in many applications such as hemodialysis and CPB.



Roller pump

Centrifugal Pumps

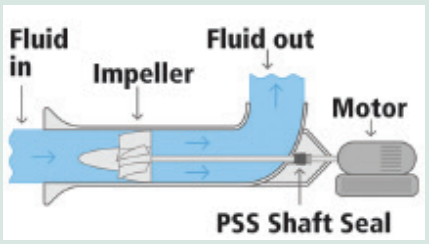
Centrifugal pumps use a rotating impeller to move blood through the tubing circuit. The pressure gradient caused by the impeller pulls blood into the pump inlet, then forcefully ejects it through the outlet. Centrifugal pumps typically produce continuous flows, although they have been configured to create pulsatile flows as well. They are widely used in heart-lung machines, ventricular assist devices (VADs), and ECMO systems.



Centrigual pump

Axial Pumps

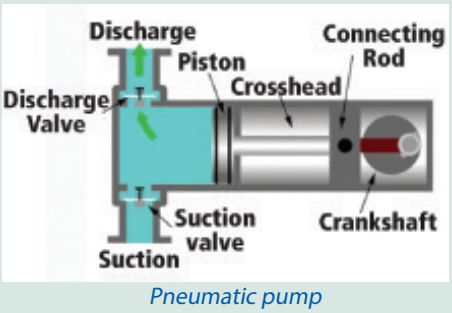
Axial pumps are advantageous due to their small size and simple design. They consist of a small cylindrical channel with an impeller suspended in the middle of the channel (sometimes magnetically). Blood is drawn in and then ejected along the same axial direction, unlike centrifugal pumps that eject blood at an angle perpendicular to where it was received. Axial pumps are being used in several early stage ventricular assist devices and total artificial hearts.



Axial pump

Pneumatic or Hydraulic Piston Pumps

Pneumatic or hydraulic piston pumps have become popular in research applications due to their ability to provide a more natural pulsatile flow profile. A piston actuator is powered by air or water and pushes blood through the tubing circuit in bursts. This is very similar to the physiologic function of the heart and is a promising solution for future mechanical circulatory support devices.



Pneumatic pump

D. Applications cont.

The Need for Mechanical Blood Pumps cont.

Pumps for Infusion

Unlike blood pumps which are designed to support the circulatory system, infusion pumps are designed to infuse fluids into the blood stream. The FDA defines an infusion pump as "a medical device that delivers fluids, such as nutrients and medications, into a patient's body in controlled amounts." Infusion pumps such as insulin pumps are in widespread use in clinical settings such as hospitals, nursing homes, and even in ambulatory and home settings.

Infusion Pumps

Infusion pumps are generally classified into large volume pumps and small volume pumps. Large volume pumps are typically used for fluid replacement (e.g. saline solution), medication delivery (e.g. antibiotics) or nutrition (e.g. solutions designed to feed patients who are not able to eat). Large volume infusion pumps are typically roller (peristaltic) pumps. Small volume pumps are used in situations where patient medication needs to be delivered in low flows and/or small doses. Typically, small volume pumps utilize a computer-controlled motor turning a screw that pushes a plunger, similar to a syringe.

Estimated Versus True Pump Flow

The true flow moving through the pump is an essential parameter to know for mechanical circulatory systems. Volume flow can be estimated using the RPM pump setting and the known pressure differential across the pump. However, this can often be inaccurate due to occlusions in the pump or circuit, recirculation, or leakage. Transonic flow measurement technology measures the true volume flow and can be used in conjunction with the pump settings to confirm that the system is running correctly. If there is a discrepancy between the true flow and estimated flow, clinicians can be alerted that there could be an issue with the system or the patient.

https://citoday.com/articles/2019-jan-feb/the-next-wave-of-mechanical-circulatory-support-devices
https://www.sciencedirect.com/topics/engineering/roller-pump
https://www.sciencedirect.com/topics/nursing-and-health-professions/centrifugal-blood-pump

D. Applications cont.

Clinical Application - MCS: ECMO

MCS: Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) is the use of prolonged extracorporeal cardiopulmonary bypass (CPB) in patients with acute, reversible cardiac or respiratory failure. The use of ECMO in adults increased during the 2009/2010 H1N1 influenza pandemic. Within a day of the flu's onset, a small percentage of adults were struck with rapid, progressive Adult Respiratory Disease Syndrome (ARDS). ECMO was used to allow the patients lungs to rest and recover while they were suffering from this virus. ECMO has also been very popular with the outbreak of the novel coronavirus in early 2020. Patients all over the world who developed ARDS as a result of COVID-19 have received ECMO treatment.

The two most common types of ECMO are veno-arterial (VA) and veno-venous (VV) ECMO. In both, deoxygenated blood is removed from the venous system of the patient and pumped through an external oxygenator. In VA ECMO the heart is also bypassed, and the oxygenized blood is returned to the arterial system and immediately sent through systemic circulation. In VV ECMO the oxygenated blood is returned to the right heart and no cardiac support is provided. Two main risks of ECMO procedures are recirculation and clot formation.

Recirculation occurs when oxygenated blood returned to the patient by the inflow cannula is immediately pulled into the outflow cannula and taken back through the ECMO circuit. This reduces the amount of oxygenated blood that reaches the patient and can cause adverse effects if it is not addressed quickly. Recirculation can occur due to poor cannula positioning, incorrect pump settings, or low cardiac output due to hypovolemia or cardiac failure. Identifying recirculation quickly and accurately alerts clinicians to assess their patient, investigate the cause, and correct the issue.

During ECMO, blood from the patient is removed from the body and circulated through a pump, oxygenator, and tubing before returning. All this foreign material introduces opportunities for the patient's blood to react and start to form clots in the ECMO circuit, especially in the oxygenator. If these clots break free from the oxygenator and travel to the patient, they could cause partial or complete blockages of the patient's blood vessels which introduces a risk of stroke, myocardial infraction, and death.

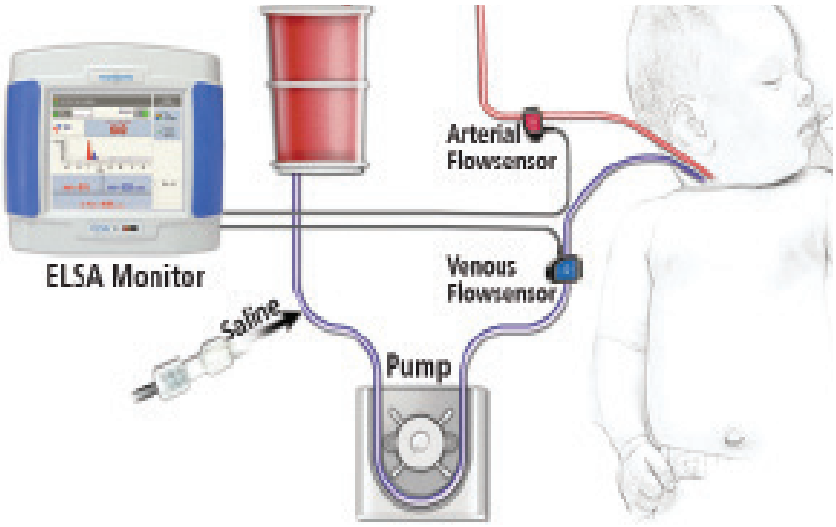


Fig. E8: Schematic of ELSA® System connected to an pediatric patient showing placement of arterial and venous sensors and cannulas in the jugular artery and vena cava.

D. Applications cont.

Clinical Application - MCS: ECMO

Transonic Solution

Transonic's Transit Time Flow (TTFM) measurement technology can accurately calculate delivered flow in the ECMO circuit. This allows clinicians to know exactly how much of the patient's blood is oxygenated. Transonic also uses ultrasound dilution technology to quantify recirculation as a percentage of the delivered flow by injecting a saline bolus upstream of the arterial Flowsensor. The concentration of the saline bolus is recorded by the arterial Flowsensor and compared to the concentration recorded on the venous Flowsensor. The ratio of venous concentration over arterial concentration is the recirculation percentage.

Ultrasound dilution technology can also be used to measure the oxygenator blood volume to identify flow limiting factors such as blood clots. A saline bolus is injected upstream of the oxygenator and the transit time it takes to be sensed by the arterial Flowsensor is recorded. The transit time multiplied by the blood flow through the oxygenator equals the oxygenator blood volume (OXBV). This measurement is taken periodically throughout the ECMO treatment. If any OXBV value is significantly lower than the initial OXBV measurement, there may be a clot in the oxygenator and clinicians can be alerted before the clot breaks free and travels to the patient. Transonic's ELSA Monitor clearly displays values for these measurements to assist clinicians in proper ECMO patient surveillance and management.

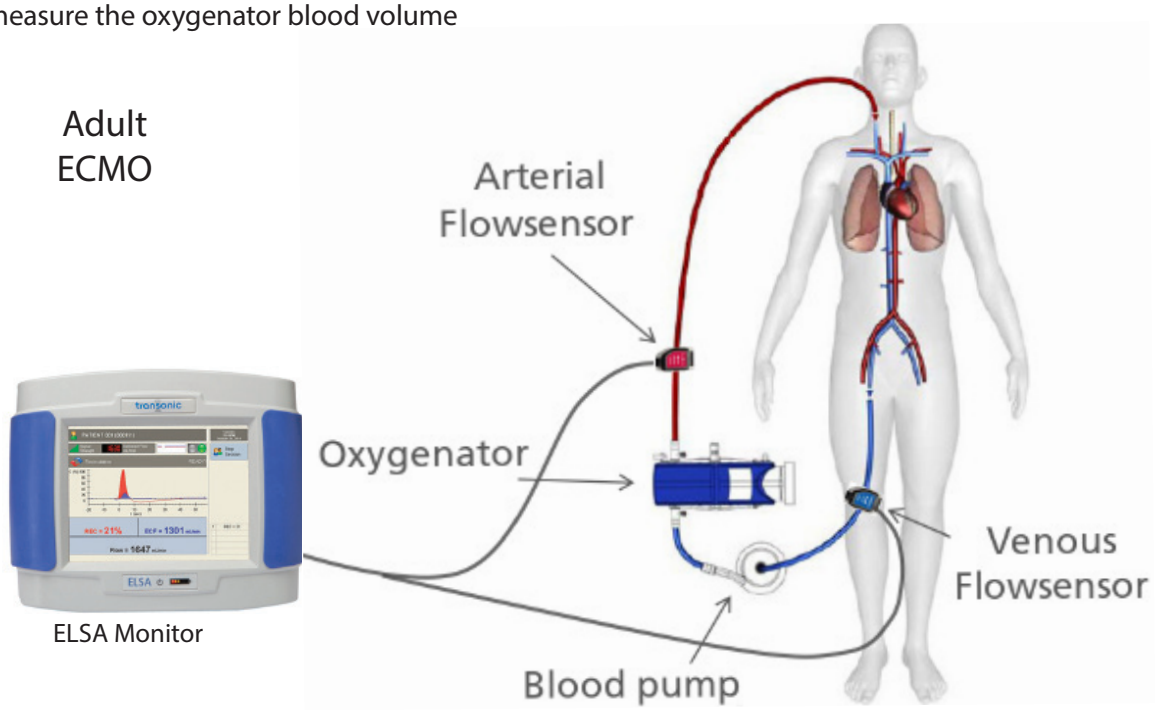


Fig. E9: Schematic of ELSA® System connected to an adult patient showing placement of arterial and venous sensors and cannulas in the femoral artery and vena cava.

D. Applications cont.

Clinical Application - MCS: VAD

MCS: Ventricular Assist Device (VAD)

Cardiogenic shock is characterized by impaired cardiac output leading to reduced systemic perfusion, increased residual volumes in both ventricles and increased cardiac filling pressures. A primary treatment for cardiogenic shock is mechanical circulatory support that increases mean arterial pressure and microvascular perfusion, ventricular unloading and myocardial perfusion. The type of ventricular assist device (VAD) used depends on the patient's degree of cardiac failure, overall health, medical history, size, and age.

VADs can be used to supplement the pumping capabilities of the left or right ventricle. In addition, two VADs, also referred to as BiVADs, can be used to provide biventricular support. Percutaneous VADs are used for short-term treatment following acute heart failure due to heart surgery or a heart attack. They can also be used as a bridge to an alternative long-term therapy. PVADs have a percutaneous catheter that transports blood from the ventricle to an external pump and back. Implantable VADs have a compact pump that is surgically connected to the weakened ventricle and directly pumps blood from the ventricle to the aorta or pulmonary artery. A single percutaneous tube travels through the patient to connect the VAD to an external control and power source.

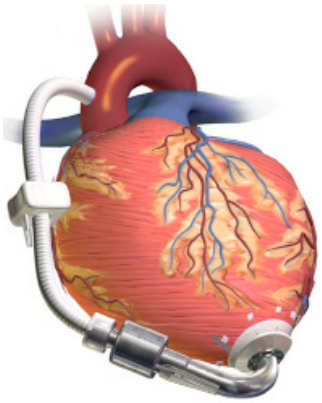


Fig. E10: Customized AU Flowprobe on outflow cannula of HeartAssist 5 LVAD.

Transonic Solution

Transonic's transit time flow measurement (TTFM) can be used for flow verification and confirmation of pump performance. In VADs, the accurate measurement of volume flow is an essential quality control and safety measure. Transonic's compact flow technology allows for the direct integration of a Flowsensor over the outflow graft of the VAD to provide quantitative data of pump performance. Additionally, this technology can be used to detect VAD failures, thrombosis or patient arrhythmias. When integrated into the alert system of the device, Transonic's measurement can detect potential adverse events and alert the patient before they realize something may be wrong.

VAD Development and Transonic

Tansonic history is providentially intertwined with the development of circulatory support and Ventricular Assist Devices (VADs). In 1971, Transonic President Cor Drost was recruited by Dr. Yukihiko Nosé at the Cleveland Clinic to work on projects that included development of centrifugal and axial blood pumps for cardiac assist.

Grant funding fell through and Mr. Drost moved to the NYS School of Veterinary Medicine at Cornell University in Ithaca, NY to work with Professor Alan Dobson to design a more reliable Doppler flowmeter to measure blood flow in conscious animals. There he invented a transit-time ultrasonic flowmeter that has been used in the engineering design and testing of almost every circulatory support device in the last quarter century.

Clinical Application - MCS: Total Artificial Hearts (TAH)

MCS: Total Artificial Hearts

For patients with end-stage irreversible cardiac failure in both sides of the heart, doctors may suggest treatment using a total artificial heart (TAH) as a bridge to transplant or as a permanent solution under an IDE clinical trial if a heart transplant is not an option. A TAH is a mechanical device with two pumps that can provide adequate blood flow through pulmonary and systemic circulation. During surgery, each ventricle is replaced by one of the TAH pumps. One pump is connected to the aorta and the other is connected to the pulmonary artery. Two percutaneous cables connect the TAH pumps to an external, portable power source.

There is a great risk for clotting with the use of a TAH because a large, foreign object is introduced to the circulatory system. Clots that form and break loose in the blood stream could be fatal. Anticoagulant medication is always administered to TAH recipients to decrease this risk. Other complications of TAH implantation include bleeding, infection, and other organ failure. Although this procedure is risky and there is still crucial ongoing care required, total artificial heart implantation can provide cardiac failure patients with an increased quality and length of life.

Fig. E11: Jarvic 7 TAH Photo: wikipedia

Transonic Solution

From the outset, cardiac pioneers such as Dr. Robert Jarvic at the University of Utah and Dr. Michael DeBakey at Houston's Baylor University recognized the need to measure and verify flow in innovative VAD and TAH devices and incorporated Transonic technology in the first MicroMed VADs developed with NASA in the early 2000s. Transonic volume flow measurements can provide valuable information to clinicians and surgeons, including total blood volume flow through each TAH pump and alerts for flow limiting factors such as clots. Transonic technology also plays an essential part in pre-market product testing using mock circulatory loops to optimize design and performance and in LCT (Life Cycle Testing) of the device.

Reference:https://www.nhlbi.nih.gov/health-topics/total-artificial-heart

Fig. E12: Dr. Michael DeBakey holding a TAH in his right hand and a MicroMed VAD in his left. Photo: wikipedia

D. Applications cont.

Clinical Application - Artificial Lung

Artificial Lung

While ECMO is known to be successful in supporting individuals with acute lung failure, it is a less than ideal solution for long-term treatment. The ECMO machine is often bulky, complicated, and has extensive tubing which increases the risk of thrombosis and embolism. Additionally, ECMO treatment usually renders the patient immobile, which leads to other systemic complications and adversely affects transplant recovery. Artificial lungs (ALs) are a new promising bridge-to-transplant device for individuals with end-stage lung failure (ESLF). There has been limited clinical use of artificial lungs, but they have been used in many animal trials to support blood oxygenation. Recent designs of artificial lungs function by drawing blood from the pulmonary artery, running it through an oxygenator, and returning the blood either to a distal portion of the pulmonary artery (PA-PA configuration) or directly to the left atrium of the heart (PA-LA configuration). The movement of blood through the AL circuit is completely powered by the native right ventricle.

A main risk of artificial lung use in the PA-PA configuration is the stress on the right ventricle, which must pump blood through the AL circuit and the native lungs. Because of this, PA-LA configuration has been widely used, although this has a significantly higher risk of thrombosis and embolism. Some recent studies have focused on optimizing the flow resistance of the AL circuit in the PA-PA configuration to decrease the stress on the heart and the risk of stroke or heart attack. If the resistance in the circuit is too high, not enough blood will enter and the patient will not receive the additional oxygenation they need. However, if the resistance is too low, up to 100% of the cardiac output could enter the circuit and the stress on the right ventricle would be extreme.

Transonic Solution

Transonic Flowsensors and Flowmeters have been used in the development of artificial lungs to quantify the exact volume flowing through the AL circuit. Transonic's transit-time ultrasound and indicator dilution technology can also assist with the optimization of flow resistance by measuring the cardiac output and how it compares to the AL flow rate. This information can alert researchers or clinicians if adjustments need to be made to their device. Quantifying these parameters and making meaningful measurements in artificial lung development is crucial to bring these life-saving devices to market.

Fig. E13: Artificial lung, University of Pittsburgh, Pittsburgh, PA.

D. Applications cont.

Clinical Application - Hemodialysis (HD)

Renal Replacement – Hemodialysis

The kidneys filter toxins and waste from the blood and maintain the body's fluid and electrolyte balance. Individuals who suffer from chronic kidney disease (CKD) cannot perform these vital functions properly. Serious complications such as high blood pressure, anemia, weak bones, and heart and blood vessel damage can occur. In such cases hemodialysis may be required to properly filter the blood of its toxins.

Hemodialysis performs the kidneys' function by removing blood from a patient, pumping it through an external filtration system and returning it to the body. This effectively achieves the same result as a functioning kidney by purifying the blood and maintaining the fluid and electrolyte balance. The frequency and amount of dialysis required is prescribed by a nephrologist. In most cases treatment is extremely time-consuming, requiring patients to dialyze for several hours multiple times a week.

Hemodialysis requires a vascular access to connect to the hemodialysis machine. Dialysis patients have three options. The most common are the creation of a native fistula or artificial graft in the individual's forearm. Catheters can be also fed directly into the central venous system although this method is prone to infection and is not preferred. In all cases, these access points will be used repeatedly for dialysis treatment, and adequate blood flow for hemodialysis delivery is paramount.

