Isolated Lung Perfusion Systems for small to large animal models

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Hypoxic Vasoconstriction Resistance & Compliance Pulmonary Metastases Respiratory Mechanics Vascular Permeability Surfactant Bioactivity Inhalation Toxicology Inhalation Therapy Lung Regeneration Tissue Engineering Lung Preservation Edema Formation Drug Absorption Ex Vivo Perfusion

The Physiology Specialists

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HUGO SACHS ELEKTRONIKHARVARDThe Physiology SpecialistsA P P A R A T U S

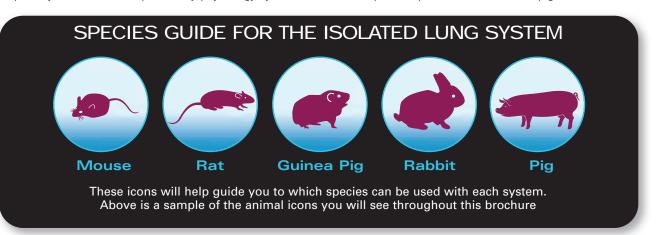
INTRODUCTION TO THE ISOLATED PERFUSED LUNG (IPL)

The IPL method has been found to be invaluable in characterizing the non-respiratory capabilities of pulmonary tissues such as pulmonary metabolic activity as well as the activities of various components (pulmonary alveolar macrophage, alveolar tissue, endothelial tissue, etc) in response to inhaled/airborne particulates/therapies. Isolated lung systems are equally useful for evaluating respiratory functions such as respiratory mechanics and gas exchange. The lungs, while being removed from the body, are still an intact functional organ, unlike other in vitro methods such as slices and cultures, and therefore can continue in their physiological function without the interference from the CNS and other systems of the living organism.



ISOLATED LUNG SYSTEM FOR SMALL RODENTS THROUGH LARGE ANIMAL

Hugo Sachs Elektronik - Harvard Apparatus has always provided top-notch, fully-integrated physiology research systems. In order to enhance the ease of acquisition and quality of data for researchers in pulmonary physiology we now introduce 4 Modular Isolated Perfused Lung systems. The IPL series of Isolated Lung perfusion systems represents a full line of in-depth respiratory mechanics and pulmonary physiology systems tailored for specific species from mouse to pig.









WHAT MAKES THE IPL SERIES SO REVOLUTIONARY?

The IPL preparation requires both the perfusion of the vascular system as well as the ventilation of the respiratory tract. Like all HSE perfusion systems the IPL series utilizes a Solid State Physiological Perfusion Circuit (S²P²C) technology, defined by the use of a solid block of material (Perspex) with precision-milled perfusion and ventilation pathways. The S²P²C is integrated into a common architecture, appropriately scaled for species, ensuring precisely repeatable non-turbulent perfusion and ventilation for the highest fidelity pressure and flow measurements. This, combined with the natural thermal properties of Perspex, creates a system that allows control, maintenance and monitoring of pulmonary parameters in a way that is more physiologically relevant than any conventional perfusion system.

Designed in collaboration with experts in the field of pulmonary physiology and isolated lung perfusion, researchers can have confidence in a system that meets their needs right out of the box.

CONSTANT FLOW VS. CONSTANT FLOW PERFUSION IN LUNGS -WHY THE OPTION?

Lungs can be perfused by either constant flow or constant pressure. Although constant flow perfusion may mimic the in vivo situation more closely, it has the disadvantage that in case of vasoconstriction hydrostatic edema becomes inevitable. Since lymph drainage is not possible in perfused lungs, extravascular water will accumulate quickly. For this reason, when using constant flow perfusion small flow rates have been used to minimize hydrostatic edema. However, small flow rates may decrease lung functions such as serotonin metabolism and protein synthesis. Constant pressure perfusion permits higher perfusate flow rates since in this case vasoconstriction decreases the perfusate flow and hydrostatic edema is unlikely to occur. Constant pressure allows the researcher to maintain lungs in a physiologically healthy way as well as to directly study edema formation caused by increased vascular permeability.

All IPL-Systems are supplied standard with the option of a simple switch between constant flow and constant pressure for maximum protocol and application flexibility.

IPL SYSTEMS FEATURES & BENEFITS

The HSE system architecture utilizes a unique technology to enable seamless switching between positive and negative pressure ventilation on all models from Mouse to Rabbit/Fetal Pig. Negative pressure ventilation is the natural method of breathing for the lung and has been demonstrated to allow a much increased pulmonary artery flow and decreased edema formation in comparison to positive pressure ventilation. Combined with constant pressure perfusion, optimal physiologic lung function can be more easily achieved.

Systems begin at basic perfusion and ventilation and can become complete Respiratory Mechanics Workstations with a range of measurement devices, signal conditioning equipment, and acquisition & analysis software, providing a superior solution for virtually any study.

Building your system is as simple as selecting the basic system for your lung model and then adding various options to suit the particular needs of your study. Should any questions arise, our expert team of scientists and engineers is always ready to assist you with system configuration, application support or custom design requests.

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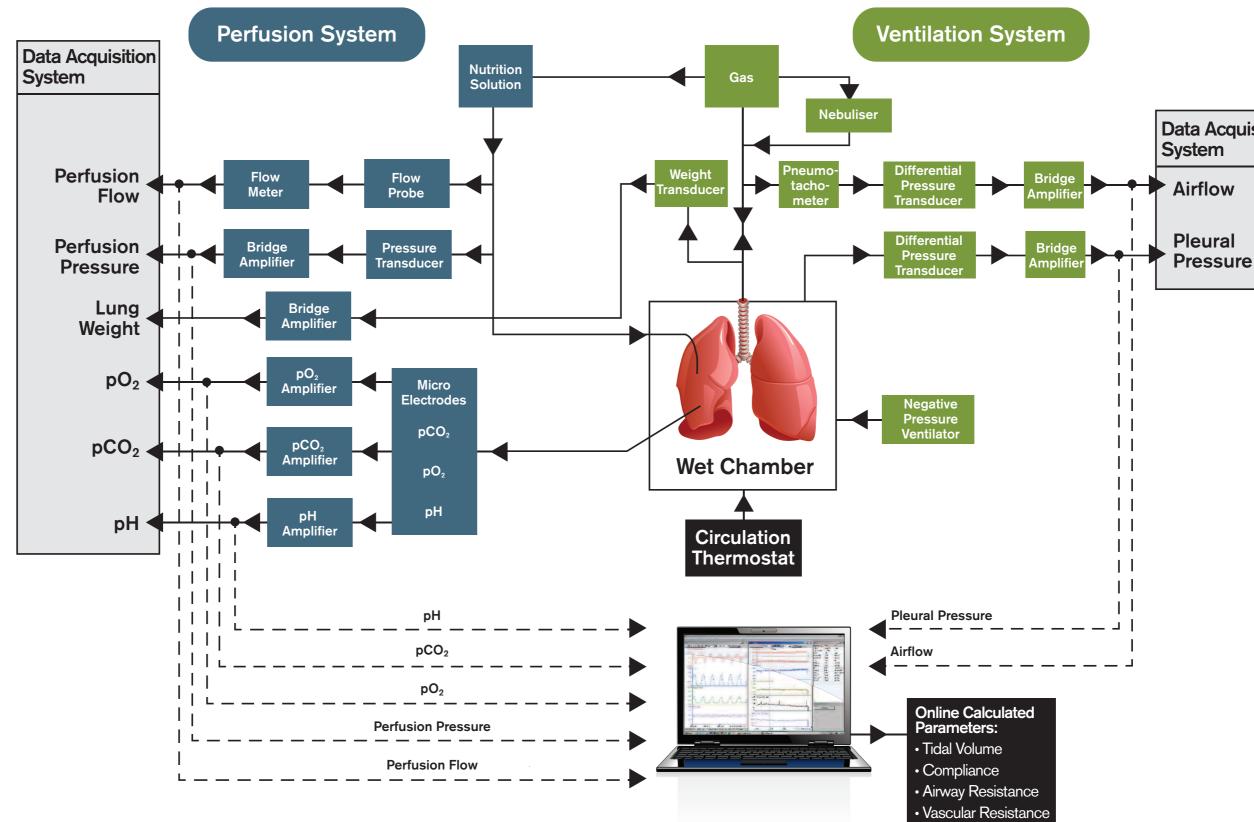
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Block Diagram for the Isolated Perfused Lung



Data Acquisition System Airflow

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IPL-1 Isolated Lung Perfusion System

POSITIVE & NEGATIVE PRESSURE VENTILATION

 Option for positive and negative pressure ventilation with one-step switch

CONSTANT FLOW & PRESSURE

Quick switch from constant flow to constant pressure for maximum application flexibility

RESPIRATORY PATH

- Built-in, warmed pneumotachometer for minimal dead space volume Milled infusion and pressure measurement paths
- allow access to closed chamber Built-in Humidifier frit prevents lung drying

- BASIC MEASURED PARAMETERS
- Perfusion (Pulmonary Artery) Pressure
- Perfusion (Pulmonary Artery) Flow
- Respiratory Flow
- Intrapleural Pressure (or Tracheal Pressure)



PRESSURE BALANCED

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Pressure-balancing vessel eliminates transmural pressure difference during subatmospheric ventilation Allows for simulation of hypertensive cardiac afterload

OPTIONS

- Simple add-on Aerosol Nebulizer Multi-Gas for hyperoxic, hypercapnic, anes-thetic or other alternative gas studies