Transonic Solution

Nephrologists determine a dialysis prescription for each patient which depends on accurate blood flow delivery. However, a dialysis pump's setting often differs from the actual flow due to negative pump pressure effects, the condition of the tubing, vascular access or needle size and placement. These can all result in under-delivery of the dialysis prescription and insufficient blood purification for the patient. Transonic's transit time flow measurement technology provides accurate, real-time measurements of delivered volume flow to ensure that the true value for blood volume pumped through the dialysis circuit is known.

Like ECMO, there is a risk of recirculation through the dialysis circuit. If purified blood is immediately pulled back through the outflow access, unpurified blood that needs to go through the circuit is displaced. The sensitivity of Transonic's ultrasound dilution technology is able to separate peripheral access recirculation from cardiopulmonary recirculation so that zero access recirculation can be measured. This unparalleled measurement has created a new hemodialysis standard. Identification of vascular access recirculation, now considered a late indicator of vascular access dysfunction, allows for on-the-spot correction. Ultrasound dilution technology can also measure vascular access flow directly, and cardiac function parameters that help clinicians identify early cardiovascular problems and avoid sudden cardiac collapse.

Hemodialysis and Transonic

Three decades ago, renown nephrologist Dr. Thomas Depner studied the wear and cavitation of tubing at different pressure pump settings and recognized that actual hemodialysis pump flow can differ from the pump's setting. He requested a way to independently measure delivered blood flow to verify the flow set by the pump during prolonged blood pump procedures such as dialysis and ECMO. This pivotal observation spurred the development of the Transonic Hemodialysis Monitor, which measures delivered pump flow directly using transit-time ultrasound Flowsensors applied to the outside of dialysis tubing. It also led to the incorporation of Transonic Flowboards and Flowsensors into new and innovative dialysis machines.

Ref:https://www.kidney.org/atoz/content/about-chronic-kidney-disease

D. Applications cont.

Clinical Application - Organ Preservation

Organ Preservation

Over 110,000 patients are awaiting a transplanted organ in the United States. In 2018, 35,663 organ transplants were performed. Due to the lack of organ availability, patients die every day awaiting an organ transplant. One of the largest problems with donation is moving the organ from donor to recipient; it must be transported properly to keep it alive and viable until it can be transplanted. Historically, organs were immediately put on ice while they traveled to their recipient. Recently, organ perfusion devices have become popular because of their ability to keep organs as close to their natural state as possible during transport.

The following chart provides the number of U.S. transplants in 2019 and hours of viability outside the body for major organs.
Organ perfusion devices are designed to conform to the organ's natural shape and supply the required nutrient supply to prolong the life of the organ as long as possible so it can be transported further and serve more patients. Extending the viability of an organ even a few hours can have a dramatic impact on the number of potential transplants. Any donated organ that is past its prime ends up going to waste instead of saving lives.

Organ	2019 Transplants	Hours of Viability Outside Body**
Kidney	23,401	24-36
Liver	8,896	8-12
Heart	3,552	4-6
Lung	2,714	4-6
Pancreas	143	12-18

* Source: UNOS
** Source: US Dept. of Health and Human Services

Transonic Solution

Transonic's transit-time ultrasound capability to measure volume flow is an ideal quality measure in organ preservation devices where consistent flow measurements can signal the difference between organ viability and failure. By using these measurements to optimize the perfusate flow, damage to the harvested organ is reduced. Transonic Flowsensors also feature unmatched zero-flow stability, allowing for accuracy at low flow (near zero) rates and can be calculated for non-blood organ perfusion solutions.

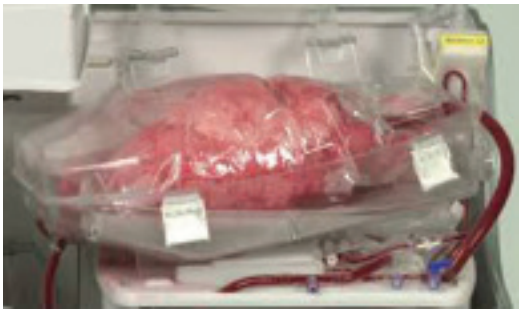


Fig. E14: Lung being preserved awaiting transplant.

D. Applications cont.

Clinical Application - Medicine Delivery / Infusion Pumps

Medicine Delivery / Infusion Pumps

An infusion pump is an automated device that delivers medications, nutrients, and other liquid therapies into a patient's circulatory system. Infusion is generally intravenous, although subcutaneous, arterial and epidural infusions are occasionally used. Infusion pumps can administer fluids in ways that would be impractically expensive or unreliable if performed manually by clinical staff. For example, they can administer as little as 0.1 mL per hour injections (too small for a drip), injections every minute, injections with repeated boluses requested by the patient (up to maximum number per hour, i.e. in patient-controlled analgesia), or injection volumes that vary by the time of day.

Infusion pumps have been a source of numerous patient safety concerns. Errors with fluid or medication delivery can have significant impacts on patient safety, clinical outcomes, and cost. Even with the adoption of smart infusion pumps, IV medication errors continue to occur at alarming rates (up to 60% in some studies). The U.S. Food and Drug Administration reported that over 56,000 medical device errors related to infusion pumps were reported between January 2005 and December 2009. The World Health Organization has called for 50% fewer errors by 2022.

Transonic Solution

By integrating Transonic's volume flow measurement into infusion pumps, the exact (not estimated) amount of fluid or medication administered to the patient can be monitored to dramatically improve dosing accuracy. Additionally, Transonic monitors can display this data clearly and alert the hospital staff if there is a problem. Obtaining true flow measurements from infusion pumps would result in fewer corresponding health risks, reduced hospital stays and costs, reduced clinician hours, and improved outcomes. It would also allow pump manufacturers and regulatory bodies to easily evaluate new infusion pumps and perform post market surveillance.

Fig. E15: Infusion pump.

D. Applications cont.

Clinical Applications - Hydrocephalus & Urodynamic System

Pediatric Hydrocephalus

More than 125,000 U.S. patients suffer from hydrocephalus – a condition demanding lifelong treatment using an implanted shunt system to drain excess cerebrospinal fluid (CSF). Treatment costs for hydrocephalus shunts reach into the billions of dollars with about half of these expenses going toward the repair of malfunctioning shunts. These costs are elevated due to the absence of non-invasive and accurate technology to evaluate a shunt's performance. This leads to delayed treatment or unnecessary intervention in nearly two-thirds of admissions. This is particularly true in children, since this group has a high risk of shunt malfunction (25 to 40% chance of failure in the first year of implantation). Understanding baseline flow conditions in shunted patients is critical for interpreting results from individual tests. Shunt flow may vary with position, time, and variations caused by individual lifestyle.

Transonic Solution

Implantable Transonic technology can accurately measure CSF output even at flows of mL/hour, diagnose blockage or lack of flow, and record real-time continuous flow data in a patient's external ventricular drains (EVD). This valuable information provides physicians the ability to calculate multiple diagnostic parameters and optimize the adjustment of shunt valves. An implantable Flowsensor placed in-line with a shunt system could also be used to noninvasively detect shunt malfunctions which would reduce the number of diagnostic tests performed, obviate the need for potentially harmful diagnostic techniques, and decrease the length and cost of hospital stay.

Urodynamic System

Uroflowmetry measures the speed and amount of urine voided during urination. Doctors may recommend a uroflow test if a patient complains of having slow urination, a weak urine stream, or difficulty urinating. The test is also used to assess the sphincter muscle that closes tightly around the bladder opening to help prevent urine leakage. Certain conditions that affect normal urine flow include benign prostatic hypertrophy (enlargement of the prostate gland which can block the urethra completely), bladder cancer, prostate cancer, urinary blockage, neurogenic bladder dysfunction, or trouble with the bladder due to a nervous system problem such as spinal cord tumor or injury. Results from the test can help a physician determine how well the bladder and sphincter are functioning or identify potential obstructions in the normal flow of urine. v

Transonic Solution

Transonic's technology can measure instantaneous volume flow, total volume flow, and total time of urination during a uroflow test. This enables physicians to assess the patient immediately and begin developing a treatment plan. Additionally, Transonic can assess urine density and hydration by measuring the concentration of proteins and other solids in urine.

D. Applications cont.

Clinical Applications - Endometrial Ablation & Ocular Surgery

Endometrial Ablation

Abnormal uterine bleeding (AUB) is a common and debilitating condition in women. Individuals who suffer from AUB may have bleeding between periods, abnormally long periods, a heavy flow, or a combination of these symptoms. Some women whose uterine bleeding is unmanageable may choose to have an endometrial ablation, a procedure to remove the endometrium, a thin layer of tissue that lines the uterus. This type of surgery has been performed over the past 15 years to stop or reduce heavy menstrual bleeding in those women who do not plan to have any children in the future. There are several modalities of endometrial ablation, including:

- Hydrothermal – Heated saline solution is pumped into the uterus to destroy its lining.
- Radiofrequency – An electrical mesh is inserted into the uterus where it is expanded. An electrical current made by radio waves is then used to destroy the lining.
- Cryoablation – A special probe is guided into the uterus and its temperature is lowered to freeze the endometrium.
- Microwave – Microwave energy is used to destroy the endometrial lining.

The major drawback to several of these methods is that they typically occur in the operating room and require general anesthesia. Consequently, the procedure itself becomes more involved and a patient's recovery is prolonged. Current methods are now designed to be performed in a doctor's office, which is more comfortable and convenient for patients and physicians.

Transonic Solution

During hydrothermal ablation, the amount of heated saline injected into the uterus must be monitored very closely in order to avoid any fluid moving into the fallopian tubes. Transonic transit time flow measurement can obtain precise values for true volume flow in real time during this procedure. Transonic's tubing Flowsensors are non-invasive and do not compromise sterility, so they can be used in virtually any setting.

Ocular Surgery – Vitrectomy

The vitreous, also referred to as vitreous humor, is a thick gel-like substance that fills the middle of the eye to maintain its shape and transmit light to the retina. Vision may be impaired due to vitreous deposits, retinal detachment, macular holes or eye bleeding induced by trauma, infections or disorders. In order to restore vision, an ophthalmologist may choose to perform a vitrectomy to remove the damaged vitreous along with any debris lodged in the eye. The affected vitreous is carefully suctioned out while clean saline solution replaces it. This must be done at equivalent flow rates so the pressure within the eye remains constant.

Transonic Solution

Transonic's flow sensing technology can provide true volume flow measurements of the removed vitreous and the administered saline solution. Any deviation from the defined flow rate can alarm the ophthalmologist and they can immediately correct the issue before causing damage to the patient's eye. Transonic's Flowsensors have an unparalleled zero flow offset and are extremely accurate even at the low flow rates required by a vitrectomy surgery.

E. Working with Transonic

Mission: 'To Advance Meaningful Measurements'

Who Is Transonic?

Transonic leverages the value of its transit-time ultrasound volume flow measurements and indicator dilution measurements to optimize the quality, accuracy and safety of biomedical devices.

Transonic's Core Values

Innovation

From pioneering transit-time technology to developing flowprobes and pressure-volume catheters small enough to make measurements in mice, we have never ceased the pursuit of innovation in the life science research arena and to bring that innovation from bench to bedside.

Collaboration

Transonic® technology is found in many heart-lung and other circulatory assist devices as the result of an OEM collaboration. Helping customers approach evolving challenges with effective customized solutions is central to our success. By placing state-of-the art technology in our customers' hands and providing prompt person-to-person technical advice, Transonic is recognized as the world leader in biomedical flow measurement technology and its applications.

Accountability

At Transonic our name is our reputation. From initial design, to production, and aftermarket support, we stand by our products knowing that we never settle for good enough when we can strive for the best.

Responsiveness

In this global economy it is vital to develop a global perspective. This is why we continue to strengthen and expand our international customer service, repair and maintenance teams.

Excellence

In the surgical arena, measurements need to be simple and quick to perform in addition to accurate and precise. Our elegant Flowprobe design and sophisticated meters provide real-time flow measurements in the operating room and at the patient's bedside.

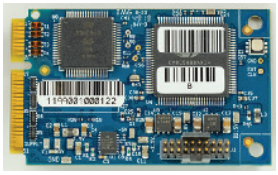
E. Working with Transonic cont.

Innovative Liquid Flow Measurement Solutions

Transonic flow measurement technology is used by a wide variety of the biomedical industry's leading manufacturers to deliver the highest accuracy and performance. Typical applications include:

- CP bypass pumps
- Ventricular Assist Devices
- ECMO systems
- Steam delivery modules
- Infusion/Transfusion/Perfusion
- Dialysis machines
- Organ perfusions systems
- Much more!

Tubing Flowsensor


Flowboard

"From Bench to Bedside"

Transonic is passionate about helping our biomedical manufacturing partners advance liquid flow measurement innovations from the early research stages to standard-of-care commercial products.

Research

Gold Standard Life Science Research Solutions
- Perivascular and tubing flow measurements for animal research and wide-ranging medical applications
- Pressure Volume Measurements with Admittance Technology to define cardiac function in pre-clinical testing.
- Implantable telemetry for flow, pressure & ECG

Development

Extensive Design and Development Know-how
- Advanced R&D and medical device design capabilities
- Highly experienced engineering team specializing in liquid flow measurement across many applications
- Deep knowledge of healthcare regulation and FDA approvals

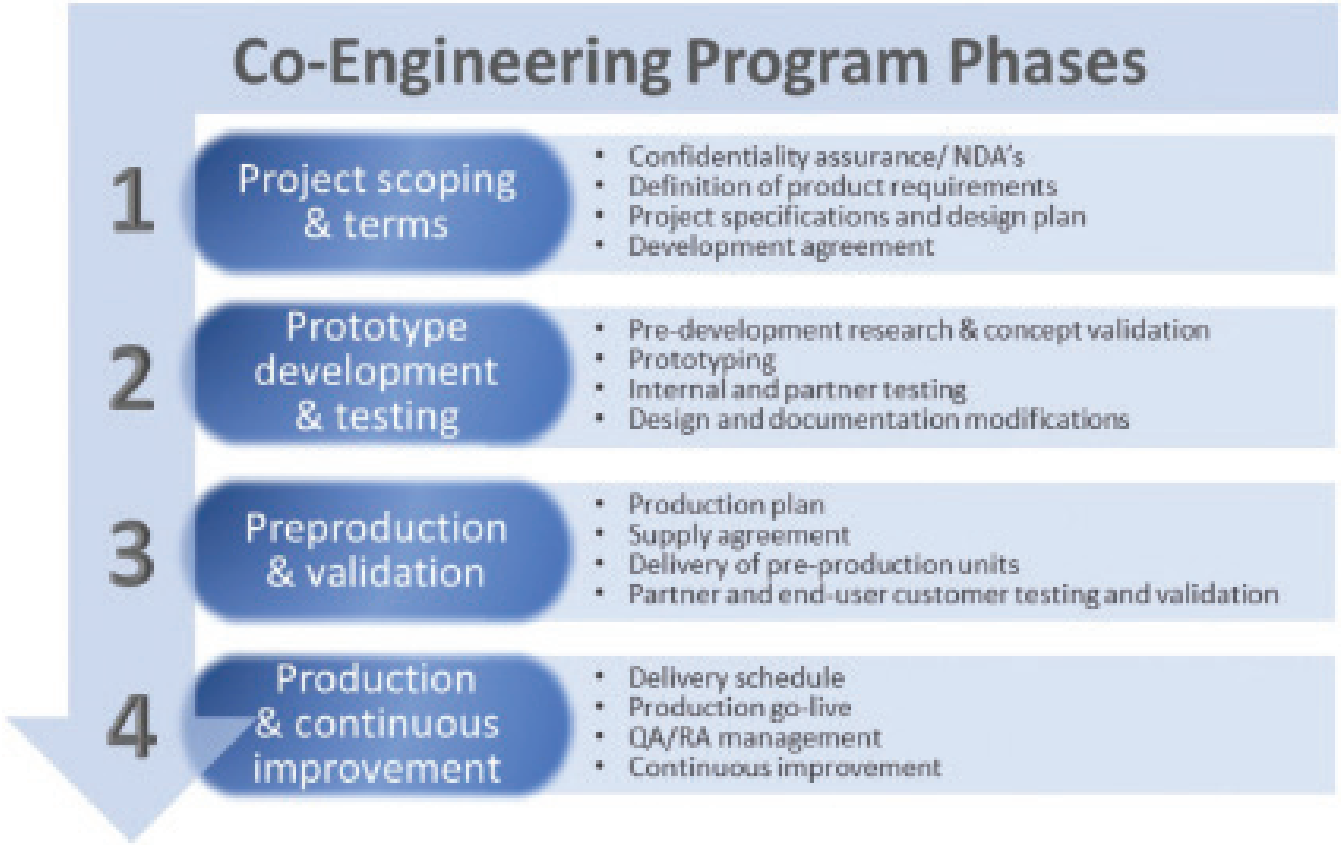
Production

World Class Manufacturing Capabilities
- ISO Certified manufacturing facility, Ithaca, NY
- Highly skilled workforce
- Process automation and scalability expertise
- Rigorous compliance and quality control standards

E. Working with Transonic cont.

Co-engineering Program

Transonic has a long history of working with both start-ups and established medical device companies to develop custom-engineered volume flow measurement solutions that suit a wealth of applications. The Co-Engineering Program is designed to meet the unique needs of each business and streamline the partnership, from prototype to production. It consists of:



E. Working with Transonic cont.

Transonic's Lineage of Intellectual Property

PATENT #	ISSUE DATE	INVENTOR(S)	TITLE
8,968,204	03/03/2015	CJ Drost	System and Method of perivascular and flow measurement
8,603,000	12/10/2013	K Wood, PC Hodgson, P Plouf	Method and apparatus for measuring blood volume
8,460,198	1/8/2013	P Plouf, B Poetschke, M Placko, K Wood, M Maymandi-Nejad	Implant Transmitter
8,348,879	1/8/2013	SX Gao, N Nazarifar,CJ Drost, Y Shkarlet	Surgical System having a Cassette with an acoustic air reflector
8,273,048	09/25/2012	NThuramalla,NMKrivitski, M Alsberge	SystemandMethodforDivertingflowtofacilitatemeasurementof system parameters
8,214,168	07/03/2012	Y Shkarlet	Noninvasive testing of a material intermediate spaced walls
8,162,843	04/24/2012	NM Krivitski	Method for measuring cardiac output via an extracorporeal cardiopulmonary support circuit
8,133,185	03/13/2012	NM Krivitski, VV Kislukhin	Catheter with common guide wire and indicator lumen
8,006,570		N Nazarifar, LJ Drost, Y Shkarlet 08/30/2011	Non-invasive flow measurement
7,803,121	09/28/2010	P Plouf, B Poetschke, M Placko, K Wood, M Maymandi-Nejad	Implant Transmitter
7,734,322	06/08/2010	NM Krivitski, DM Starostin	Blood volume determination and sensor calibration
7,549,965	06/23/2009	NM Krivitski, VV Kislukhin	Compensation method for thermodilution catheter having an injectate induced thermal effect in a blood flow measurement
7,481,114	12/30/2008	LC Lynnworth	Noninvasivemeasurementofliquidcharacteristicsusingreversibly deformed conduit (bought patent)
7,469,598	12/30/2008	Y Shkarlet, CJ Drost	A method of employing a transit time ultrasound sensor
7,275,447	10/02/2007	NM Krivitski, CJ Drost	Methodandapparatustodetermineaninitialflowrateinaconduit
7,261,696	08/28/2007	NM Krivitski, CJ Drost	Method and apparatus for measuring cardiac output via an extracorporeal cardiopulmonary support circuit
7,210,359	05/01/2007	NM Krivitski	Methodandapparatustodetermineaninitialflowrateinaconduit
7,194,919	03/27/2007	NM Krivitski, CJ Drost	Acoustically coupled ultrasonic transit time flow sensor
7,121,150	10/17/2006	Y Shkarlet, CJ Drost	Methodandapparatustodetermineaninitialflowrateinaconduit
7,112,176	09/26/2006	NM Krivitski, VV Kislukhin	Compensation method for thermodilution catheter having an injectate induced thermal effect in a blood flow measurement
6,986,744	01/17/2006	NM Krivitski,	Method and apparatus for determining a blood flow during a vascular corrective procedure
6,868,739	03/22/2005	NM Krivitski, CJ Drost	Method and apparatus for determining a blood flow during a vascular corrective procedure

E. Working with Transonic cont.

Transonic's Lineage of Intellectual Property cont.