UNIQUE CANNULAE

- Cannulae are matched to the size of mouse vessels
- Tip occlusion protectors and mini-ball holder system minimize the incidence of vascular occlusion
- Pulmonary Artery Cannula incorporates secondary bubble trap to prevent air emboli during perfusion

MOIST LUNG CHAMBER

- Access ports for additional measurements or other sensors
- Integrated heat exchanger-bubble trap for minimal system volume
- Mini Ball-Joint system secures cannulae in optimal position
- Fully Water-Jacketed Base and Lid for Superior Temperature Control

IPL-1 BASIC: The Most Popular Mouse Isolated Perfused Lung System



The IPL-1 is engineered for the most demanding applications. As a result the basic system can easily be upgraded to add capability modules for virtually any ex-vivo pulmonary assay. For detailed descriptions of system extensions and options see pages 9-11, 31-33.

Due to the fragile nature of the mouse lung, its suspension from the tracheal and vascular cannulae is difficult to accomplish without the rapid occurance of edema. In collaboration with experts in pulmonary physiology, an alternative design was implemented which allows for ventilation and perfusion with the lungs remaining in situ at a slight incline. This novel approach simplifies cannulation of the pulmonary artery and left atrium of the heart and dramatically reduces edema formation.

MEASURED SIGNALS & PARAMETERS ON AN IPL-1 BASIC SYSTEM:

The Following Signals are Recorded as Raw Data:

- Pulmonary Artery (Perfusion) Pressure
- Perfusion Flow
- Intrapleural (artificial thorax) Pressure or Tracheal Pressure
- Respiratory Flow

The Following Parameters can be calculated from the Raw Data*:

- Tidal Volume, Minute Volume
- Respiratory Volume
- Peak Inspiratory & Expiratory Airflow
- Vascular Resistance
- Respiration Rate
- Inspiratory Time & Expiratory Time
- End Inspiratory & Expiratory Pressure
- Dynamic Airway Resistance & Compliance
- * Calculations are automatic when HSE PULMODYN software is used.

FEATURES & BENEFITS

- Exclusive artificial thorax chamber for isolated lung with integrated changeover system for switch between simple positive-pressure ventilation and physiological negative (subatmospheric pressure ventilation)
- Integrated surgery table to reduce damage during preparation
- Unique built-in pneumotachometer and air humidifier with small dead volume
- Drug injection pathway built directly into pulmonary perfusate stream
- Low flow resistance and dead space volume minimize perfusion artifacts
- Proprietary cannulae are matched to mouse vessel and feature tip occlusion protectors and Mini Ball system which allow cannulae to be fixed, further reducing the incidence of vascular occlusion

The IPL-1 Basic Consists of the Core System & Selections Among the Following Options

Core System: 73-4292 (115V) or 73-4291 (230V):

Basic IPL-1 System Includes:

- IPL-1 Base Unit for Isolated Mouse Lungs
- Thermocirculator
- Analog Roller Pump
- Perfusion Pressure Measurements
- Low Range Pressure Transducer
- TAM-D PLUGSYS Transducer Amplifier Module
- Perfusion Controller Module, SCP (for constant flow or constant pressure perfusion)
- PLUGSYS Basic System Case, 603
 - Utilizes 8 of 20 Available Slot Units*
- Respiratory Flow Measurement
- Differential Low Pressure Transducer DLP
- TAM-A PLUGSYS Transducer Amplifier Module
- Artificial Thorax Pressure
 - Differential Low Pressure Transducer MPX
 - TAM-A PLUGSYS Transducer Amplifier Module
- Clamps and Stand for Secure Mounting of Transducers
- 0.5 L Perfusate Reservoir
- * If your chosen options require more than 20 Slot Units you will need to add a case extension. See page 33.

For a working unit, the core system requires the addition of a selection of one of the option VCMP, VCMR-1 or PPV-1.

FEATURES & BENEFITS

- VCM Ventilator Options:
- VCM modules allow for the physiological negative pressure ventilation of the lung and positive ventilation during preparation
 - 30-100 breaths per minute
 - I:E ratio can be set between 10 & 90% in 10% steps
 - End-inspiratory, End-expiratory, sigh and negative pressures can be individually set
- TCM timer counter module allows periodic sigh (hyperinflation) breaths to minimize edema formation and mimic natural breathing

Option VCMP: 73-4279

Negative Pressure Ventilation Controller with Pump to Core IPL-1 & 2

- Choose this ventilation option when:
- * performing standard positive- and negativepressure ventilation studies

Includes:

- VCM-P PLUGSYS Ventilation Control Module with Integral Pump
- TCM PLUGSYS Timer Counter Module for introduction of periodic Sigh Breaths (hyperinflation)
- Utilizes 6 Slot Units

Option PRGS-1: 73-2789

Alternative Gas Supply to Core IPL-1 with Option VCMP

Choose this ventilation option when:

* delivering alternative gases during negative pressure ventilation

Includes:

Pressure Free Gas Supply Adapter

Option VCMR-1: 73-4293

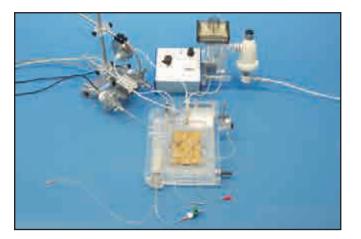
Negative Pressure Ventilation Controller with Pressure Regulator to Core IPL-1

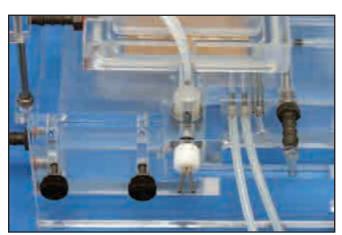
* Requires pressurized gas supply from tank or house air in the range of 2-8 bar (29 – 116 PSI)

Choose this ventilation option when:

- * performing standard positive- and negative-pressure ventilation studies
- * delivering alternative gases during both negativeand positive-pressure ventilation

- VCM-R PLUGSYS Ventilation Control Module with Regulator
- TCM PLUGSYS Timer Counter Module for introduction of periodic Sigh Breaths (hyperinflation)
- Pressure Free Gas Supply Adapter
- Utilizes 6 Slot Units





Option PPV-1: 73-4306 (115V) OR 73-4305 (230V):

Positive Pressure Ventilation to IPL-1

Choose this ventilation option when only positive pressure ventilation is desired

Includes:

- Minivent Mouse Ventilator
- Y-Adapter to Connect External Ventilator

FEATURES & BENEFITS

- Ventilation Rate from 60 to 400 Breaths per Minute
- Stroke Volume 30-350 µl , Simple Adjustment while Running
- Compact size Allows Positioning Close to System for Minimal System Volume
- Valveless Piston will not Clog, Easy to Clean



Option AG-1: 73-4294

Aerosol Nebulizer Kit to IPL-1

FEATURES & BENEFITS

- Low particle sizes (100% of the particles are below 10 μm)
- No Solution Warming Required
- Recommended for Nebulizing Drugs Sensitive to Ultrasonics
- Aerosol is Automatically Transported by Compressed Air at a Pressure of 1.5 bar (22 PSI)

Includes:

- Multi-Gas Adapter and Connection Kit for IPL-1



Option DEOX150-1: 73-4307

Deoxygenation Unit to Core IPL-1 System

FEATURES & BENEFITS

- Deoxygenation of Blood or Buffers Containing Protein (e.g. Albumin) or Erythrocytes
- 19 ml Priming Volume
- MediSulfone[®] Membrane Material with 0.25 m² Deoxygenating Surface Area

Includes:

- Stand Alone Fiber Oxygenator Holder
- D150 Fiber Oxygenator Pack 5
- Triangular Stand with Clamp

Option pHC-1: 73-4308

pH Control Unit to Core IPL-1 System

FEATURES & BENEFITS

- CO₂ Delivery to Maintain pH when System is not Deoxygenated with N₂/CO₂ Gas Mixture
- pHCM Controller Delivers Gas (Commonly CO₂) by Bubbling into Mixed Buffer to Maintain a Desired pH Set Point Dictated by pHCM Module
- Minimizes Foaming of Perfusates due to Minimal Gassing of 100% Gas to maintain pH

Includes:

- pHMM PLUGSYS pH Measurement Module
- pHCM PLUGSYS pH Control Module
- Flushtrode[®] pH Electrode & Connection Cable
- Electrolyte
- Modified Cover to 0.5 L Reservoir
- Utilizes 4 Slot Units
- * Magnetic Stirrer and Stirbar sold separately

Please see pages 31-33 for Additional Measurement Options for Venous Pressure; pH, pO₂, pCO₂ Measurement, Data Acquisition Hardware & Software Packages, Drug Application Pump, and more.

References:

- Uhlig, U., Fehrenbach , H., Lachmann, R., Goldmann, T., Lachmann, B., Vollmer, E., & Uhlig, S. (2004). Phosphoinositide 3-oh kinase inhibition prevents ventilation-induced lung cell activation. American Journal of Respiratory Critical Care Medicine, 169(2), 201-8.
- Kuebler, W., Uhlig, U., Goldmann, T., Schael, G., Kerem, A., Exner, K., Martin, C., & Vollmer, E. (2003). Stretch activates nitric oxide production in pulmonary vascular endothelial cells in situ. American Journal of Respiratory Critical Care Medicine, 168(11), 1391-8.
- Held, H., Boettcher, S., Hamann, L., & Uhlig, S., (2001). Ventilation-Induced Chemokine and Cytokine Release Is Associated with Activation of Nuclear Factor- κ B and Is Blocked by Steroids. American Journal of Respiratory Critical Care Medicine, 163(3), 711-716.
- von Bethmann, A., Brasch, F., Nüsing, R., Vogt, K., Volk, H., Müller, K., Wendel, A., & Uhlig, S. (1998). Hyperventilation induces release of cytokines from perfused mouse lung. American Journal of Respiratory Critical Care Medicine, 157(1), 263-272.
- Held, H., & Uhlig, S. (2000). Basal lung mechanics and airway and pulmonary vascular responsiveness in different inbred mouse strains. Journal of Applied Physiology, 88(6), 2192-8.
- Vanderpool, R., Naeije, R., & Chesler, N. (2009). Impedance in isolated mouse lungs for the determination of site of action of vasoactive agents and disease. Annals of Biomedical Engineering, 38(5), 1854-61.
- Busch, C., Spohr, F., Motsch, J., Gebhard, M., Martin, E., Weimann, J., (2010). Effects of ketamine on hypoxic pulmonary vasoconstriction in the isolated perfused lungs of endotoxaemic mice. European Journal of Anaesthesiology, 27(1), 61-66.

IPL-1 references continued on page 34.

IPL-2 Isolated Lung Perfusion System (~) - ()

NEGATIVE PRESSURE VENTILATION

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 Option for positive and negative pressure ventilation with one-step switch Configurable periodic sigh (hyperinflation) breaths to minimize edema formation

CONSTANT FLOW OR PRESSURE PERFUSION

 Quick switch from constant flow to constant pressure for maximum application flexibility

OPERATING TABLE

- Surgery takes place at hydrostatically neutral elevation minimizing unphysiological hydro-static pressure perturbations
- Removable cannulation block allows:
 - Optimized Cannulation and Intubation of Lung
 - Continuous Ventilation to Prevent Lung Collapse and Negate the Need for Reinflation
 - Continuous Perfusion to Maintain Tissue Viability and Metabolism
- Plastic Trough Collects Waste
- Table is Easily Removable for Cleaning After Lung is Placed in Chamber

Ventilation

MODE

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to Negative Pressure

UNIQUE LUNG CHAMBER

Fully-Thermostated Lung Chamber

- Unique Chamber Lid Incorporates:
 - Heating Coil/Bubble Trap
 - Pneumotachometer
 - Positive Pressure Ventilation Head (Used During Surgical Preparation)
 - Perfusion and Ventilation Ports
 - Integrated Humidifying Frit
- Custom Cannulae Designed to Access Pulmonary Vasculature Via the Heart
 - Tip Occlusion Protectors Inhibit Vascular Occlusion to Maintain Desired Flow

IPL-2 BASIC: The Standard for most Isolated Lung Preparations



The IPL-2 is the standard for most isolated lung preparations. The guinea pig IPL preparations are preferred for inhalation studies while rat lungs, popular for use in pulmonary metabolism studies, are an ideal size for ease of preparation, as well as being cost effective for the researcher. The basic system can be easily upgraded to add capability modules for virtually any ex-vivo pulmonary assay - with additions for multiple nebulizers, lung weight measurement, and more.

For detailed descriptions of system extensions and options see pages 15-19, 31-33.

MEASURED SIGNALS & PARAMETERS ON AN IPL-2 BASIC SYSTEM:

The Following Signals are Recorded as Raw Data:

- Pulmonary Artery (Perfusion) Pressure
- Intrapleural (artificial thorax) Pressure or Tracheal Pressure
- Respiratory Flow

The Following Parameters can be calculated from the Raw Data*:

- Tidal Volume, Minute Volume
- Respiratory Volume
- Peak Inspiratory and Expiratory Airflow
- Vascular Resistance
- Respiration Rate
- Inspiratory Time & Expiratory Time
- End Inspiratory and Expiratory Pressure
- Dynamic Airway Resistance & Compliance
- * Calculations are automatic when HSE PULMODYN software is used.

FEATURES & BENEFITS

- Optimized temperature conditions for the isolated lung, unique jacketed thoracic chamber
- Operating table for non-damaging in-situ preparation
- Negative-pressure ventilation similar to in-vivo condition or positive-pressure ventilation available
- Low flow resistance and dead space volume, minimize perfusion artifacts
- Unique built-in pneumotachometer and air humidifier with small dead volume
- Drug injection pathway built directly into pulmonary perfusate stream
- Unique compensation system for vascular transmural pressure changes
- Dedicated option for continuous measurement of lung weight (edema)
- More measurement parameters than any other system

IPL-2 BASIC: The Most Functionally Diverse Isolated Lung System for Rat &/or Guinea Pig

Core System: 73-4276 (115V) or 73-4275 (230V):

Basic IPL-2 System Includes:

- IPL-2 Base Unit for Isolated Rat/Guinea Pig Lungs
- Thermocirculator
- Analog Roller Pump
- Perfusion Pressure Measurements
 - Low Range Pressure Transducer
 - TAM-D PLUGSYS Transducer Amplifier Module
- Perfusion Controller Module, SCP (for constant flow or constant pressure perfusion)
- PLUGSYS Basic System Case, 603
 - Utilizes 8 of 20 Available Slot Units*
- Respiratory Flow Measurement
 - Differential Low Pressure Transducer DLP
 - TAM-A PLUGSYS Transducer Amplifier Module
- Artificial Thorax Pressure
 - Differential Low Pressure Transducer MPX
 - TAM-A PLUGSYS Transducer Amplifier Module
- 2L Perfusate Reservoir
- Operating Table for Stable Perfusion Pressure During in-situ Preparation
 - Operating Table 30 cm x 18.5 cm
 - Ball Joint for Positioning Table
 - 4 Paw Clamps, 2 Thorax Retractors
 - Holder for Cannulae Head for in-situ Cannulation
 - Plastic Trough for Collecting Waste
- * If your chosen options require more than 20 Slot Units you will need to add a case extension. See page 33.

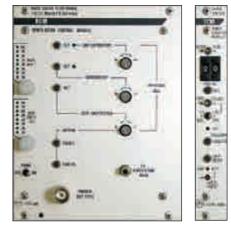
For a working unit, the core system requires the addition of a selection of one of the options CAN-R or CAN-P as well as one of the options VCMP, VCMR-2 or PPV-2 in combination with PPV-683 or PPV-Inspira.

Option CAN-R: 73-4277

Cannulae Set for Rat to Core System IPL-2

Includes:

- Rat Cannulae Set: OD 2.0 mm and 2.5 mm
- Rat Pump Tubing/Tubing Set



FEATURES & BENEFITS

- VCM Modules allow for the physiological negative pressure ventilation of the lung
 - 30-100 breaths per minute
 - I:E ratio can be set between 10 & 90% in 10% steps
 - End-inspiratory, End-expiratory, sigh and negative pressures can be individually set
- TCM Timer Counter Module allows periodic sigh (hyperinflation) breaths to minimize edema formation

Option VCMP: 73-4279

Negative Pressure Ventilation Controller with Pump to Core IPL-1 & 2

Choose this ventilation option when:

* performing standard positive- and negative-pressure ventilation studies

Includes:

- VCM-P PLUGSYS Ventilation Control Module
 with Integral Pump
- TCM PLUGSYS Timer Counter Module for introduction of periodic Sigh Breaths (hyperinflation)
- Utilizes 6 Slot Units

Option CAN-GP: 73-4278

Cannulae Set for Guinea Pig to Core System IPL-2

- Guinea Pig Cannulae Set: OD 3.0 mm and 3.5 mm
- Guinea Pig Pump Tubing/Tubing Set



Option PFGS-2: 73-3448

Alternative Gas Supply to Core IPL-2 with Option VCMP

Choose this ventilation option when:

* for delivering alternative gases during negative pressure ventilation

Includes:

Pressure Free Gas Supply Adpater for IPL-2

Option VCMR-2: 73-4280

Negative Pressure Ventilation Controller with Regulator to Core IPL-2

* Requires pressurized gas supply from tank or house air in the range of 2-8 bar (29 – 116 PSI)

Choose this ventilation option when:

- * performing standard positive- and negative-pressure ventilation studies
- * delivering alternative gases during both negative- and positive-pressure ventilation

Includes:

- VCM-R PLUGSYS Ventilation Control Module with Regulator
- TCM PLUGSYS Timer Counter Module for introduction of periodic Sigh Breaths (hyperinflation)
- Adapter for Alternate Gas Supply f/ IPL-2
- Utilizes 6 Slot Units

Option ML: 73-4108

Addition to Perfuse Mouse Lungs on IPL-2 System

*This is compatible with the Lung Weight Measurement System for IPL-2

Includes:

- Small Volume Heat Exchanger
- Mouse Pneumotachometer
- Tracheal, Pulmonary, and Venous Cannulae

Option PPV-2: 73-3635

Adapter for Positive-Pressure Ventilation for IPL-2

Choose this option when only positive pressure ventilation is desired or when an external ventilator may be used

* Multiple appropriate ventilators for Rat and Guinea Pig are available – sold separately

Includes:

• Adapter for Positive-Pressure Ventilation on IPL-2

Positive Pressure Ventilation Options



Option PPV-Inspira:

Inspira Advanced Safety Ventilator

- **55-7058:** Inspira Advanced Safety Ventilator Volume Controlled (ASVv)
- **55-7059:** Inspira Advanced Safety Ventilator Pressure Controlled (ASVp)
- **55-7061:** Inspira Advanced Safety Ventilator with Inspiratory Hold Volume Controlled (ASVv-IH)
- **55-7062:** Inspira Advanced Safety Ventilator with Inspiratory Hold Pressure Controlled (ASVp-IH)