PATENT #	ISSUE DATE	INVENTOR(S)	TITLE
6,746,408	06/08/2004	NM Krivitski, CJ Drost	Indicatordilutioncatheterforbloodflowmeasurementinarterio-venous hemodialysis shunts
6,718,190	04/06/2004	NM Krivitski, DM Starostin	Sensor calibration and blood volume determination
6,623,436	09/23/2003	NM Krivitski, VV Kislukhin	Retrogradecatheterwithreducedinjectateinducedtemperature offset
6,548,017	04/15/2003	NM Krivitski, VV Kislukhin	Method for real time monitoring of blood volume in a filter
6,494,832	12/17/2002	MD Feldman, JW Valvano, JA Pearce	Multifrequencyconductancecatheter-basedsystemandmethodto determine LV function in a patient (Licensed patent)
6,308,737	10/30/2001	NM Krivitski	Deformable flow diverter
6,155,984	12/05/2000	NM Krivitski	Methodandapparatusformeasuringcardiacoutputthroughan arterial cannula
6,098,466	08/08/2000	Yuri Shkarlet	Ultrasonic flow sensor incorporating full flow illumination
6,061,591	05/09/2000	NM Krivitski	Methodandapparatusforpredictingintradialyticmorbidevents through the monitoring of a central blood volume
6,041,246	03/21/2000	NM Krivitski, DM Starostin	Singlelightsensoropticalprobeformonitoringbloodparameters and cardiovascular measurements
6,036,645	03/14/2000	CJ Drost, Y Shkarlet, A Kopychev, L Ostergren, I Sergeeva	Ultrasonic Probe
5,928,180	07/27/1999	NM Krivitski, VV Kislukhin	Methodandapparatusforrealtimemonitoringofbloodvolumein a filter
5,595,182	01/21/1997	NM Krivitski	Cardiovascular measurements by sound velocity dilution

F. Transonic Flowsensing Products

Flowmeters, Flow Monitors and Flow Boards

Transonic Systems' flowsensing devices were designed to provide accurate measurement solutions to fill biomedical researcher and clinicians' needs for volume flow data. These products are available in specialized systems to fit a host of applications from tubing to "in vivo" measurements of flow in most vessels from mice to man, with Flowmeters for use by cardiothoracic surgeons, in the ICU suite, dialysis clinic, bioprocess industry and research laboratory.

The systems consist of an ultrasound Flowsensor/Flowprobe and Flowmeter electronics to process the signals and output the data. What form this system package takes depends on the application and the market requirements. Underlying this presentation is the philosophy that Transonic can address new flow applications and work toward a custom solution to achieve the best flow measurement suited to the application. Below is a sample of our flowmeter systems.

SamplingofFlowmeters,MonitorandFlowboard

Fig. G1: T400 Research Flowmeter console with Tubing module on left, Perivascular module in center and Pressure module on right.

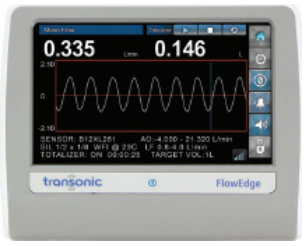


Fig. G2: FlowEdge Bioprocess Flowmeter

Fig. G3: Hemodialysis Monitor that pairs with H4FX Flow/dilution Sensors

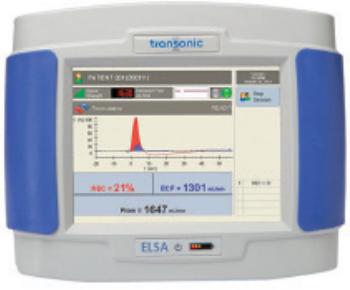


Fig. G4: ELSA Monitor that pairs with Flow/dilution Sensors

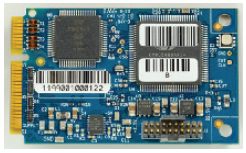


Fig. G5: 1199 Flowboard with electric circuitry for integration into medical devices

Fig. G6: Optima Surgical Flowmeter to whichintraoperativePerivascular FlowprobeandClamp-onTubing Flowsensors connect.

F. Transonic Flowsensing Products cont.

Clamp-on Flowsensors

Transit-Time Flow Measurement for Tubing Applications

Transonic's Clamp-on Flowsensors have revolutionized flow measurement in medical tubing. These Sensors clip onto the outside of flexible tubing to measure the flow within. They have become the gold standard for medical design and pre-clinical extracorporeal use by providing non-invasive measurement with high accuracy and stability. Measurements are reliable even in challenging electromagnetic environments. Clamp-on Flowsensors achieve precision accuracy by calibration for the tubing type, fluid and operational temperature at which they will be used. They can store calibration information for four distinct operating environments.

Fig. G7: Closed clamp-on sensor with tubing inserted.

Fig. G8: Open clamp-on sensor with tubing inserted.

Key Advantages

- Sensors range in size to fit tubing from 1/8" OD to 1-1/4" OD
- No physical contact with fluid, does not break flow circuit sterility
- Can be designed as a custom "Transonic Inside" Flowsensor to integrate seamlessly with another device

Applications

- Extracorporeal fluid management circuits such as ECMO or CPB;
- Bioprocessing;
- Ex-vivo organ support and perfusion;
- Any application where maintaining sterility is required

Calibration Considerations

- Fluid – the density of the fluid will affect the transit time of the Flowsensor's ultrasonic beam; custom calibration with the specific fluid is available for blood analogues, glyerine/water, saline etc.
- Tubing Material – the material properties of the tubing will affect the transit time of the Flowsensor's ultrasonic beam; factory calibration must be performed on the type of tubing (pvc, silicone, most flexible tubing materials).
- Fluid Temperature – temperature also affects the speed of sound; each Flowsensor is factory calibrated for use at a specific temperature.
- Expected Flow Rate – each Flowsensor can be calibrated to a specific flow range to achieve the highest accuracy possible in the flow range of interest.
- Certificates of Calibration – NIST traceable calibration data is available for Quality management

F. Transonic Flowsensing Products cont.

Inline Flowsensors

Transonic's Inline Flowsensors utilize a unique scheme of ultrasonic illumination to manufacture a flow-through sensor with a smooth, cylindrical interior without compromising measurement accuracy. These Flowsensors offer more flexibility than Clamp-on Flowsensors as measurement calibration does not depend on the type and exact size of tubing on which they are used.

Inline Flowsensors can achieve precise flow measurement for low or high flow rates and steady state or pulsatile flow profiles. Flow resolution is scaled to sensor size, and flow is measured accurately across the sensor's full dynamic range with little effect from turbulence.

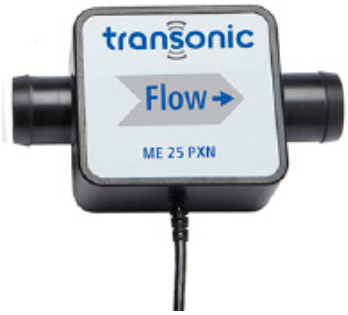


Fig. G9: From top to bottom, 16 and 25 mm PXN Inline Tubing Flowsensors.

Key Advantages

- Flexibility for tubing circuits that may vary or are still in the design phase
- Very precise in low flow applications
- Mock Circulatory Loops, bioengineering and device test applications that do not require sterility

Applications

- Low flow applications such as perfused organ studies;
- Any application requiring maximum flow sensitivity.

Calibration Considerations

- Fluid – the density of the fluid will affect the transit time of the Flowsensor's ultrasonic beam; custom calibration with the specific fluid is available for blood analogues, glycerine/water, saline etc.
- Fluid Temperature – temperature also affects the speed of sound; each Flowsensor is factory calibrated for use at a specific temperature
- Expected Flow Rate – each Flowsensor can be calibrated to a specific flow range to achieve the highest accuracy possible in the flow range of interest
- Certificates of Calibration – NIST traceable calibration data is available for Quality management

Tubing Diameter

Transonic Inline Flowsensors are available in a range of sizes to mate with standard laboratory tubing from 3/64" to 1" ID. Sensor ends are barbed. Sensor numerical size is in mm. Sensor size should match the tubing circuit to avoid disruptions in fluid dynamics and reduce resis

F. Transonic Flowsensing Products cont.

How to Choose the Best Sensor by Specifica-

Technical specifications and accuracy claims are often presented as "best case" scenarios without consideration for the diverse application requirements of their use that may impact the measurements they make. Transonic attempts to capture these use variations by not inflating accuracy claims, instead presenting specifications to help guide the user to the most appropriate sensor for the application.

Clamp-on Sensors are sized by tubing outer diameter (in 1/16" increments). Inline Sensors size is determined by tubing ID (in mm). However, size is not the only consideration to make the best sensor choice. Scale, Resolution and Zero Offset are critical to choosing the best tool for the measurement.

Scale

What is the dynamic range of the expected flow to be measured? A mock circulatory model may use a pulse duplicator that creates a mid range average flow, but has high pulse peaks that would be "clipped" if the flowsensor maximum range is too low. Transonic specs show the 1 volt output values for both "low" and "standard" scale settings. The flowmeter output is linear up to 5 times the scale (5 volts).

Zero Offset

In a perfect world, zero is zero. In Transonic's measurement, the offset measured at zero is exceptionally low, stable under stable conditions, and can be nulled. Electronics, transducer matching and tubing variation all contribute to imperfections in measurement that are captured in the zero offset spec. When choosing a Flowsensor, it is important to consider the effect of the offset on the measurement range and whether a smaller sensor that has a lower offset would be advised without compromising changes in diameter that might cause resistance.

Resolution

Transonic Flowsensors sample flow in pico-second time to present instantaneous flow data and capture pulsatile flow waveforms accurately. The data output from the flowmeter is available as a pulsatile signal filtered to 10, 40, 160 Hz, and also as a continuous rolling average filtered to 0.1 Hz.

Absolute Accuracy and Linearity

The specification for the accuracy of Transonic devices is defined as a "system" (flowmeter and flowsensor) and is a composite of all real life conditions that may contribute to the error in the measurement. For example, Perivascular Flowprobes are spec'd at ± 10% because the in vivo measurement may be made on blood vessels that are not an exact fit, or have more or less connective tissue attached, etc. Clamp-on Tubing Flowsensors are also specified to be within ± 10% of actual flow due to tubing variations and other conditions that affect measurement accuracy such as temperature fluctuation, flow profile and fluid composition. PXN Inline Flowsensors are held to a tighter specification of ± 4% since this measurement is not dependent on the clamping of the sensor around the tubing. In all instances, we maintain a tighter linearity specification: ± 4% error (Clamp-on sensors) and ± 2% error (Inline sensors & perivascular flowprobes). Overall accuracy can be improved to the linearity value if the Flowsensor is calibrated on-site as a system (Flowsensor with Flowmeter) under the actual conditions (tubing, fluid, flow rate) of use. Research Flowmeters (TS410, FlowEdge) allow the user to adjust the sensor gain to "tweak" a correction or recalibrate the sensor on-site for different conditions. In this way, the user has direct impact and can get the best accuracy possible, particularly for novel applications that might require very low flow rates, incremental viscosity changes or other nonstandard conditions.

F. Transonic Flowsensing Products cont.

Tubing Flowsensor Specifications

SENSOR SIZE	BIDIRECTIONAL FLOW OUTPUTS				SYSTEMACCURACYSPECIFICATIONS2			ULTRA-SOUND FREQUENCY
	RESOLUTION1	LOW FLOW (¼ SCALE)	STANDARDFLOW SCALE	MAXFLOW(STD SCALE)	MAXZERO OFFSET	ABSOLUTE ACCURACY	LINEARITY	
	ml/min	1Voutput(mL/min)	1Voutput(mL/min)	5Voutput(L/min)	mL/min	% of reading	%	MHz
2PXL	0.5	50	200	1	± 4.0	± 10	± 4	3.6
3PXL	1.0	100	400	2	± 8.0	± 10	± 4	3.6
4PXL	1.0	100	400	2	± 8.0	± 10	± 4	2.4
5PXL	1.0	100	400	2	± 8.0	± 10	± 4	2.4
6PXL	2.5	250	1 L	5	± 15	± 10	± 4	2.4
7PXL	5	500	2 L	10	± 30	± 10	± 4	1.8
8PXL	5	500	2 L	10	± 30	± 10	± 4	1.8
9PXL	5	500	2 L	10	± 30	± 10	± 4	1.8
10PXL	10	1 L	4 L	20	± 60	± 10	± 4	1.2
11PXL	10	1 L	4 L	20	± 60	± 10	± 4	1.2
12PXL	10	1 L	4 L	20	± 60	± 10	± 4	1.2
14PXL	25	2.5 L	10 L	50	± 150	± 10	± 4	1.2
16PXL	25	2.5 L	10 L	50	± 150	± 10	± 4	1.2
20PXL	50	5 L	20 L	100	± 300	± 10	± 4	0.9

SENSOR SIZE	BIDIRECTIONAL FLOW OUTPUTS				SYSTEM ACCURACY SPECIFICATIONS2			PHYSICALSPECIFICATIONS				ULTRA-SOUND FREQUENCY
	RESOLUTION1	LOW FLOW (¼ SCALE)	STANDARD FLOWSCALE	MAX FLOW (STD SCALE)	MAXZERO OFFSET2	ABSOLUTE ACCURACY	LINEARITY	TOTAL LENGTH W/ TUBE ENDS		CASELENGTH W/O TUBE ENDS		
	at 10 Hz (mL/min)	1V output (mL/min)	1V output (mL/min)	5V output (L/min)	mL/min	%ofreading	%	in	mm	in	mm	MHz
1PXN	± 0.02	5	20	100	± 0.4	± 8	± 2	3.9	100	0.3	8	9.6
2PXN	± 0.02	10	40	200	± 0.6	± 4	± 2	3.9	100	0.5	12	9.6
3PXN	± 0.05	25	100	500	± 1	± 4	± 2	3.9	100	0.6	14	7.2
4PXN	± 0.1	50	200	1 L	± 2	± 4	± 2	1.0	25	0.6	16	4.8
5PXN	± 0.2	100	400	2 L	± 4	± 4	± 2	1.2	32	0.8	20	3.6
6PXN	± 0.5	250	1 L	5 L	± 10	± 4	± 2	1.6	41	1.0	26	2.4
10PXN	± 1	500	2 L	10 L	± 20	± 4	± 2	2.0	51	1.3	33	1.8
13PXN	± 2	1 L	4 L	20 L	± 40	± 4	± 2	2.7	69	1.8	45	1.2
16PXN	± 5	2.5 L	10 L	50 L	± 70	± 4	± 2	3.3	83	2.1	52	0.9
19PXN	± 5	2.5 L	10 L	50 L	± 100	± 4	± 2	4.0	101	2.5	64	0.9
25PXN	± 10	5 L	20 L	100 L	± 200	± 4	± 2	5.0	128	3.1	80	0.6

Calibration is dependent on tubing material, wall thickness, ultrasound velocity of liquid flowing through the tube & temperature.

1. Resolution represents the smallest detectable flow change at 0.1 Hz filter (average flow output).
2. StatedsystemaccuracyspecificationsapplytoPXLandPXNFlowsensorswithTS410FlowModules.(a)Absoluteaccuracyiscomprisedofzerostability, resolutionandlinearityeffects.Statedvaluesapplywhenflowrateisgreaterthan5%ofmaximumrangeandzerooffsetisnulled.(b)IftheSensoris calibratedon-sitewiththesystemFlowModulefor thetubingandliquidinuse,absoluteaccuracymaybeimprovedtotheLinearityvalue.(c)On-site calibrationisrecommendediftheSensorisroutinelyusedtomeasureflowslessthan5%ofthemaximumrangetoaccountfornon-linearitiesassociated with flow profile.

F. Transonic Flowsensing Products cont.

Perivascular COnfidence Flowprobes®

Transit-Time Flow Measurement for Continuous Vascular Monitoring

Transonic's COnfidence Perivascular Flowprobes measure cardiac output in humans and animal models with great accuracy, enhanced reliability and ease of use. The X-pattern full flow ultrasonic illumination allows for gold standard volume flow measurements, and its slim, ergonomic footprint allows for use in adults, pediatrics, and even neonates. These Flowprobes need little acoustic coupling to achieve and maintain excellent signal quality. The form fitting UltraFit Liner encircles the vessel and slips into the transducer shell to stay in place without a clip. Dynamic flow measurements can be recorded immediately following probe placement during surgery.

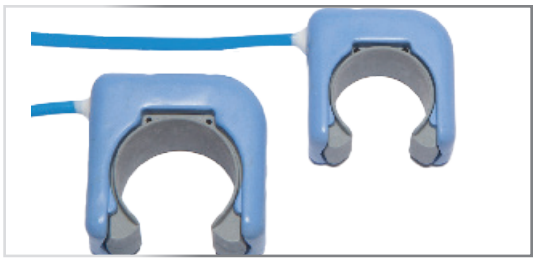


Fig. G10: Two COnfidence Flowprobes with Ultrafit Liners inserted inside the Flowprobe.

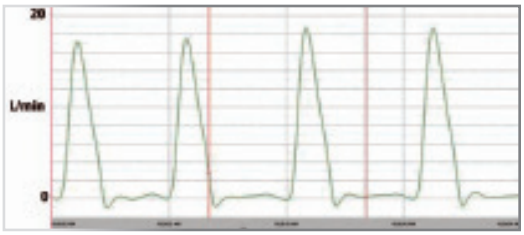


Fig. G11: Ascending aorta flow of 22 kg female mongrel dog from a PAU COnfidence Flowprobe. Data of animal at rest, standing up and calm on treadmill.

Key Advantages

- Implantable technology with immediate measurements
- Maximizes signal continuity during intraoperative applications for continuous measurement
- Flexible UltraFit Liners protect the vessel during implant
- Can read through many artificial grafts (Dacron materials suitable)

Applications

- Cardiovascular physiology, including cardiac output measurements
- Ventricular assist devices (VADs)
- Congenital heart defect repairs in pediatric patients

Perivascular Flowprobe Sizes

COnfidence Flowprobes are available for vessels 4 - 36 mm diameter. While these were designed for the great vessels (ascending aorta and pulmonary artery), they may be used wherever direct flow measurements on vessels is required. Smaller Perivascular Flowprobes are available for measurement in microvessels such as lymphatic flow or cardiovascular research in rodent models from 0.5 mm and above.

F. Transonic Flowsensing Products cont.

COnfidence Flowprobe Specifications

SPECIFICATIONS

Precision Probe Series	Ultrafit Liner mm (diameter)	Vessel OD mm MA-PROBES acute application	Vessel OD mm MC-PROBES chronic application	Bidirectional Flow Resolution[1] mL/min	Scale Settings[2] Low Flow ml/min	Normal Flow ml/min	Maximum Range[3] ml/min	Accuracy Zero Offset[4] mL/min	Absolute Accuracy[5] %	Relative Accuracy %	Ultrasound Frequency MHz
8 PAU	8	6 - 8	6 - 7	4	500	2L	10L	± 20	± 10	± 2	3.6
10 PAU	10	8 - 10	8 - 9	4	500	2L	10L	± 20	± 10	± 2	3.6
12 PAU	12	9 - 12	9 - 11	8	1L	4L	20L	± 40	± 10	± 2	2.4
14 PAU	14	11 - 14	11 - 13	8	1L	4L	20L	± 40	± 10	± 2	2.4
16 PAU	16	12 - 16	12 - 15	20	2.5L	10L	50L	± 100	± 10	± 2	1.8
20 PAU	18, 20	16 - 20	16 - 19	20	2.5L	10L	50L	± 100	± 10	± 2	1.8
24 PAU	22, 24	19 - 24	19 - 23	40	5L	20L	100L	± 200	± 10	± 2	1.2
28 PAU	26, 28	22 - 28	22 - 27	40	5L	20L	100L	± 200	± 10	± 2	1.2

[1] Resolution: represents the smallest detectable change in flow, a factor in accuracy.

[2] Transonic Flowprobes operate in one of two scales: low flow or normal flow, determined by the range of flow under study. Flowprobes measure bidirectional flow up to 5 times the selected scale setting. The scale settings calibrate the 1 volt reference signal for data collection; the linear range of the Flowmeter is equal to ± 5 volts. By using the “low flow button”, measurement sensitivity is increased by a factor of four. For example, a 14 PAU probe set on “lo flo” can process and display up to 5 x 1L/min or 5L/min. This linear overrange is important for the proper recording of highly pulsatile peak flows.

[3] Maximum Range for each probe reflects the highest flow rate that can be processed and displayed via the analog connector.

[4] Zero offset on individual probes is often lower than this value.

[5] In all cases, the Absolute Accuracy percentage can be raised to relative accuracy levels (± 2%) by *in situ* calibration.

F. Transonic Flowsensing Products cont.

Ultrasound Flow/Dilution Sensors

Transit-Time Flow Flow and Ultrasound Dilution Measurements in Extracorporeal Blood Loops

Fig.G12:PairedFlow/dilution sensors.

Transonic's signature blood flow measurement technology is paired with indicator dilution technology in the HD03 Hemodialysis Monitor and Extracorporeal Life Support Assurance (ELSA) Monitor used during extracorporeal membrane oxygenation (ECMO). Paired arterial and venous Flowsensors clip onto a patient's blood lines to measure volume blood flow from the extracorporeal pump and a host of other parameters derived from ultrasound velocity. A simple bolus of isotonic saline introduced into the blood stream dilutes the protein concentration of the blood and thereby reduces the ultrasound velocity of the liquid. The first sensor records the velocity of the saline bolus to produce a calibration curve; the second sensor records the velocity of the diluted saline to produce a second dilution curve. From the two dilution curves, measurements of recirculation, vascular access flow, cardiac output and oxygenator blood volume can be calculated from classic Stewart-Hamilton equations. Matched arterial/venous sensor sets are available for most common hemodialysis blood tubing lines and standard adult & pediatric ECMO tubing sets.

Key Advantages

- Measures true Delivered Blood Flow independent of the extracorporeal pump
- Uses innocuous isotonic saline indicator to yield quantitative measurements
- Repeated measurements can be made safely without compromising the patient or prescription delivery
- Trended data can give early warning signs of access compromise, cardiac failure

Applications

- During Hemodialysis: Measurements of Recirculation, Access Flow, Cardiac Output and Delivered Blood Flow
- During ECMO: Measurements of Recirculation, Cardiac Output, Delivered Blood Flow and Oxygenator Blood Volume (to assess clotting)
- Congenital Heart Repair surgery

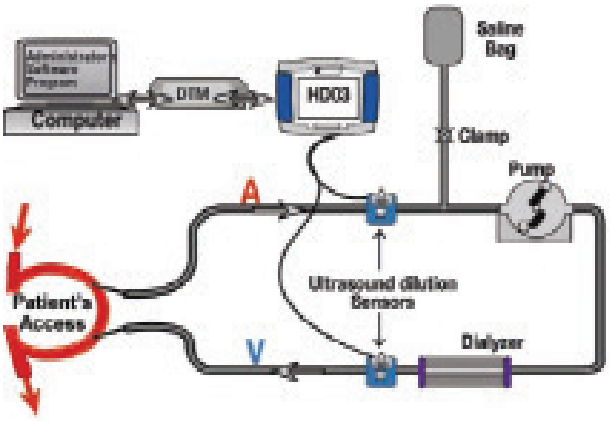


Fig.G13:SchematicshowingpairedFlow/dilutionsensors connected to the HD03 Hemodialysis Monitor on hemodialysis blood lines.

Considerations

These sensors are calibrated for blood and standard medical tubing blood lines. Proprietary Transonic software automatically calculates and displays measurement values derived from the curves and records patient data. The signals are also available with
Transonic Research Flowmeters for developmental use.

Cardiovascular Physiology

1. Circulatory System

Blood flow sustains life. Every 60 seconds life-giving blood flows through the body's 66,000-mile circulatory system (over twice the circumference of the earth) to nourish each cell in the human body. The circulatory system is a closed system of blood vessels with the heart as the pump. Blood vessels are dynamic and can proliferate depending upon the needs and composition of the body. Almost 200 extra miles of blood vessels are found in each pound of fat.

The Heart - A Dual Pump

Propelled by a fist-sized, four-chamber, two-pump heart, blood moves from the right ventricle of the heart and traverses the lungs where it rids the blood of carbon dioxide and replenishes it with oxygen. This freshly oxygenated blood is then pumped by the heart's left ventricle and flows via a second (systemic) circulatory loop taking it throughout the body to nourish the cells and remove wastes.

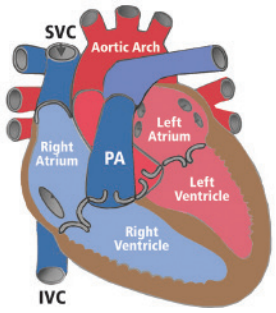


Fig. A1: Human heart

Blood Vessels

There are three types of blood vessels:

- Arteries carry blood away from the heart to tissues.
- Veins return blood to the heart.
- Capillaries allow for exchange of nutrients for waste products between blood and surrounding tissues at the cellular level. Because capillaries have direct contact with cells of tissues, they can directly serve the needs of those cells.

Structure of Blood Vessel Walls

Arteries and veins are made of three layers of tissue surrounding a cavity called the lumen. These layers provide strength and flexibility, but are too thick to allow significant exchange of gases between the blood and surrounding tissue. The three layers are the:

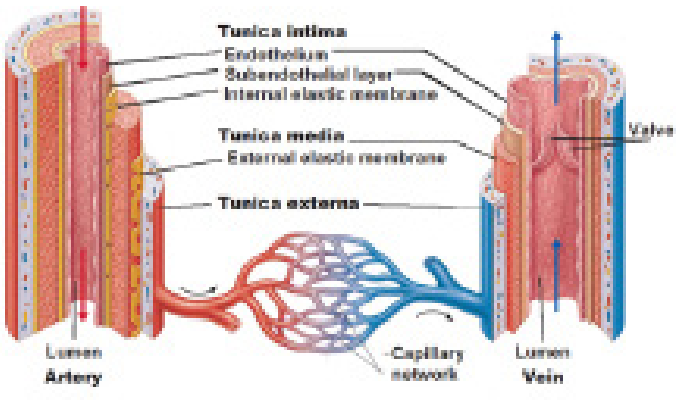


Fig. A2: Structure of human blood vessels.

1. Tunica intima (or interna) is the innermost layer. It consists of endothelial tissue that lines the blood vessel and an underlying layer of connective tissue with elastic fibers. The endothelial tissue provides a slick surface to minimize friction with the flowing blood. A basement membrane of subendothelial connective tissue is found in vessels larger than one millimeter in diameter.

2. The middle layer Tunica media is comprised of concentric rings of smooth muscle in a framework of loose connective tissue. Collagen fibers bind this layer with the inner and outer layers. In arteries the Tunica media that also has elastic fibers is the thickest layer. It is regulated by the sympathetic nervous system and controls the vasodilation and vasoconstriction of the vessel.

3. The outermost Tunica externa (or adventitia) is a layer of fibrous connective tissue of collagen and elastic fibers which adds strength and support to the vessel. In veins, this is generally the thickest layer. Connective tissue blends into surrounding tissue to anchor the vessels. This layer is innervated and vascularized (vasa vasorum).

Arterial System

Three types of arteries with somewhat different

Cardiovascular Physiology cont.

properties carry the blood as it first leaves the heart and travels to the capillaries.

They are:

1. Elastic arteries
2. Muscular arteries
3. Arterioles

Elastic Arteries

(also referred to as conducting arteries) Elastic arteries are large vessels designed to transport large volumes of blood to major regions of the body. The tunica media of these vessels contains a larger proportion of elastic fibers, and a smaller proportion of smooth muscle.

In response to ventricular systole, these vessels expand to accommodate blood from the heart and dampen the increase in pressure. As blood moves through the vessels and the ventricles enter diastole, these vessels contract and dampen the drop in pressure. By the time blood reaches the arterioles, fluctuations in pressure are eliminated.

- Largest in diameter.
- These are most elastic nearest the heart.
- Elastin is found in all 3 tunic layers.
- Have the highest pressure fluctuations.
- The elastic properties of these vessels allow for maintenance of a constant flow and therefore constant pressure, moving through the arterial system.
- Elastic arteries offer low resistance with their large lumens.
- Despite containing a large amount of smooth muscle, elastic arteries do not play much of a role in vasoconstriction or vasodilation.
- In atherosclerosis, there is damage to the endothelial lining and lipid deposits form in the tunica media. With this "hardening" the elastic dampening capacity is reduced. This can result in high blood pressures in the aorta or peripheral blood vessels.

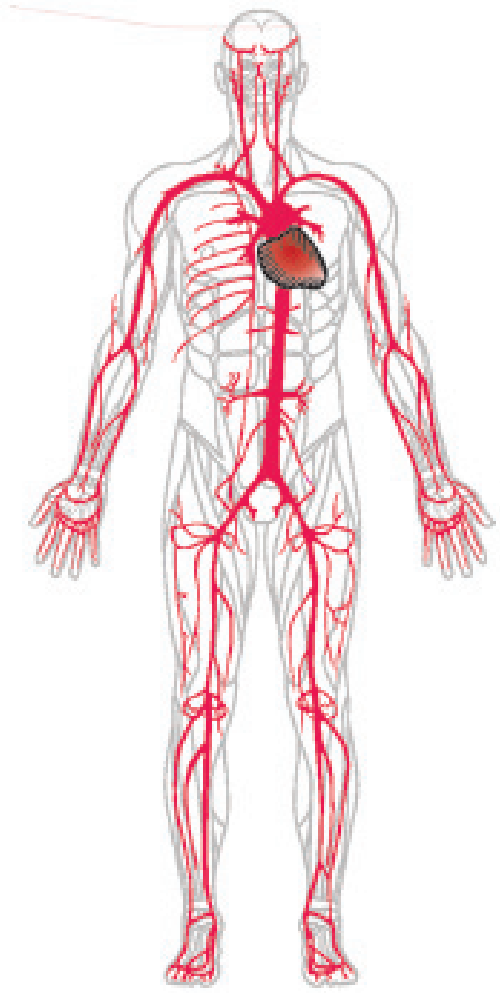


Fig. A3: The human arterial tree.

Muscular Arteries

(also referred to as conducting or distributing arteries) Muscular arteries distribute blood throughout the muscles and organs. These vessels contain a higher proportion of muscle than the elastic arteries.

- Muscular arteries have the thickest tunica media of all vessels.
- They contain more smooth muscle and less elastic tissue.
- These arteries are active in vasoconstriction.

Arterioles

With some help from the muscular arteries, arterioles are responsible for regulating the

Cardiovascular Physiology cont.

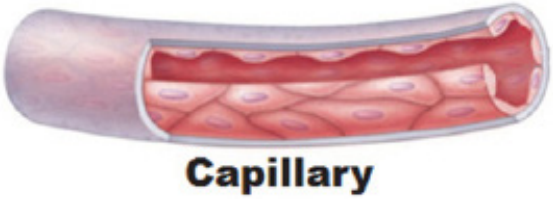


Fig.A4: Capillary showing single endothelial layer of cells.

amount of blood that flows to a particular set of capillaries. They do this by either contracting or relaxing to either restrict or increase the amount of blood flowing through them. Contraction or relaxation either increases or decreases the resistance to flow through the vessel.

Capillaries

Capillaries, also known as exchange vessels, are the smallest and most numerous blood vessels in the human body with a total count of over 10 billion.

Capillaries connect arterioles to venules. Their walls only consist of a one-cell thick endothelial layer to allow efficient gas exchange between blood and its surrounding tissues. A capillary lumen is so tiny that only a single red blood cell can pass through at one time.

The thin walls of capillaries are possible because of their very low blood pressure (20-40 mm Hg) which protects them from rupture. Capillaries contain smooth muscle-like cells termed pericytes that help maintain the structural integrity of the capillary. Most tissues have many capillaries while others, such as ligaments and tendons, have few. Tissues like the epidermis, cartilage and cornea that have no blood supply are called avascular.

There are three types of capillaries:

Continuous Capillaries

Continuous capillaries are the most common. Their endothelial cells form a continuous lining without pores. These endothelial cells are held together with tight junctions (zona occludens), but there are some gaps that allow small amounts of fluids to pass between cells. They permit diffusion of water, small solutes, and lipid-soluble materials, but prevent the loss of plasma proteins and blood cells.

An exception to this is found in the capillaries of the brain, in which tight junctions form a complete barrier (the blood-brain barrier) to prevent the movement of fluids between cells.

Continuous capillaries are found in connective tissue, skin, the lungs, skeletal and smooth muscle. They contain pinocytotic vesicles that act as transport "ferries" to move fluids across the capillary wall.

Fenestrated Capillaries

Fenestrated capillaries contain endothelial cells that have "windows" or pores which make these capillaries considerably more permeable to fluids and solutes than continuous capillaries. The fenestrated capillaries are typically found where active absorption of materials into the blood is required, such as in the small intestine and endocrine organs. They are also found in the nephron of the kidneys where filtration occurs, as well as the ciliary processes of the eyes and choroid plexuses of brain ventricles.

Sinusoidal Capillaries

Sinusoidal capillaries have large lumens, few tight junctions between endothelial cells, and fenestrations. Thus, they tend to be especially leaky. This permits the passage of large molecules like blood cells and proteins between the blood and surrounding tissues. These capillaries are often used by leukocytes to move in and out of the blood vessels. Sinusoidal capillaries are found primarily in the liver, bone marrow, spleen, anterior pituitary, parathyroid and other lymphoid organs.

Blood Flow through Capillaries and

Cardiovascular Physiology cont.

Capillary Dynamics

One arteriole can give rise to dozens of capillaries. One of the major functions of capillaries is diffusive exchange of respiratory gases, oxygen, carbon dioxide and fluids.

Vasomotion is the process of blood flow through capillaries. This flow is intermittent because of the alternation of contraction and relaxation of the precapillary sphincters. Vasomotion occurs at a rate of 5-10 times/minute (resting) and can be made faster or slower, according to the needs of the tissue at any given time. Blood is usually flowing through only about 25% of the capillaries in an area at one time (at rest), unless tissue demand changes.

Capillary Beds

Capillaries function as part of interconnected networks referred to as capillary beds. A capillary bed is the site of microcirculation and connects the flow of blood from an arteriole to a venule.

The metabolic needs of the tissue will dictate the amount of blood that will flow through a particular network so that all capillaries within a bed may not be filled with flowing blood all the time. Capillary beds contain two types of vessels:

1. Vascular shunts are metarterioles that function as thoroughfare channels and control flow of blood through different parts of a capillary network.
2. True capillaries are the exchange vessels.

Precapillary sphincters are cuffs of smooth muscle that regulate the flow of blood through various capillaries. Thoroughfare channels are direct connections between arterioles and venules that allow blood to bypass most of the capillaries in a capillary bed. Blood flow must be carefully regulated to the parts of the body that need it. Vasomotor nerves and local chemical conditions regulate blood flow so that the capillary bed can either be bypassed or flooded. A human does not have enough blood in his or her body to fill up all the capillaries in all the capillary beds at the same time.

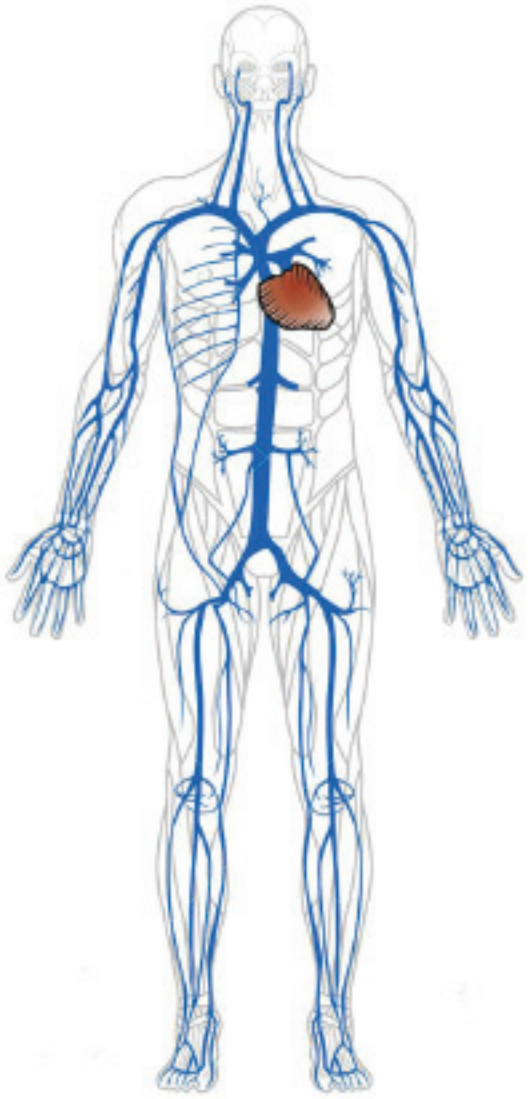


Fig. A5: Human venous system.