FEATURES & BENEFITS

- Ventilates mice to cats with one ventilator with 2 cylinder sizes (included) (15 g to 10 kg)
- Easy to use
- Airway pressure monitoring detects over/under pressurization of lungs
- Built in sigh breath maintains optimal lung functioning
- Adjustable I:E ratio (1:4 to 4:1)
- Ability to ventilate with air or non-flammable anesthetic, hypoxic, hypercapnic or other gases
- Quiet operation
- NEW Inspiratory Hold option Ideal for imaging or lung compliance studies
- SafeRange[™] Software to ensure safe delivery of appropriate tidal volume to specific species
- Sigh breath and PEEP features to maximize physiologically normal respiratory function while mechanically ventilating
- Audible alarms for over and underpressure
- Analog output of pressure data



Option PPV-683: 55-0000

683 Small Animal Ventilator

FEATURES & BENEFITS

- Ability to apply PEEP (Positive End **Expiratory Pressure**)
- New tubing graduated sizing connectors that accommodate different size tubing easily
- 30-150 strokes per minute
- Tidal volume settings from 0 to 5cc in 0.5cc increments
- Permanent etched volume graduations on cylinder so they can't rub off
- Volume and rate control are now linear

Option LW-2: 73-4286

Lung Weight Measurement to Core System IPL-2

FEATURES & BENEFITS

- Monitor and Measure Edema Formation Over Time
- Raw Data is Weight, Calculated Parameter is weight change over time and rate of change (dW/dt)
- Assess Vascular Permeability by Calculating the Filtration Coefficient Derived from Weight Changes Induced by Increasing and Decreasing Perfusion Pressure
- Range of ±30 g, displacement 2 µm/gram
- Measure Changes of Less than 10 mg

Includes:

- HSE Weight Measurement Transducer and Alternate Lung Chamber Cover
- CFBA PLUGSYS Carrier Frequency Bridge Amplifier Module
- Utilizes 2 Slot Units



Option OCC2: 73-4322

Perfusion Occlusion System to IPL-2

FEATURES & BENEFITS

- Allows double occlusion for:
 - measurement of segmental vascular resistances (precapillary and postcapillary resistance) - measurement of microvascular pressure
- Allows individual arterial and venous occlusion for: - determination of large- and small-artery
 - resistances
 - determination of large- and small-vein resistances
 - determination of vascular compliance

- Stand
- 2 pinch valves
- Controller for perfusion occlusion
- The peristaltic pump requires external ON/OFF control



Lung Weight Measurement





FEATURES & BENEFITS

- Low particle sizes (100% of the particles are below 10 μm)
- No Solution Warming Required
- Recommended for Nebulizing Drugs Sensitive to Ultrasonics
- Aerosol is Automatically Transported by Compressed Air at a Pressure of 1.5 bar (22 PSI)

Option AG1-2: 73-2111

Aerosol Nebulizer Kit to IPL-2 Includes:

- Nebulizer
- Tubing
- Aerosol Filter
- Mounting Hardware

Option AG2-2: 73-2112

Addition for Second Aerosol Nebulizer Kit to IPL-2 Includes:

- Nebulizer
- Tubing
- Aerosol Filter
- Mounting Hardware for Second Nebulizer

Option FLOW-2: 73-4339

Real Time Flow Measurement to Core IPL-2 System

FEATURES & BENEFITS

- Direct Real-Time Flow Measurement
- Custom Built Flow Through Probe Allows Visualization of Trapped Air Bubbles that Could Interfere with Measurement

Includes:

- Flow Probe Type 2N
- TTFM PLUGSYS Transit Time Flowmeter Module
- Utilizes 4 Slot Units



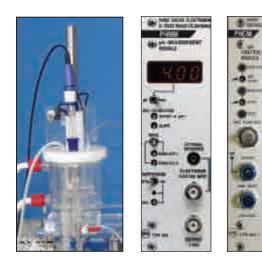
Option DEOX150-2: 73-4290

Perfusate Deoxygenation to Core IPL-2 System

FEATURES & BENEFITS

- Deoxygenation of blood or buffers containing protein (e.g. Albumin) or erythrocytes
- 19 mL priming volume
- MediSulfone[®] Membrane Material with 0.25 m² Deoxygenating Surface Area

- Stand Alone Fiber Oxygenator Holder
- D150 Fiber Oxygenator, Pack 5
- Triangular Stand With Clamp
- D150 Fiber Oxygenator Connection Kit



Option pHC-2: 73-4283 (115V) or 73-4282 (230V)

Perfusate pH Control to Core IPL-2 System: pH is Controlled by Feedback System which Regulates CO₂ Gas Bubbling into Dedicated Small Volume Reservoir for Minimizing Foaming of Perfusate