Venous System

Several capillaries converge to form venules. Venules unite to form veins. Veins collect blood from the tissues and return it to the heart. Venous walls are thinner than those of arteries because of lower blood

Cardiovascular Physiology cont.

pressures. Venules are the smallest veins where the tunica media is generally absent. Larger venules have one or two layers of smooth muscle that make up the tunica media.

In venules and medium-sized veins where the blood pressure is so low that it cannot overcome the force of gravity, valves exist to prevent the back-flow of blood.

Veins are made up of the same three layers as arteries but characteristics vary:

- Tunica intima is thinner than that of arteries with no internal elastic lamina.
- Tunica media is much thinner, with only very small amount of smooth muscle and elastic fibers. The amount of smooth muscle is enough to allow veins to alter their diameter to some extent. Compared to arteries of similar size, vein walls are thinner and the lumen is larger in diameter.
- Tunica externa is the thickest layer. It contains more collagen and elastic fibers.

Veins are also called capacitance vessels, with a typical vein being able to stretch to about 8 times its lumen diameter. The porous nature of venoles allows fluid and white blood cells to move easily from the bloodstream through the vessel walls.

Blood pressure in the venous system is even lower than that of the capillaries, about 20 mm Hg at the venules, and almost zero at the vena cava close to the right atrium. Venous pressure – right atrial pressure = 5-10 mmHg. Venous pressure is generally steady and changes very little during the cardiac cycle. While a lacerated artery flows in spurts, a lacerated vein demonstrates an even blood flow.

Central venous pressure or the pressure in the thoracic vena cava near the right atrium is an important parameter because it is the driving force for blood flow to return to the heart. Therefore, a decrease in venous pressure decreases venous return. A decrease in venous return causes a decrease in end-diastolic volume, which, in turn, causes a decrease in stroke volume, cardiac output, and blood flow to all organs.

Varicose Veins/Hemorrhoids

Most veins have valves that are flaps or cusps of the tunica intima designed and oriented to maintain blood flow in the proper direction. If the walls of the veins near the valves weaken or become stretched and distorted, the valves may not work properly. Varicose veins occur when valves sag or fail. Blood pools in these areas and the wall eventually stretches and balloons, creating varicosities.

The effects of this ballooning range from mild discomfort and cosmetic issues, like those seen in superficial varicose veins in the thighs and legs, to painful distortion of adjacent tissues, as in hemorrhoids.

Venous Sinuses

In some sites in the body such as the heart and brain, veins are highly specialized to form venous (vascular) sinuses. Their thin walls consist of endothelium supported by surrounding dense connective tissue. There is no tunica media, tunica externa or smooth muscle.

Factors That Affect Venous Return

- Skeletal muscle contraction promotes venous return.
- Respiratory activity during inspiration can increase venous return by decreasing right atrial pressure.
- Decreased venous compliance due to sympathetic activation of veins results in increased venous pressure and promotion of venous return.
- Vena cava compression as seen in valsalva maneuver and pregnancy can decrease venous return.
- Gravity – upon standing, hydrostatic forces cause the venous pressure in the dependent limbs to increase, causing a decrease in venous return.

Venous blood pressure alone cannot adequately return blood to the heart. It is aided by the:

1. Respiratory "pump"- The respiratory pump helps return blood in the thoracic cavity and abdomen back to the heart. These changes in pressure within the thorax during respiration "pump" the blood in the area back toward the heart.

Cardiovascular Physiology cont.

2. Muscular "pump"- Many veins are located between skeletal muscles. The contraction and relaxation of these muscles help "pump" blood located in these veins back toward the heart.

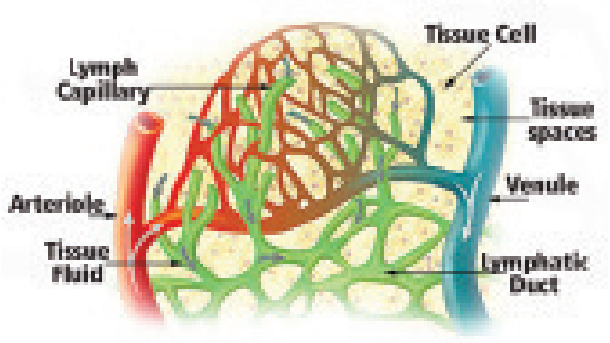


Fig. A6: Human lymph.

Lymphatic System

The lymphatic system is an extensive vascular network made up of one-way vessels that provide an accessory route by which fluid can be returned to the blood from the interstitium.

Lymph is a part of the interstitial fluid. It becomes lymph when it enters a lymphatic vessel. Lymph will deliver bacteria to lymph nodes to be destroyed. It can also transport absorbed fat and return excess interstitial fluid and protein to the blood stream.

Lymph travels to at least one lymph node before emptying into the subclavian vein, where it mixes with blood before entering the right atrium.

The lymphatic circulation is driven by factors similar to that of the venous circulation:

1. Muscle activity
2. One-way valves
3. Respiration
   - Lymph = plasma proteins;
   - Lymphatic circulation collects fluid not reabsorbed by the capillaries;
   - Lymph is filtered in nodes before return to blood circulation.

Edema

Edema is the excess accumulation of interstitial fluid in tissue spaces. This can be caused by excess filtration or from inadequate reabsorption. Decreased plasma protein levels can lead to a decrease in blood colloid osmotic pressure, which reduces reabsorption and Edema can result. This is seen in burns, heart failure, malnutrition and kidney disease.

Edema can also result from a blockage of lymphatic flow.

Cardiovascular Physiology cont.

2. Tissue Perfusion

Blood flow through tissues is called perfusion. Each organ in the body typically has a small number of arteries bringing blood to it. Once these arteries enter the organ they rapidly branch into arterioles and capillaries. Proper delivery of oxygen and other nutrients to the organ depends on properly matching the demand for blood by the organ to the supply of blood to the organ.

Autoregulation

- It is important that the body be able to specifically regulate blood flow to individual organs based on their changing demands for blood. This is typically accomplished by autoregulation, in which local conditions affect flow to a particular organ.
- Arterioles are generally able to respond automatically to changes in blood pressure. Stretch of vascular smooth muscle tends to cause vasoconstriction. Reductions in stretch cause increased tone and vasodilation.
- Declining nutrient levels in an organ stimulate vasodilation of nearby arterioles and relaxation of precapillary sphincters to allow more blood and more nutrients into the organ.

Fluid Exchange:

Between Capillaries and Tissues

Hydrostatic pressure is the mechanical pressure acting on a fluid. Hydrostatic pressure is higher in arteries than in veins. Thus, hydrostatic pressure is greater at the arterial end of a capillary than at the venous end. Along the entire length of the capillary, the hydrostatic pressure within the capillary (HPc) is generally greater than the hydrostatic pressure in the interstitial spaces (Hpi). This means that hydrostatic pressure tends to drive fluid out of the capillaries, especially at the arterial end.

Colloid osmotic pressure is created by the presence of large molecules such as proteins that cannot diffuse across the capillary wall. These molecules attract water and create osmotic pressure. The concentration of molecules that create colloid osmotic pressure tends to be greater in the blood than in the interstitial spaces. Thus the colloid osmotic pressure within the capillary (Opc) is generally greater than the colloid osmotic pressure in the interstitial spaces (Opif). This means that colloid osmotic pressure tends to draw fluid into the capillaries.

At the arterial end of a capillary bed, HP typically exceeds OP, and there is net loss of fluid from the capillaries. At the venous end of the capillary bed, OP typically exceeds HP, and there is a net gain of fluid into the capillaries. Overall, there tends to be a net loss of fluid from the capillaries. This fluid is absorbed into the lymphatic system.

Movement In and Out of Capillaries

Only the blood in capillaries can exchange material with tissue cells. Because of their size, two things typically do not leave the blood – large proteins and formed elements. Movement in and out of capillaries occurs three ways:

1) Diffusion: Diffusion is the movement of substances from regions of higher concentration to regions of lower concentration. According to Fick's Law, this movement goes from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the concentration gradient. Diffusion is bidirectional along the length of the capillary.
   a) Simple diffusion is the most important way by which substances enter and leave capillaries. This method requires no energy expenditure.
   b) Facilitated diffusion is a method for some substances to move through the endothelial plasma membrane. The substances still move from areas of higher to lower concentration, but use carrier molecules to allow diffusion through the cell membrane. Substances that are transported via facilitated diffusion include most plasma

Cardiovascular Physiology cont.

solutes, amino acids, CO2, O2, glucose, and steroid hormones.

2) Transcytosis is a form of pinocytosis or uncommon vesicular transport. Large, non-lipid soluble molecules moved this way. Two forms of transcytosis exist: endocytosis, the way of moving substances that are outside of the cell to the inside of the cell; exocytosis, the process of moving substances that are inside the cell to the outside of the cell. Insulin entering blood and antibodies crossing the placenta are examples of transcytosis.
3) Bulk flow is the passive movement in the same direction of large numbers of particles which are dissolved or suspended in fluid. A pressure differential causes this type of movement. This movement is faster than diffusion and moves fluids and solutes both into and out of capillaries.
   a) Filtration is the movement of substances out of capillaries and into the interstitium.
   b) Reabsorption is the movement of substances from the interstitium back into capillaries.

Bulk flow helps deliver nutrients and oxygen to cells and remove waste and CO_2 from cells. Its most important function is to regulate the volumes of blood and interstitial fluid.
Two forces encourage filtration which predominates at the arterial end of a capillary.
a) Blood hydrostatic pressure = blood pressure
b) Interstitial fluid osmotic pressure – normally a small factor, since normal interstitial fluid contains only a small amount of protein.
Two forces encourage reabsorption which predominately occurs at the venous end of the capillary.
a) Blood colloid osmotic pressure – Proteins in the blood become more concentrated as fluids and solutes leave, creating a greater pressure differential encouraging fluid to return to the capillary.
b) Interstitial fluid hydrostatic pressure – A minor factor. This pressure differential would encourage fluid movement back into the capillary. This pressure is normally very low, often zero.

Filtration/Reabsorption

Starling's Law of the Capillaries demonstrates that the volume of fluid reabsorbed should be almost the same as the volume of fluid filtered. However, reabsorption does not quite equal filtration. About 85% of the fluid filtered from the arterial ends of capillaries is reabsorbed at the venous ends. The remaining 15% of the filtered fluid and plasma proteins that are not reabsorbed into blood capillaries are returned to the bloodstream by the lymphatic system. About 20 liters of blood are filtered out of capillaries, 17 liters are reabsorbed, and 3 liters enter the lymphatic system in the average human daily. Fluid movement is explained by the Starling Force:

Starling force = (Pc + Πi) – (Pi + Πp)
Pf = hydrostatic pressure in capillary
Πi = colloid osmotic pressure of the interstitial fluid
Pi = hydrostatic pressure in the interstitial fluid
Πp = colloid osmotic pressure of the blood plasma

Vascular Anastomoses

Vascular anastomoses are areas where vessels unite or interconnect. Most organs receive blood from more than one arterial branch. Arteries supplying the same area often merge, forming arterial anastomoses that provide alternative pathways for blood to reach a given body region (collateral circulation). If one arterial branch is blocked, arterial anastomoses provide the region with an adequate blood supply. Arterial anastomoses are abundant in abdominal organs, the heart, brain, and around joints, where active movement may hinder blood flow through one channel.

- Because of the many anastomoses among the smaller branches of the coronary arteries, a coronary artery can be 90% occluded by atherosclerosis (plaque) before a myocardial infarction (heart attack) occurs.
- Some organs are supplied by arteries that do not anastomose or that have poorly developed collateral circulation. These organs are particularly at risk if their arterial blood flow is interrupted. This is true for the retina, kidneys, and spleen.
- Venous anastomoses are more common than arterial and because of abundant collateral circulation occlusion of a vein rarely blocks enough blood flow to lead to tissue death.

3. Blood Distribution & Circulation Patterns

Circulation Time

Circulation time is the amount of time required for a drop of blood to pass from the right atrium, through the pulmonary circulation, to the left atrium, then through the systemic circulation and back to the right atrium. At rest, this should be about one minute. Despite the slow velocity, blood is in a capillary only a short period of time – only about 1-2 seconds on average.

Blood Distribution

At rest, blood is distributed:

1. 60% in systemic veins and venules
2. 5% in systemic capillaries
3. 15% in systemic arteries and arteioles
4. 8% in heart
5. 12% in pulmonary vessels

Systemic veins and venules are known as blood reservoirs. Blood contained in them can be quickly diverted to other vessels when needed. The major blood reservoirs are in the veins of the skin, liver, and spleen. Some examples of when blood must be diverted to other areas of the body include:

1. During exercise when blood diverted to skeletal muscle
2. During hemorrhage when blood diverted to circulation

After birth, blood follows two major circulatory pathways:

1. Systemic circulation includes all blood vessels carrying oxygenated blood from the left ventricle to all of the body's tissues (except for lungs) and back to the right atrium
2. Pulmonary circulation circulates deoxygenated blood from right ventricle through the lungs and back to the left atrium.

Systemic Circulation

Systemic arteries branch off the aorta to supply oxygenated blood to the systemic tissues. Blood returns to the heart through the systemic venous system, which start as venules and join together to eventually form the superior and inferior vena cavae.

Pulmonary Circulation

Pulmonary circulation carries deoxygenated blood from the right ventricle to the lungs and back to the left atrium. Blood leaves the right ventricle through the pulmonary trunk, which divides into the right and left pulmonary arteries to each lung. In the lungs, the arteries branch and eventually form capillaries, which surround the air sacs (alveoli) of the lungs. O_2 passes from the alveoli into the blood. The now oxygenated blood leaves the lungs through four pulmonary veins, returning to the left atrium for the systemic circulation.

Pulmonary arteries carry deoxygenated blood; pulmonary veins carry oxygenated blood. Much less pressure is needed to move blood through the lungs, so the right ventricle normally produces only about one fifth of the systolic pressure of the left ventricle.

Hepatic Portal Circulation

This specialized part of the systemic circulation detours venous blood from the digestive tract and spleen through the liver before returning it to the heart. This blood to the liver is carried by the hepatic portal vein formed by the union of the superior mesenteric veins and the splenic vein. The blood it carries is deoxygenated but rich in nutrients. The liver functions as a filter for potentially toxic substances.

The liver receives oxygenated blood from the hepatic artery. Hepatic veins merge and eventually drain into the inferior vena cava.

Cardiovascular Physiology cont.

4. Physiology of Circulation

- Cardiac output/blood flow
- Resistance
- Systemic blood pressure
- Maintaining blood pressure
- Short term – baroreceptors, chemoreceptors, vasomotor , hormonal
- Long term – direct renal, RAAS (indirect renal)

A liquid will flow through a tube as a result of differences in pressure at different points in the tube. The fluid always flows in the direction from high pressure to low pressure. The relationship between flow through a tube and the pressure gradient is given by the following equation:

$$F = \Delta P/R$$

where: F = flow; Δ
P = pressure gradient ;
R = resistance to flow

Cardiac Output

Flow through the entire circulatory system is equivalent to cardiac output (CO); the difference in pressure is approximately equal to the mean blood pressure (BP); and resistances comes primarily from friction in the small vessels of the periphery (total peripheral resistance, TPR). Thus, the equation given above becomes the following equation:

$$CO = BP_{(blood\ pressure)}/TPR_{(total\ peripheral\ resistance)}$$

$$CO = SV_{(stroke\ volume)} \times HR_{(heart\ rate)}$$

$$CO = 5.25 L/min$$

Resistance

Resistance to the flow of blood through a blood vessel is determined by three factors:

1. The viscosity of the blood
2. The length of the blood vessel
3. The diameter of the blood vessel

Viscosity is generally very constant but can vary with a number of diseases, such as anemia or polycythemia. Blood vessel length generally does not change in the adult. The longer the blood vessel, the greater the resistance to blood flow. The variable with the greatest influence on resistance is the diameter of the vessel. When considering vessel diameter, recall that resistance within a vessel is inversely proportional to the fourth power of the radius (Poisuille's equation). For example, if the radius is doubled, the resistance is 1/16 as much. Thus, resistance to blood flow is greatly effected by:

1. Vasoconstriction, the narrowing of the vessel diameter by contraction of the muscles surrounding the vessel.
2. Vasodilation, the widening of the vessel diameter by relaxation of the muscles surrounding the vessel.

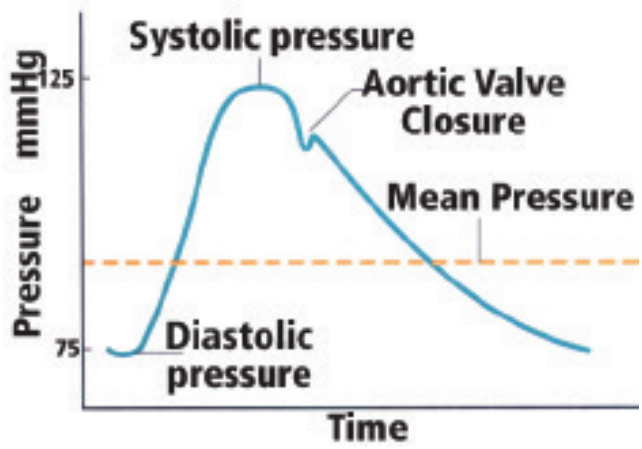
Cardiovascular Physiology cont.

Blood Pressure in Vessels

Systemic Blood Pressure

Systemic blood pressure is the force per unit area exerted by blood against a vessel wall. It is expressed in mm Hg. Blood pressure is highest at the aorta and lowest at the vena cava. Thus, blood expelled by the left ventricle flows down its pressure gradient until it reaches the right atrium.

Pressure varies significantly with the beating of the heart until blood reaches the arterioles. Pressure is highest in the arteries after the ventricles contract and expel blood into the arteries. This peak in pressure is called the systolic blood pressure (approximately 120 mm Hg in healthy adults). Elastic arteries expand to absorb some of the pressure. As the ventricles enter diastole, the pressure drops to what we call the diastolic blood pressure (approximately 70 to 80 mm Hg in healthy adults). This is the lowest level of arterial pressure during the ventricular cycle. Elastic arteries contract to keep the pressure from dropping too low. The difference between systolic pressure and diastolic pressure is called pulse pressure, and the differences is what is felt when someone palpates a pulse.



Blood Pressure waveform showing diastolic pressure before the aortic valve opens, and an increase in pressure as the ventricles contract (systolic pressure).

- Mean arterial pressure (MAP) is the average blood pressure in the arteries.
- MAP = diastolic BP + 1/3 (systolic BP-diastolic BP), making its value closer to diastolic BP
- MAP can also be expressed as CO X Resistance
- MAP and pulse pressure both decline with increasing distance from the heart.
- Blood pressure varies considerably over a 24 hour period. BP peaks in the morning possibly due to increased sympathetic nervous system activity. Most myocardial infarctions occur in the morning, but the exact relationship is unclear.
- Age, sex, weight, race, mood, posture, socioeconomic status, and physical activity may also cause variations in BP.

Alterations in Blood Pressure

Hypertension, a major cause of heart failure, stroke, renal failure and vascular disease is defined as condition of sustained arterial pressure of 140/90 or greater. Transient elevations are normal and can be caused by pain, fever, physical exertion, and emotional upset.

Measuring Blood Pressure

1. An inflatable blood pressure cuff is placed around the upper arm to squeeze the brachial artery.
2. A stethoscope is placed over the artery distal to the cuff.
3. The cuff is inflated with air. The cuff is connected to a gauge that measures pressure in mm Hg.
4. Inflation continues until the pressure measured is about 30 mm greater than that required to collapse the brachial artery.
5. Air is slowly released from the cuff. When pressure drops below systolic blood pressure, blood flow through the brachial artery will resume.
6. Blood enters at first at peak systolic pressure heard through the stethoscope because of turbulent flow. This is systolic pressure.
7. As further air is released, the sounds change. When cuff pressure falls below diastolic blood pressure, blood flow becomes laminar, and the sound becomes quite muffled or disappears. This is the diastolic pressure.
8. The sounds heard are Korotkoff sounds.

Cardiovascular Physiology cont.

1. Primary or essential hypertension - No underlying cause, but risk factors include smoking, obesity, age over 40 years, race, heredity, and diets high in sodium. 90% of hypertensive patients have primary hypertension.
2. Secondary hypertension – due to identifiable disorders, including excessive renin secretion, renal vascular disease, and endocrine disorders.
3. Hypotension is a condition defined by low BP in which systolic pressure is less than 90 mm Hg (some sources 100 mm Hg).
   - Orthostatic hypotension – temporary low BP and light headedness when suddenly arising from a seated or reclined position.
   - Chronic hypotension – sometimes seen with poor nutrition. May be a sign for Addison's Disease (adrenal insufficiency)
   - Acute hypotension – A sign of volume depletion or circulatory shock

Maintaining Blood Pressure

Because flow depends upon blood pressure, it is important to keep blood pressure high enough to maintain sufficient transport of gases and nutrients. However, a blood pressure that is too high may result in hemorrhaging or aneurysms. The body has both short- and long-term mechanisms to regulate blood pressure. By rearranging the equation noted previously, you can see that blood pressure can be altered via changes in cardiac output and total peripheral resistance:

The main factors influencing Blood Pressure are:
1. Cardiac output (CO)
2. Peripheral resistance (PR)
3. Blood volume

Blood pressure varies directly with CO, PR, and blood volume.

$$BP = CO \times TPR$$

Where:
BP = blood pressure;
CO = cardiac ouptut;
TPR is the combined resistance of all vessels

Cardiac Output

$$CO = \text{Stroke Volume (SV)} \times \text{Heart Rate (HR)}$$

Cardiac output is determined by venous return and neural and hormonal controls. At rest, the heart rate is controlled by the cardioinhibitory center via the vagus nerves.

- Under stress, the cardioacceleratory center increases heart rate and stroke volume.
- Also under stress, the end systolic volume (ESV) decreases and MAP increases

Increased blood pressure is caused by:
1. Increased blood volume
2. Increased cardiac output
3. Vasoconstriction

Decreased blood pressure is caused by:
1. Decreased blood volume
2. Decreased cardiac output
3. Vasodilation

Hyperemia

Active hyperemia is an increase in blood flow that delivers more O_2 and removes more CO_2.Reactive hyperemia is an increase in blood flow in response to a previous decrease in blood flow. The reduction of flow allows for increase of metabolites and a decrease in O_2. When flow is resumed, there is increased flow due to low resistance, metabolites are removed and O_2 is delivered. Active and reactive hyperemia are likely manifestations of local blood flow autoregulation.

Longor Short-term Mechanisms

Long or short-term regulation of blood pressure is mediated by the nervous system and chemicals in the blood. Neural control generally is accomplished via reflex arcs that involve baroreceptors or chemoreceptors, the vasomotor center of the medulla, and sympathetic efferent pathways. The effectors of these reflex arcs are vascular smooth muscles, primarily of the arterioles.

- The effect on the arterioles alters peripheral resistance.
- The vasomotor center is constantly sending some

Cardiovascular Physiology cont.

stimulation along these sympathetic pathways, leading to some constant level of constriction, called vasomotor tone. Baroreceptors sense increased pressure in the blood vessels as the vessels are stretched. They are located in the carotid arteries, the aortic arch, and in most other larger arteries of the neck and thorax.

- Stimulation of the baroreceptors sends afferent signals along the glossopharyngeal nerves that inhibit the vasomotor center.
- Afferent impulses from the baroreceptors also inhibit the cardioacceleratory center and stimulate parasympathetic activity. The baroreceptor system functions to protect against harmful short-term changes in blood pressure, and they are ineffective in protecting against long-term changes.
- Baroreceptor reflexes change peripheral resistance, heart rate, and stroke volume in response to changes in blood pressure.
- Chemoreceptors in the aortic arch and large arteries of the neck monitor the concentration of CO2 in the blood. As the level of CO2 rises, the chemoreceptors stimulate the cardioacceleratory and vasomotor centers. A similar effect is caused by decreasing levels of oxygen in the blood.
- The hypothalamus and cortex can also modify arterial blood pressure by signaling the medullary centers.
- Baroreceptors and chemoreceptors work via reflex pathways. Higher brain centers can also affect blood pressure. For example, the hypothalamus can cause a strong rise in blood pressure during the fight-or-flight response. The cerebrum can also affect blood pressure.

Hormonal Regulation

Renin-angiotensin-aldosterone (RAA) system: Renin is secreted by the juxtaglomerular apparatus of the kidney tubule when blood flow through the kidney is decreased. This is the beginning of a process that leads to the production of angiotensin II. This can increase blood pressure in two ways:

1. Can cause vasoconstriction, which acts quickly.
2. Can stimulate the secretion of aldosterone, which increases reabsorption of sodium and water in the kidney thereby raising overall blood volume. This is a slower process.

Epinephrine and norepinephrine made in the adrenal medulla increase cardiac output and cause vasodilation of heart and skeletal muscle vessels, while causing vasoconstriction of cutaneous and abdominal vessels.

Antidiuretic hormone (ADH), also known as vasopressin is made in posterior pituitary. It causes vasoconstriction. Inhibition of its release will result in vasodilation.

Atrial natriuretic peptide (ANP) is produced by cells in the cardiac atria. It is an antagonist to aldosterone and lowers BP by causing vasodilation and by causing loss of salt and water in the urine.

Cardiovascular Center

The cardiovascular center is located in the brain stem's medulla oblongata. After evaluating information obtained from baroreceptors, chemoreceptors, proprioceptors (which monitor movement of joints and muscles), cerebral cortex, limbic system and the hypothalamus, one or more of the following three areas (groups of neurons) of the CV center become active:

1. Cardiostimulatory (cardioacceleratory) center – cardiac accelerator nerves carry sympathetic impulses to the heart which cause an increase in rate and force of contraction;
2. Cardioinhibitory center – sends parasympathetic impulses to the heart via the vagus nerve to decrease heart rate;
3. Vasomotor center – sympathetic impulses only are carried by vasomotor nerves to smooth muscle in the walls of blood vessels. These affect all larger vessels but arterioles most of all. A moderate amount of vasoconstriction is maintained at all times (vasomotor tone). The effect of increased sympathetic impulses is vasoconstriction in small arteries and arterioles, raising BP. These same sympathetic impulses cause vasodilation in skeletal muscle and the heart (remember fight-or-flight).

Cardiovascular Physiology cont.

Sympathetic stimulation in veins causes constriction that moves blood from the reservoirs into the circulation. Even though some vessels dilate, more constrict, so the net response is a rise in BP.

Neuro Regulation

Baroreceptors are nerve cells that detect changes in pressure. They are located in the walls of arteries, veins and the right atrium and act as negative feedback systems for:

1. Carotid sinus reflex – maintains sufficient blood flow to the brain. The carotid sinus is a widening of the proximal internal carotid artery. Baroreceptors here detect a drop in BP to the brain and send impulses to the CV center in the medulla. These result in a quick increase in sympathetic impulses to raise BP by increasing both heart rate and force of contractions and by vasoconstriction. Baroreceptors also report an increase in BP. In this case the CV center responds by causing a decrease in heart rate and force of contractions, and by vasodilation.
2. Aortic reflex – baroreceptors in the aorta are concerned with systemic BP.
3. Chemoreceptor reflexes – chemoreceptors are nerve cells that monitor the chemical content of the blood. They are located in the carotid bodies and the aortic bodies. If O_2 or pH drop or if CO_2 rises, these chemoreceptors send impulses that result in sympathetic stimulation to arterioles and veins.

Chemicals

- Vasodilators.
- Nitric Oxide (NO) is produced by vascular endothelium in response to high blood flow and signals the surrounding smooth muscle to relax thus promoting systemic and localized vasodilation increasing blood flow. NO is also known as the endothelium-derived relaxing factor, or 'EDRF'
- Alcohol inhibits antidiuretic hormone release and the vasomotor center, resulting in vasodilation.
- Endothelium-derived factors promote vasoconstriction and are released in response to low blood flow. Endothelin and prostaglandin-derived growth factor (PDGF) are both vasoconstrictors.

Long-term Mechanisms

Long-term regulation is accomplished by the kidneys and it involves changes in blood volume. The kidneys act to regulate blood volume both directly and indirectly.

- The direct renal mechanism of blood pressure regulation is fairy simple and intuitive: when blood pressure is high, the amount of filtration of fluid into the kidneys naturally increases, and more urine is formed. Blood volume decreases and blood pressure decreases. When blood pressure is low, less fluid is filtered into the kidneys and fluids are conserved. Combined with intake of fluids, this results in an increase in blood volume and blood pressure.
- The indirect renal mechanism of blood pressure regulation involves various chemicals that act to elevate blood pressure in response to a decline in blood pressure. A drop in blood pressure causes the kidneys to release the enzyme, renin, into the blood. Renin leads to the production of the chemical, angiotensin II, which is a strong vasoconstrictor. Angiotensin II also stimulates the release of the hormone, aldosterone, from the adrenal cortex. Aldosterone promotes the retention of sodium by the kidneys, and the release of ADH by the pituitary gland.

Local Autoregulation of BP

Blood flow in a particular area of the body can be regulated locally in addition to the effect of changes in systemic BP.

1. Physical changes - Warming a body part can cause vasodilation and cooling can cause vasoconstriction.

Cardiovascular Physiology cont.

2. Chemical changes - Low O_2 levels, high CO_2 levels, and stretch of tissues can cause cells in the area to release vasoactive factors. These are chemicals like NO and endothelin. These influence the blood vessel diameter locally.

Shock

There are different types of shock:

- Hypovolemic is defined as the loss of blood or fluid volume. This can be from hemorrhage or volume loss from severe burns, vomiting, diarrhea leading to dehydration, etc.
- Cardiogenic is defined as inadequate heart function from myocardial infarction, heart failure, or severe dysfunction of heart valves
- Vascular is defined as widespread inappropriate vasodilation. There are three types of vascular shock:
  1. Anaphylactic shock is a severe allergic condition in which large amounts of histamine and histamine-like substances are released.
  2. Neurogenic shock results from damage to the cardiovascular center of the brain.
  3. Septic shock is a response to a widely disseminated infection
- Obstructive is defined as a blockage of blood flow at any site in the cardiovascular system such as pulmonary embolism, cardiac tamponade, etc.

Stages of Shock

- Compensated: In this stage, the body's compensatory mechanisms are able to maintain some degree of tissue perfusion. Usually occurs with the loss of up to 10% of total blood volume.
- Decompensated: In this stage, the body's compensatory mechanisms fail to maintain tissue perfusion and blood pressure falls. Usually occurs with the loss of 10-15% of total blood volume. Medical interventions can reverse the changes.
- Irreversible: In this stage, tissue and cellular damage is so extensive that the organism dies even if perfusion is restored.

Physiological Stages of Shock

The first physiological factor in the development of shock:
$VO_2 < MRO_2$
Metabolic demands for O2 exceed the body's oxygen consumption. Therefore, the first symptoms you would expect to find are:

- o increased respiratory rate
- o increased heart rate

Often the second physiological response to the development of shock is peripheral vasoconstriction. Symptoms would you expect to see are:

- o pale skin
- o cool skin
- o weakened peripheral pulses

As shock progresses physiological effects seen are:

- o End-organ perfusion falls
- o Symptoms seen
- o Altered mental status
- o Decreased urine output

As compensatory mechanisms fully engage, signs and symptoms seen are:

- o Tachycardia
- o Tachypnea
- o Pupillary dilation
- o Decreased capillary refill
- o Pale, cool skin

When compensatory mechanisms fail signs and symptoms seen are:

- o Hypotension
- o Falling SpO2
- o Bradycardia
- o Loss of consciousness
- o Dysrhythmias
- o Death

Stages of shock from www.bryanbledsoe.com/data/pdf/handouts/PowerPoint/Shock.ppt

Flow Dynamics

Hemodynamics is the physics of blood in circulation described in terms of the flow, pressures and velocities within blood vessels. Blood flow through the vascular system occurs from an area of high energy or pressure to an area of lower energy (pressure), with the heart pumping blood as the source of energy.

Flow is defined as the volume or quantity of fluid that passes a specific point in the circulation in a given period of time as expressed in mL/min or L/min.

F = Q (volume, quantity)/T (time)

Flow volume (quantity) should not be confused with flow velocity which is the speed at which flow passes a point in time as expressed in meters per second or minute.

The total blood flow of an adult at rest is about 5 L/min (cardiac output = amount of blood pumped by the heart in one minute).

There are two distinct configurations of flow: laminar and turbulent.

Laminar Flow

When blood flows at a steady rate through a long smooth tube, it flows in layers or concentric laminae, with each layer of fluid remaining the same distance from the wall of the tube. The velocity of the flow laminae at the center of the tube is much greater than the velocity of flow at the outer edges of the tube or vessel where wall friction causes fluid molecules to touch and adhere to the tube or vessel's wall. If the mean velocity of flow is v, molecules at the center of a tube are moving at approximately 2v, while molecules near the side of the tube or vessel are almost stationary. For example, when walking across a river, the water near the bank can be nearly stationary, while water in the middle of the river is moving considerably faster. Flow of a fluid in a tube or vessel is usually considered to be laminar when the flow rate is low.

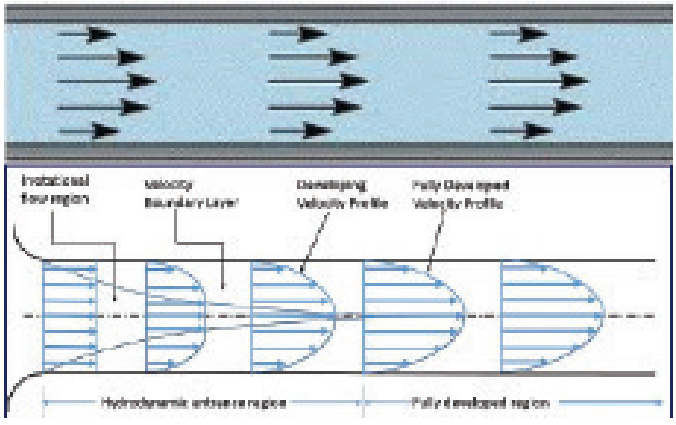


Fig. B1: Schematics showing the development of a laminar velocity flow profile with the laminae at the center of the tube or vessel moving quicker at higher velocities than the laminae near the walls of the tube or vessel where friction causes the flow molecules to touch and adhere.

Resistance (R) = change (delta) in pressure (P) divided by rate of change of mass or volume (V).

$$R = \Delta P / \Delta V$$

Turbulent Flow

Turbulent flow occurs when, instead of molecules moving in ordered layers, molecules become more disorganized and begin to swirl and form eddy currents (figure below).

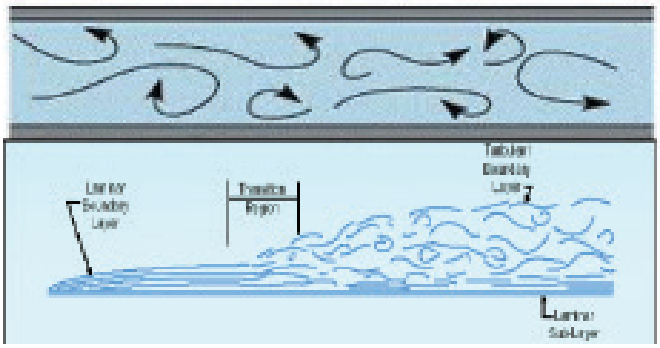


Fig. B2: Schematics showing the development of a turbulent velocity flow profile where, at high velocities, the laminae change from parallel layers to whirls and eddy currents as the flow passes an obstruction of bend in the tubing or vessel.

Flow Dynamics cont.

Eddy currents tend to react to each other, increasing the resistance to flow. As a result, greater energy input is required for a given flow rate, when compared to laminar flow.

With laminar flow, the flow rate is directly proportional to the pressure gradient. In turbulent flow, the flow rate is proportional to the square root of the pressure gradient. This means that, for turbulent flow, to double the flow, the pressure across the tube must be quadrupled.

Clinically, turbulent flow may lead to post-stenotic dilatation and aneurysms, as well as atherogenesis. An artery can narrow as a result of an atherosclerotic plaque, but the same amount of blood wants to travel through this partially blocked conduit. This is much like kinking a garden hose where turbulent flow can result.

Where blood vessels branch, or where atherosclerotic plaques narrow a vessel's lumen, turbulent flow can occur even at normal physiologic blood flow velocities. Turbulent flow can cause pieces of the plaque in vessels to break off creating emboli, which can travel to the brain with devastating consequences.

Resistance: Ohm's Law

Flow is related to resistance. Resistance is the force that opposes flow. Because electric current was once thought of as a type of fluid, Ohm's law can be used to represent the inverse relationship between flow (current) and resistance.

$$V = IR$$

where V = voltage; I = current; R = resistance.

Resistance can also be thought of in terms of a pressure differential required to produce a given rate of flow of a fluid through a vessel. Resistance arises from the viscosity (stickiness) of blood, vessel length and vessel diameter. Of these variables, the diameter of the vessel has the greatest effect on resistance. As the diameter of the vessel increases, the resistance drops exponentially.

Clinically, resistance can also be created by the vascular bed or "run off" distal to a bypass graft. Therefore, the graft itself may not be the cause if there is poor flow through a bypass.

The law of Conservation of Mass determines that volume flow will decrease as a vessel continues to branch. Multiple vascular resistances are cumulative within a single circuit.

Reynolds Number

Both a decrease in blood viscosity and increased blood velocity are factors that will increase the probability of turbulent flow and increase the corresponding Reynolds number.

The Reynolds number (Re) predicts laminar versus turbulent flow. It has no units.

$$Re = \frac{\text{diameter x velocity x density}}{\text{viscosity}}$$

The Reynolds equation expresses that viscous stresses tend to stabilize flow while excessive fluid inertia (diameter, velocity and density) will disrupt flow and lead to turbulence.

Thresholds:

Laminar flow Re	= <2300,
Transitional flow	= 2300-4000
Turbulent flow	= > 4000

The Reynolds number has clinical importance, because as vessels branch, narrow or bend, the velocity increases, turbulent flow is likely to occur and can cause physiologic heart murmurs in patients who have increased cardiac output and normal aortic valves. A bruit is the sound of turbulent flow passing plaque.

Flow Dynamics cont.

During exercise, cardiac output can increase up to five fold resulting in an increase in blood velocity and possible turbulence. This demonstrates that for a given flow in a tube, flow becomes turbulent once a critical velocity is reached. The critical Reynold's value is reached in the aorta during the opening of the aortic valve, when momentarily there is a peak velocity of 50 cm/sec. Reducing the aorta radius by 20% increases the average flow velocity from 30 cm/sec to 47 cm/sec and changes Reynolds number from 1590 to 2491 into the critical range.

Disturbances in the path of flow will create turbulence at much lower Reynolds numbers, and turbulence may occur at sudden changes proportional to the fourth power of the radius. Halving the radius of a tube/vessel increases the resistance to fluid movement by a factor of 16. As blood travels through a stenosis, its velocity will increase by a factor of the square of the change in radius. As blood travels through a stenosis, its velocity increases by a factor of the square of the change in radius. (e.g. a 50% reduction in diameter produces a fourfold increase in velocity). When this faster moving flow reenters a blood vessel of normal diameter beyond the stenosis, turbulent flow occurs creating a bruit or thrill.

Physical Characteristics of Flow

Flow is affected by a number of other physical characteristics:

Tube/Vessel Diameter: Flow is directly proportional to diameter. Therefore, if the tube diameter is halved, the flow through it reduces to one sixteenth. More fluid can be administered through a 16g cannula than a 22g cannula.

Length: If the length is doubled, the flow is halved. Flow is inversely proportional to the length of the tube. A central line is much longer than an IV cannula. For the same diameter, fluid delivered through a cannula can be given much more rapidly.

Viscosity: is the resistance to flow. This is a measure of the frictional forces within the laminae. Flow and viscosity are inversely proportional; as viscosity increases, flow will decrease. Represented as the Greek letter eta (H), viscosity of blood is generally considered to be constant. Whole blood viscosity is approximately four times that of water.

Temperature – although body temperature is generally within a narrow window, small variations in body temperature can affect blood viscosity. As body temperature decreases, blood viscosity increases. For each 1 degree C decrease in temperature, viscosity of blood increases by 2%.

Hagan-Poiseuille Equation

Hagen-Poiseuille's equation combines all the variables that determine flow, including a theoretical constant. This equation applies to laminar flow through a straight tube and assumes constant viscosity. The viscosity of blood changes with velocity since blood is not a uniform fluid. Viscosity is much lower in capillaries than the rest of the system. Blood vessels are also not straight or uniform.

$$Q = \frac{(\text{pressure difference})(\pi)(\text{radius of tube})^4}{(8)(H)(\text{length of tube})}$$

Where: ΔQ = flow;
H = viscosity

The Hagan-Poiseuille equation can be expressed in terms of resistance. The effective resistance in a tube/vessel is inversely proportional to the fourth power of the radius. Therefore, halving the radius of a tube/vessel increases the resistance to fluid movement by a factor of 16.

Flow Dynamics cont.

Clinical Applications for Flow

The circulatory system can be considered as a pump and a series of tubes/vessels that transport fluid. Properties of physics can be applied to both normal physiology and pathologic states.

Perfusion

In human physiology, the purpose of blood flow is to deliver a fluid (blood) to an organ or tissue to supply nutrients and oxygen, in exchange for carbon dioxide. This defines perfusion.

Fahraeus-Lindquist Effect

The Fahraeus – Lindqvist effect is an effect where the viscosity of a fluid (blood), changes with the diameter of the tube/vessel it is traveling through. In particular, viscosity decreases as the tube/vessel's diameter decreases (only if the vessel diameter is between 10 and 300 micrometers). This is because erythrocytes move over the center of the vessel, leaving plasma at the walls of the vessel.

Effect of Hematocrit on Viscosity

Blood is considerably more viscous than water. As viscosity increases, it becomes more difficult for blood to flow through a blood vessel. As the hematocrit (percentage of cells in the blood) increases, the friction between layers of blood increases. This friction determines viscosity. Therefore, as the hematocrit of the blood increases, the viscosity of blood increases. Generally, however, the blood viscosity is considered to be constant.

Conductance

Conductance, expressed as mm/sec/mm Hg, is a measure of flow through a blood vessel for a given pressure difference. It is the reciprocal of resistance. Slight changes in the diameter of a vessel cause considerable change in its ability to conduct blood. Conductance of a vessel increases in proportion to the fourth power of the diameter.

A four-fold increase in vessel diameter increases flow 256 times according to Hagan- Poiseuille's Law.

Compliance (Capacitance)

Many blood vessels have the ability to store energy during left ventricular systole and release energy into the system during diastole. This allows pulsatile ejection of blood by the heart to be converted to a more continuous flow throughout the cardiac cycle. The total quantity of blood that can be stored in a given portion of the circulation for each mmHg pressure increase is the vessel's compliance or capacitance expressed as:

$$\text{Compliance} = \frac{\text{Volume increase}}{\text{Pressure increase}}$$

Capacitance, the ability of a blood vessel to store energy during systole and dissipate it during diastole, is a function of the ratio of elastic to collagen fibers in a vessel wall. Elastin within vessel walls can expand or be stretched to an additional 50% - 70% of its resting length, while collagen extensibility is only 2% - 4%. Because of the relative decrease in elastin in more distal arteries as a person ages, they have less capacitance than arteries close to their heart. The compliance of a vein is about 24 times that of its corresponding artery because it is about eight times more distensible.

Flow Dynamics cont.

Pressure

The change in pressure measured across a given distance is a pressure gradient. The pressure gradient results in a net force that is directed from high to low pressure. This force is responsible for triggering the initial movement of fluid. This is the force that drives flow.

Sources of pressure differential that causes flow may be gravity or motion imparted by a pump.

$$\Delta\Delta P \text{ (pressure)} = \text{flow} \times \text{resistance}$$

For a given tube, the volume flow rate increases linearly with the applied pressure. The greater the pressure, the greater the flow.

Blood pressure is the force exerted by the blood against any unit area of the vessel wall expressed in millimeters of mercury (mmHg). For instance, squeezing an IV bag increases the pressure difference between the bag and the vein resulting in quicker fluid delivery.

$$\text{Flow} = \frac{\Delta\text{Pressure} \times \text{Diameter}}{\text{Viscosity} \times \text{Length}}$$

Flow = Pressure/Resistance
Resistance = Viscosity x Length/Diameter
Flow = Pressure/Viscosity x Length/Diameter

In human vascular physiology, blood viscosity and vessel length are generally considered to be constants. Vessel diameter is dynamic.

Pressure is Not Proportional to Flow or a Flow Surrogate

Pressure creates flow but is not a surrogate for flow. Stepping on a garden hose will decrease or completely stop flow, yet pressure to create flow remains. While it is universally accepted that a change in cardiovascular pressure gradient drives cardiovascular flow, McDonald's Blood Flow in Arteries presents a cardiovascular pulsatile flow and pressure wave in which, ironically, the flow pulse precedes the pressure pulse.

$$P = Q \cdot Z$$

where: Q = flow; ΔP = pressure differential over a vessel segment carrying flow (Q); Z = Impedance (=dynamic resistance) to flow of vessel Segment

A physiological pressure measurement is a spot measurement. It is not a differential pressure measurement across a vessel segment. Therefore, a single pressure measurement can never serve as a flow surrogate. Flow, the primary parameter in surgical procedures, cannot be deduced from a simple arterial pressure measurement.

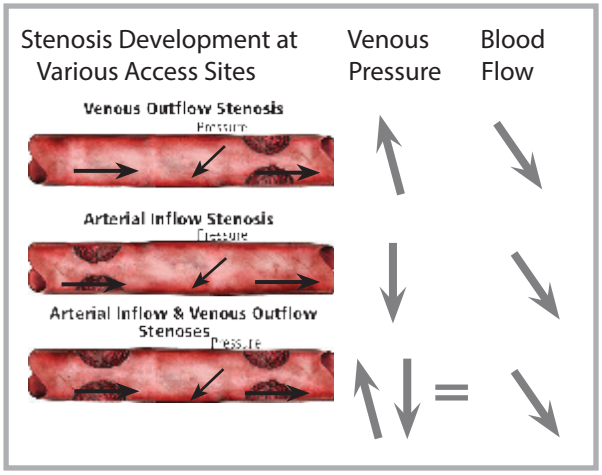


Fig. B3: The graphic of stenotic vessels on the right demonstrates that spot venous pressure, depending on the site of the stenosis, can at times increase as flow decreases; decrease as flow decreases or equalize with flow. The top graphic demonstrates increased resistance caused by a stenosis located past the venous pressure measurement site. Venous pressure increases; flow decreases. With an inflow stenosis, before the point where pressure is measured (middle graphic), venous pressure decreases. If multiple stenoses occur (bottom), one before the pressure measurement site, and another after, the two pressure components can cancel out one another.

Flow Dynamics cont.

Windkessel Effect

The Windkessel (German for elastic reservoir)effect is the term used to describe the recoiling effect of large arteries. The walls of large arteries (eg. aorta, carotid, subclavian, pulmonary arteries and their larger branches) contain elastic fibers. that allow these arteries to increase their diameters when the blood pressure rises during systole and decrease their diameters when the blood pressure falls during diastole. The diameter changes result in the large arteries retaining more blood during systole and discharging it during diastole.

This Windkessel compliance effect prevents excessive rises in blood pressure during systole. resulting in a lower mechanical load on the heart from fluid.

In many elderly persons, the Windkessel effect lessens because the walls of the aorta and other arteries become less elastic as a result of arteriosclerosis/ atherosclerosis.

Then, for the same amount of blood ejected from the heart during systole of the same duration, pressure increases in the large arteries. Such elevated systolic pressures have increasingly been shown to be associated with strokes, cardiac enlargement, heart failure and other undesirable events.

Flow Volume Versus Flow Velocity

Flow volume or quantity is often confused with flow velocity or speed. Flow volume is measured in mL/min or L/min. Flow velocity is measured in mm/sec or m/ sec. They do not have similar profiles as shown in the following graphic of five stages of stenosis in a vessel.

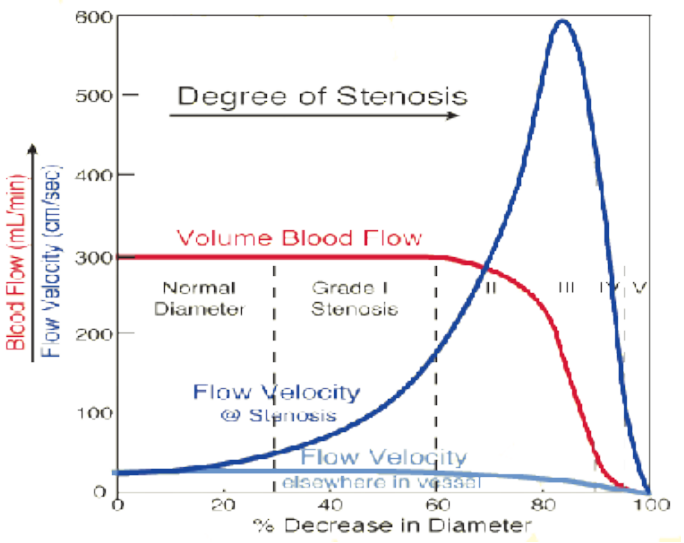


Fig. B4: Schematic that demonstrates the difference in a volume blood flow profile vis á vis a flow velocity profile as the size of a stenosis progresses. Note that flow volume remains steady until the diameter decreases more than 60 percent. At 80% diameter decrease, flow drops precipitously. On the other hand, flow velocity increases as the diameter of the tube or vessel decreases and spikes between 80 and 90 percent before suddenly dropping off. From Spencer P, Reid, JM, "Quantification of Carotid Stenosis with Continuous-Wave (C-W) Doppler Ultrasound," Stroke 1979; 10(3) 326-330.)

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ELSA UDT (REC & OxBV)

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Artificial Organ Development

Heart

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Kidney

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Lungs

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Womb

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Glossary of Terms

ACCURACY: The ability to obtain a measurement value close to the true value.

ABSOLUTE ACCURACY: the accuracy of an instrument's measurement at most physiological flows; offset error is insignificant compared to slope error. The term absolute accuracy has therefore evolved as a synonym for the range of error resulting from an incorrect slope.

RELATIVE ACCURACY: the accuracy of the instrument: often a linear correction with a slope and offset. Relative accuracy is often known as linearity.

ACOUSTIC WINDOW/FIELD: the area defined by the pathway of the ultrasound beam between the transducers or reflectors in the Flowprobe.

ACTIVATED CLOTTING TIME (ACT): A blood test that measures how many seconds it takes for the blood to clot. Monitored at least once every hour.

ACUTE RESPIRATORY DISEASE SYNDROME (ARDS) a severe, life-threatening medical condition characterized by widespread inflammation in the lungs. Occurs when fluid builds up in the tiny, elastic air sacs (alveoli) in the lungs that deprives the body of oxygen. It is often fatal.

AFTERLOAD The mean tension produced by a chamber of the heart in order to contract. It can also be considered as the 'mechanical load' that the heart must eject blood against. Afterload is therefore a consequence of aortic large vessel compliance, wave reflection and small vessel resistance (LV afterload) or similar pulmonary artery parameters (RV afterload). Ventricular afterload describes the hemodynamic resistance imposed on the heart by the arterial system. Myocardial afterload" refers to the peak force (or wall stress) generated during a contraction of the heart.

AMERICAN ASSOCIATION FOR THORACIC SURGERY (AATS): An association to promote scholarship, innovation, and leadership in thoracic and cardiovascular surgery.

AMERICAN INSTITUTE FOR MEDICAL AND BIOLOGICAL ENGINEERING (AIMBE): A non-profit organization, founded in 1991, that represents 50,000 medical and biomedical engineers, and academic institutions, private industry, and professional engineering societies.

AMERICAN SOCIETY OF ARTIFICIAL INTERNAL ORGANS - ASAIO: As a crossroads of science, engineering, regulatory and clinical practice, ASAIO serves as a venue for young investigators, a home for visionaries and entrepreneurs, a society which promotes a culture that respects all ideas.

AMERICAN SOCIETY OF NEPHROLOGY (ASN): Representing more than 21,000 kidney health professionals working to help people with kidney diseases and their families, ASN's goal is to create a world without kidney diseases.

ANGIOGRAPHY: A medical technique in which still images or moving images are taken to visualize the blood filled areas of the body.

ARTERIAL ELASTANCE (Ea) A measure of arterial load and its impact on the ventricle. Calculated as the simple ratio of ventricular end-systolic pressure to stroke volume.

BLENDER: A device that mixes room air with oxygen to create the desirable composition of sweep gas to be delivered to the gas side of the oxygenator. (see oxygenator)

ANALOG OUTPUT SIGNAL: The voltage output corresponding to the parameter measured by a device. The signal generated is calibrated by a scaling factor. The voltage range of Transonic ultrasound Flowmeters is -5 to +5 volts DC with 1 volt equivalent to full scale of the Flowsensor used.

APPLICATIONS: documented uses for Transonic Flowmeters.

BI-DIRECTIONAL FLOW: flow measured in positive and negative directions.

BI-DIRECTIONAL ILLUMINATION: with ultrasonic transit-time, Transonic Flowprobes, a tube or vessel is positioned between transducers which generate wide beams of ultrasound to fully illuminate the vessel or tube. The ultrasound beams alternately intersect the flowing liquid in upstream and downstream directions. The Flowmeter derives an accurate measure of the changes in "transit time" (time it takes for the wave of ultrasound to travel from one transducer to the other) influenced by the motion of the liquid.

BIO-IMPEDENCE: Refers to the electrical properties of a body, e.g. to what extent the body is a good conductor. Bioimpedance is a measure of how well the body impedes electric current flow. Fat has high resistivity, blood, lower resistivity. Impedance is measured by applying a small electric current via 2 electrodes and picking up the resulting small voltage with another pair of electrodes: The lower the voltage the lower the tissue impedance for a given current.

BIOMEDICAL ENGINEERING SOCIETY (BIMES): Founded in early 1968, BIMES is a professional society for biomedical engineering and bioengineering.

BLOOD GAS: Test that measures levels of venous and arterial oxygen, cabon dioxide, hematocrit, pH, bicarbonate, calcium, sodium, potassium, glucose, creatinine, and lactate. These are drawn usually every hour, and help guide the flow rate of the pump and gas settings on the oxygenator.

CALIBRATION: (often misused as a synonym for validation)
In Situ: adjustment or correction made to a measurement device for errors produced under actual conditions of use by comparing the measurement with a known standard.
In Vivo: adjustment or correction made to a measurement device during use in a living body.

Glossary of Terms cont.

CANNULA (pl. cannulas): A plastic tube that allows the drainage of blood from, or return to, the body. Also known as a catheter.

CANNULATE/CANNULATION: Placing cannulas or tubes into the blood vessel. This will be performed surgically or by percutaneous method

CARDIAC CONTRACTILITY The intrinsic ability of the heart to contract independent of preload and afterload. On a cellular level it can be characterized as the change of developed tension at given resting fiber length. Used interchangeably with Cardiac Inotropy.

CARDIAC INOTROPY The ability of the heart muscle to generate force through contraction. Used interchangeably with Cardiac Contractility.

CARDIAC INDEX (CO): Cardiac output normalized to body surface area (BSA).

CARDIAC OUTPUT (CO): The amount of blood pumped by the heart IN UNIT TIME (liters/min) and equivalent to the product of stroke volume (SV) and heart rate (HR).

CAVITATION: high negative pressure can pull air out of solution, and the bubbles will travel through the circuit and patient until they lodge in small passages, such as the oxygenator, or patient capillary beds.

CENTRAL VENOUS PRESSURE (CVP): The mean pressure in the systemic venous system.

CHECKSUM: A calibration factor stored in a Flowsensor's EPROM memory.

CLAMP-ON TUBING FLOWSENSOR: A sensor that is applied to the outside of flexible plastic tubing that measures the flow moving through the tubing.

COMPLIANCE (CAPACITANCE): The ability of a blood vessel to store energy during systole and dissipate it during diastole

COUPLING RATIO Indication of transfer of power from the ventricle to the peripheral vasculature.

DECANNULATE/DECANNULATION: The process of removing cannulas from the blood vessels. If the cannulas were placed by percutaneous method, they will be pulled out like an IV and pressure held for at least 20 to 30 minutes. Cannulas that were placed surgically will require a small operation to remove them. This can be performed at the bedside.

DERIVATIVE OF PRESSURE (dP/dt) Reported as max and min rate of pressure change in the ventricle. dP/dt are dependent on load and heart rate. LV dP/dt max occurs before aortic valve closure.

DERIVATIVE OF VOLUME (dV/dt) Rate of volume change in the ventricle. Maximum and minimum values of dV/dt are normally reported.

DIASTOLE: The phase of the cardiac cycle during which contractile properties return to their completely resting state.

ECLS: Extracorporeal Life Support: A common alternative term for ECMO, intended to differentiate a circuit with an oxygenator to a circuit without one. While ECLS is more descriptive, ECMO is still the most common collective term for both types of support.

ECMO: Extracorporeal Membrane Oxygenation mechanical circulatory support traditional term associated with use of prolonged extracorporeal cardiopulmonary bypass, usually via extrathoracic cannulation, in patients with acute, reversible cardiac or respiratory failure who are unresponsive to conventional medical or pharmacologic management.

ECMO FLOW: The amount of blood traveling through the ECMO circuit each minute. This flow is measured in cc per minute. This relates to how much support the patient is receiving.

EJECTION FRACTION (EF%) The ratio of the volume of blood ejected from the ventricle per beat (stroke volume) to the volume of blood in that ventricle at the end of diastole. It is widely clinically misunderstood as an index of contractility, but it is a load dependent parameter. Healthy ventricles typically have ejection fractions greater than 55%.

ELASTANCE: The ratio between stroke volume and end-diastolic volume (EF=SV/EDV). EF is the most commonly used index of contractility, mostly because it is relatively easy to measure in the clinical setting.

ELSA MONITOR: Extracorporeal Life Support Assurance Monitor that measures delivered flow, recirculation and oxygenation clotting with ultrasound dilution technology during ECMO.

ELECTRICAL ISOLATION: grounding of the Flowmeter's circuitry to prevent accidental electrical conductance between the Flowmeter and the subject.

E-MAX Maximum point in the pressure-volume relationship occurring at the end of systole. E-max is directly related to the contractile state of the ventricle chamber. This number is different for each individual heart beat, representing the maximal systolic elastance (E-max) at that moment in time.

END-DIASTOLIC PRESSURE-VOLUME RELATIONSHIP (EDPVR): The relationship between pressure and volume in a heart chamber (ventricle or atrium) at the instant of complete relaxation (end-diastole)

END-DIASTOLIC PRESSURE (EDP or Ped): The pressure in a heart chamber at the end of diastole.

END-DIASTOLIC VOLUME (EDV or Ved) The volume in a heart chamber at the end of diastole.

Glossary of Terms cont.

END-DIASTOLIC PRESSURE VOLUME RELATIONSHIP (EDPVR)
The EDPVR describes the passive filling curve for the ventricle and thus the passive properties of the myocardium. The slope of the EDPVR at any point along this curve is the reciprocal of ventricular compliance (or ventricular stiffness).

END-SYSTOLIC PRESSURE (ESP or Pes)
The pressure in a heart chamber at the end of systole.

END-SYSTOLIC VOLUME (ESV or Ves)
The volume in a heart chamber at the end of systole.

END SYSTOLIC ELASTANCE (Ees)
Slope of the end systolic pressure volume relationship. E(T) Time Varying volume elastance provides means to discriminate end systole from the end of ejection as they might not happen at the same time. Normal LV ejects every shortly after end systole.

END-SYSTOLIC PRESSURE (ESP)
Pressure in the ventricle at the end of systole.

END-SYSTOLIC PRESSURE VOLUME RELATIONSHIP (ESPVR) The maximal pressure that can be developed by the ventricle at any given cardiac chamber volume. This implies that the PV loop cannot cross over the line defining ESPVR for any given contractile state.

END-SYSTOLIC VOLUME (ESV) Volume in the ventricle at the end of systole.

EPROM: (Acronym for "electrically erasable programmable read only memory") programmed component that contains the identification and calibration information specific to each Flowsensor.

EXCITATION-CONTRACTION COUPLING The cellular relationship between electrical stimulus and contraction which is primarily influenced by Na+, K+ and Ca2+ ions and the neural, hormonal and exogenous agents which influence their behavior in the cell.

EUROPEAN ASSOCIATION OF CARDIO-THORACIC SURGERY (EACTS): Founded in 1986 as a European organisation devoted to the practice of cardio-thoracic surgery, there are now 4000 active members including surgeons, perfusionists and allied health professionals from all over the world.

EXTRACORPOREAL: measurements outside a body.

EXTRACORPOREAL LIFE SUPPORT ORGANIZATION (ELSO): An international non-profit broad multidisciplinary consortium of health care institutions collaboration who are dedicated to the development and evaluation of novel therapies for support of failing organ systems.

FILTERS: in electronics, a circuit that only passes certain signals. For blood flow measurement, a low pass filter is often used to strip out high frequency noise, leaving only the biological components of interest.

FLAT FREQUENCY RESPONSE:
When the sensitivity or gain of the instrument is equal for the entire operating range of frequencies. A usual requirement is that the frequency of input signal should not exceed 60% of the natural frequency of the measuring instrument.

FLOW: volume movement of a liquid (blood, saline, isotonic solutions) passing a given point in a given time (measured in L/min or ml/min).

FLOW/DILUTION SENSOR: a paired sensor that measures volume flow by transit-time ultrasound technology and concentration of the blood by standard dilution technique. Technology used by Transonic Hemodialysis, COstatus and ELSA Monitors.

FLOW VELOCITY PROFILE: the distribution of velocity across the vessel.

FLOWMETER: a device for measuring velocity or volume of flow of liquids or gases passing a given point per unit of time. For Transonic Flowmeters, the box which houses the power supply and signal processing circuitry for a digital readout of flow.

FLOWMETRY: the study of flow parameters.

FLOWPROBE/SENSOR: a sensor which measures flow. Ultrasonic transducers within Transonic ultrasound Flowprobes/sensors insonate vessels or tubing to measure volume flow of blood, buffers & other liquids;

FLOWSENSOR: a device which measures the volume of a liquid passing through tubing by transit-time ultrasound technology.

FRANK-STARLING LAW or Starlings Law "The heart will pump what it receives"-Starling's law of the heart Stroke Volume vs End diastolic volume: a statement in physiology: the strength of the heart's systolic contraction (stroke volume SV) is directly proportional to its diastolic expansion with the result that under normal physiological conditions the heart pumps out of the right atrium all the blood returned to it without letting any back up in the veins.

GAIN: a linear factor in electronic circuitry used in a device as a multiplier after calibration. The sensitivity of a Sensor is adjusted by changing the gain.

HAGAN-POISUEILLE EQUATION:
The effective resistance in a tube is inversely proportional to the fourth power of the radius.

HEART RATE (HR) Number of times the heart beats per minute.

ISA: International Society of Automation

ISO: International Organization for Standardization

ISOVOLUMIC RELAXATION CONSTANT (TAU) Tau represents the exponential decay of the ventricular pressure during isovolumic relaxation. Several studies have shown that Tau is a preload independent measure of isovolumic relaxation.

Glossary of Terms cont.

HEMODIALYSIS MONITOR: Measures delivered flow, recirculation vascular access flow and cardiac output during hemodialysis using flow/dilution technology.

HEMOFILTRATION: A hemoconcentrator, identical to a hemodialysis filter, used to remove extra fluid that a patient's own kidneys can't remove. It is inserted into the ECMO circuit.

HYSTERESIS: When an instrument produces unequal output for the same input during increasing and decreasing trends. This can produce misleading errors.

HZ: a cycle or repetition per second. In ultrasound: Transonic specification for the frequency of the ultrasound from the sensor crystals is listed in Megahertz (MHz).

INERTIA: In fluid dynamics, inertia is the momentum that propels fluid forward in a tube.

INTERNATIONAL SOCIETY OF MECHANICAL CIRCULATORY SUPPORT (ISMCS): A society that provides a broad international forum for intensive discussion of research, development, clinical use and social acceptance of rotary blood pumps and all related forms of mechanical circulatory support.

INTRA-AORTIC BALLOON PUMP (IABP): A catheter with a balloon at its distal end that is inserted into the descending aorta that is inflated during diastole (to increase pressure in the aorta and increase blood flow to the coronary arteries) and deflates during systole to reduce the resistance to blood flow out of the left ventricle, in principle, to increase cardiac output.

IN VITRO: In vitro comes from the Latin term "in glass." It refers to the technique of performing a given procedure/test in a controlled environment (such as a laboratory) outside of a living animal.

IN VIVO: In vivo refers to a procedure that is performed inside the body. It is often contrasted with in vitro testing performed outside the body in a laboratory.

JUGULAR VEIN: A large blood vessel in the neck. The ECMO cannula that drains blood into the circuit is often placed in this vein.

KIDNEY INNOVATION ACCELERATOR (KIDNEYX): A public-private partnership between the US Department of Health and Human Services and the American Society of Nephrology to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases.

LAMINAR FLOW: Concentric layers (laminae) of fluid that stay at the same distance from the wall of the tube. The velocity of the flow laminae at the center of the tube is much greater than those at the outer edges where wall friction causes fluid molecules to touch and adhere to the tube's wall.

LINEARITY: A constant gain over an entire range of measurements.

LINES (ECMO):
ARTERIAL LINE: the line from the oxygenator to the patient, even if it returns to a vein in the patient

VENOUS LINE: the line from the patient to the ECMO circuit, even if it returns to an artery in the patient.

LUSITROPY The relaxation properties of the heart during the diastolic phase.

MECHANICAL CIRCULATORY SUPPORT: Devices or therapies used to augment circulation due to heart failure.

MEMBRANE OXYGENATOR: An artificial lung. Carbon dioxide is removed and oxygen is added.
MICROPROCESSOR: miniaturized integrated circuit capable of processing a high volume of signals to report results or control functions of instruments or machines.

MOCK CIRCULATORY LOOP: A mechanical system used to simulate hemodynamic response of the human circulatory system for different physiological states.

MYOCARDIAL OXYGEN CONSUMPTION (MVO2) Amount of oxygen consumed by the heart as a measure of energy consumption. MVO2 is dependently correlated with cardiac total mechanical energy (TME).

OEM SYSTEMS: Original Equipment Manufacturer (OEM) systems: Transonic custom engineered systems to be embedded within clinical OEM products such as bypass pumps, ECMO apparatus, infusion/transfusion/perfusion systems, dialysis apparatus and organ preservation apparatus.

OXIMETRY: The measuring of oxygen saturation of the blood by means of an oximeter.

OXYGENATE: To combine or supply with oxygen. When oxygen enters the blood, as in the lungs, it becomes oxygenated. This is known as arterial blood.

OXYGENATOR: An artificial lung that adds oxygen and removes carbon dioxide from the blood as it passes through. The oxygenator is divided into two separate chambers by a semipermeable membrane. The venous blood enters the oxygenator and travels along one side of the membrane termed the BLOOD SIDE. Fresh SWEEP GAS is delivered to the other side termed the GAS SIDE. Gas exchange (oxygen uptake and carbon dioxide elimination) takes place across the membrane.

PERCUTANEOUS: ECMO cannulae are placed like an IV. The other option is to surgically place the cannulas. The surgeon will decide which method is best for each individual case.

POISEUILLE'S LAW: a pressure gradient across a vessel varies directly with a fluid's flow, its viscosity and the length of the tube, and varies inversely with the radius of the vessel.

Glossary of Terms cont.

POTENTIAL ENERGY (PE) Elastic potential energy of the heart is defined by the area between the ESPVR and EDPVR curves to the left of the PV loop. PE = ESP(ESV-V0)/2 -EDP(EDV-V0)/4 where V0 is the theoretical volume when no pressure is generated.

PRECISION: the quality of repeatable recognition of minute changes in measurements. An instrument may be precise but inaccurate or vice versa.

PRELOAD The "load" imposed on a heart chamber at the end of diastole. Preload is described as the stretching of a single cardiac myocyte immediately prior to contraction and is, therefore, related to the sarcomere length. Since sarcomere length cannot be determined in the intact heart, other indices of preload such as end diastolic volume, end-diastolic pressure and end-diastolic wall stress are used.

PRELOAD RECRUITABLE STROKE WORK (PRSW) PRSW is determined by the linear regression of stroke work with the end diastolic volume. The slope of the PRSW relationship is a highly linear index of myocardial contractility that is insensitive to preload and afterload.

PRESSURE-VOLUME AREA (PVA) The PVA represents the total mechanical energy (TME) generated by ventricular contraction. This is equal to the sum of the stroke work (SW), encompassed within the PV loop, and the elastic potential energy (PE).

PRESSURE-VOLUME LOOP (PV LOOP) Graph of pressure (y-axis) and volume (x-axis) of a ventricle over a single cardiac cycle. Several loops are often shown superimposed upon one another.

PRESSURE: the product of a fluid's density, gravitational force and height of the fluid column. It is the force exerted by a fluid against any unit area of a tube's wall as expressed in millimeters of mercury (mmHg).

PRESSURE-VOLUME AREA (PVA): The area on the pressure-volume diagram circumscribed by the systolic portion of the pressure-volume loop, the ESPVR and the EDPVR. PVA is considered to be a measure of the total mechanical work performed by the heart during a beat and consists of the sum of the external stroke work (SW) and the potential energy stored in the myocardium at the end of systole.

PUMP, AXIAL: a pump with a propeller inside of a tube. It consists of a screw type impeller that spins pushing fluid through the tube.

PUMP, CENTRIFUGAL: a pump having vanes that rotate in a casing and whirl the fluid around so that it acquires sufficient momentum to discharge the fluid.

PUMP, ROTARY: a pump for transferring water or other fluids by the rotating action of its components.

pVAD: (percutaneous ventricular assist device) a temporary mechanical circulatory support device to bolster a failing heart's performance.

RANGE: the set of numbers between the limits of the maximum and minimum values measurable or the amplitude and frequency of input over which the device is expected to operate.

RESISTANCE: The ratio between pressure (P) and flow (F) through a vascular structure: R=P/F. If pressure is in units of mmHg and flow is in units of ml/sec, R is in units of mmHg.sec/ml.

REPRODUCIBILITY: The ability for a device to obtain consistent results when measurements are repeated.

RESOLUTION: the smallest detectable change in flow. Probe resolutions are generally specified at 0.1Hz filtering.

REYNOLD'S NUMBER: The ratio of the a fluid's inertial force to its viscous force. In straight, smooth tubes and vessels, flow will be laminar at Re <2,000, turbulent at Re > 4,000 and in transition between laminar and turbulent between these values.

SAMPLING RATE: number of samples taken per unit of time. In digital signal processing (Nyquist theory), it is necessary to sample twice as fast as the highest frequency component.

SENSITIVITY: The smallest range of a variable and parameter that can be measured by the instrument (ratio of output signal magnitude to input signal magnitude). In electronic systems, sensitivity is referred to as gain; in mechanical devices, sensitivity is referred to as amplitude.

SENSITIVITY ERROR: error resulting from incorrect gain. Total error is the sum of sensitivity error and the offset error.

SERVO-REGULATION: an electronic pump-speed controller that slows and speeds the pump to match the venous return.

SIGNAL-TO-NOISE RATIO: The ratio of the output magnitude of the instrument to the underlying noise level. For ideal measurements, this is infinity.

STROKE VOLUME (SV): The amount of blood ejected from a cardiac chamber during a given heart beat. SV is the difference between the end-diastolic and end-systolic chamber volumes: SV = EDV - ESV.

STROKE WORK (SW): The energy generated per beat and equals the area within the pressure-volume loop; SW roughly equals mean arterial pressure (MAP) and stroke volume (SV).

SYSTOLE: The first phase of the cardiac cycle which includes the period of time during which the electrical events responsible for initiating contraction and the mechanical events responsible for contraction occur. It ends when the muscles are in the greatest state of activation during the contraction.

Glossary of Terms cont.

TRANSDUCER: a device that transforms a physical parameter into an electrical signal. In a Transonic ultrasound Flowsensor, ultrasound signals generated by piezoelectric crystals are transformed and converted into electrical signals proportional to volume flow.

TRANSIT-TIME: time it takes for a pulse of ultrasound to travel from one transducer to another in a Flowsensor.

TRIAL-OFF: Temporary clamping of the ECMO circuit, to determine the underlying effort the patient is able to maintain. When the patient can sustain their own cadiopulmonary needs, ECMO is discontinued.

TURBULENT FLOW: flow moving in whirls or eddy currents rather than in concentric laminae. Occurs when flow passes a blockage or makes a sharp turn at high velocities.

ULTRASONIC: relating to energy waves similar to those of audible sound but of higher frequency (above 30,000 Hz)

ULTRASONIC COUPLANT: a material that propagates acoustical waves; for blood flow measurement, a material is chosen that mimics the acoustic characteristics of biological tissue.

ULTRASONIC SIGNAL COUPLING: a term used to describe sound propagation between a transducer and tissue; degraded by air bubbles and materials that do not conduct sound.

ULTRASONIC TRANSIT TIME: a technology to measure volume flow of liquids by using wide-beam illumination; transducers pass ultrasonic signals back and forth, alternately intersecting a flowing liquid in upstream and downstream directions. The Transonic® Flowmeter derives an accurate measure of the "transit time" it took for the wave of ultrasound to travel from one transducer to the other. The difference between the upstream and downstream integrated transit times is a measure of volume flow.

ULTRASOUND DILUTION: a technology which unites dilution and ultrasonic transit time to measure the changes that occur in the velocity of a liquid when diluted with isotonic saline; measures recirculation, access flow and cardiac output during hemodialysis.

UNOXYGENATED BLOOD: Blood that has delivered most of its oxygen to the tissues of the body and is lower in oxygen. Also called venous (blue) blood.

VAD: (ventricular assist device) a mechanical circulatory support device to bolster a failing heart's performance as a bridge to transplant or as a "destination therapy."

VALIDATION: test to confirm calibration and accuracy of a measurement, usually by comparing to a known standard such as timed collection.

VENTILATOR: A breathing machine that delivers oxygen, pressure and a rate of breathing to the patient by a breathing tube. Also known as a respirator.

VISCOUS: A force caused by the friction from closely packed fluid particles between a fluid's concentric laminae layers that counteracts an inertial force.

WEANING: ECMO blood flow rate being decreased gradually as the patient improves, and is able to maintain adequate blood flow and oxygenation, without assistance.

WORLD HEALTH ORGANIZATION (WHO): Headquartered in Geneva, Switzerland with more than 7000 staff from more than 150 countries, WHO, as the directing and coordinating authority on international health within the United Nations, promotes the principles of human rights, universality and equity. Its mission is to promote health, keep the world safe and serve the vulnerable.

WIDE-BEAM ILLUMINATION: the use of an ultrasonic beam wider than the vessel of interest. Wide-beam illumination is fundamental for volume flow measurement with ultrasonic transit-time technology.

WINDKESSEL EFFECT: The phenomenon in which large elastic arteries such as the aorta store up to 50% of the stroke volume of each systole and discharge that volume with diastole. This helps to decrease the load on the heart, minimize systolic flow and maximize diastolic flow in the arterioles.

(X) CROSS BEAM ILLUMINATION: Ultrasonic illumination of a vessel or tube positioned between four transducers that generate wide beams of ultrasound that alternately intersect the flowing liquid in upstream and downstream directions. The Flowmeter derives an accurate measure of the changes in "transit time" of the wave resulting from the motion of the liquid. The integrated difference between the upstream and downstream transit times is a measure of volume flow.

ZERO OFFSET: the measurement registered by the instrument under conditions of zero input. In blood flow, this is the Flowmeter reading when flow is known to be zero due to occlusion of the vessel or other means. A two point calibration can be performed by combining a zero offset determination with a timed collection.

ZERO OFFSET DRIFT: the change in zero offset over time. Caused by fluctuations in a flowmeter's oscillations due to variations in acoustic transit-times as a result of temperature or other liquid property changes that are picked up by a Flowmeter's sensitive receiver amplifiers and detectors.

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Transonic Systems Inc. is a global manufacturer of innovative biomedical measurement equipment. Founded in 1983, Transonic sells "gold standard" transit-time ultrasound Flowmeters and Monitors for surgical, hemodialysis, pediatric critical care, perfusion, interventional radiology and research applications. Transonic also provides pressure and pressure volume systems, laser Doppler Flowmeters and telemetry systems.

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