FEATURES & BENEFITS

- CO₂ Delivery to Maintain pH when System is not Deoxygenated with N₂/CO₂ Gas Mixture
- pHCM Controller Delivers Gas (Commonly CO₂) by Bubbling into Mixed Buffer to Maintain a Desired pH Set Point Dictated by pHCM Module
- Minimizes Foaming of Perfusates due to Minimal Gassing of 100% Gas to maintain pH

Includes:

- pHMM PLUGSYS pH Measurement Module
- pHCM PLUGSYS pH Control Module
- Flushtrode[®] pH Electrode & Connection Cable
- Electrolyte
- Holder for Jacketed Container
- Reglo Analog Pump
- Perfusate Mixer
- Utilizes 4 Slot Units

IPL-2 References:

- Martin , C., Held, H., & Uhlig, S. (2000). Differential effects of the mixed et(a)/et(b)-receptor antagonist bosentan on endothelin-induced bronchoconstriction, vasoconstriction and prostacyclin release. Naunyn-Schmiedeberg's Archives of Pharmacology, 362(2), 128-36.
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IPL-2 references continued on page 34.

ISOLATED LUNG PERFUSION SYSTEM

Please see pages 31-33 for Additional Measurement Options for Venous Pressure; pH, pO₂, pCO₂ Measurement, Data Acquisition Hardware & Software Packages, Drug Application Pump, and more.

(HSE) HUGO SACHS ELEKTRONIK

IPL-4 Isolated Lung Perfusion System

BVP

UNIQUE LUNG CHAMBER

 Heating Coil and Bubble
 Trap at Inlet of Perfusate for Precision Temperature Control of Perfusate

Lung Weight Measurement Option Can

- be Built into Chamber Lid Heated Pneumotachometer
- has Low Dead Space and Mounts Directly On System

10 A 10

HIGHER FLOW CAPACITY

Larger Analog Pump and Reservoir to Accommodate Higher Flow and Perfusate Volumes for Larger Lungs (e.g. Rabbit, Fetal Pig, etc).

BENEFITS

 Fully Thermostated Lung Chamber for Superior Temperature Control Compact System for Small Lab Spaces Drug Injection Pathway Built Directly Into Perfusate Stream

OPTIMIZED IN SITU PREPARATION

- Knob Opens Lung **Chamber and Angles** Cannulation Head Positioned for Simple In Situ Cannulation and
- Intubation Removable Operating Table and Plastic Drip
- Tray for Easy Clean Up

PLUGSYS

CUSTOM CANNULAE

- Cannulae are Specially Designed for Easy Insertion into the Pulmonary Artery and Left Atrium of Heart
- Thin-Walled Stainless Steel for Low **Resistance and Laminar Flow**

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ATED

PERFUSION

SYSTEM



Unique Compensation System for Vascular **Transmural Pressure** Changes Simulate Cardiac

Hypertension by Raising Vessel

 PLUGSYS Modular Amplifier System with Transducers, Features: Perfusion Pressure & Flow, Constant Flow or Constant Pressure Capable in One System - Respiratory Flow & Tracheal Pressure - Lung Weight Option Available - pH & pH Control Option Available - VCM Ventilator Control Allows for Both Positive & Negative **Pressure Ventilation** Compact System Case with Power Switch on Front

IPL-4 BASIC: Isolated Perfused Lung System for Rabbit to Fetal Pig



The IPL-4 system is specially designed for Rabbit or Fetal Pig lung. The unique in-situ cannulation system allows the researcher to align the cannulation head with the operating table while simultaneously retracting the lung chamber. No parts of the system need to be removed during cannulation. The basic system can easily be upgraded to add capability modules for virtually any ex-vivo pulmonary assay – with additions for a nebulizer, lung weight measurement, and more. For detailed descriptions of system extensions and options see pages 22-24, 31-33.

MEASURED SIGNALS & PARAMETERS ON AN IPL-4 BASIC SYSTEM:

The Following Signals are Recorded as Raw Data:

- Pulmonary Artery (Perfusion) Pressure
- Perfusion Flow
- Intrapleural (artificial thorax) Pressure or Tracheal Pressure
- Respiratory Flow

The Following Parameters can be Calculated From the Raw Data*:

- Tidal Volume, Minute Volume
- Peak Inspiratory and Expiratory Airflow
- Vascular Resistance
- Respiration Rate
- Inspiratory Time & Expiratory Time
- End Inspiratory and Expiratory Pressure
- Dynamic Airway Resistance & Compliance
- * Calculations are automatic when HSE PULMODYN software is used.

FEATURES & BENEFITS

- Optimized temperature conditions for the isolated lung, unique jacketed thoracic chamber
- Operating table for non-damaging in-situ preparation
- Negative-pressure ventilation similar to in-vivo condition or positive pressure ventilation available
- Low flow resistance and dead space volume, minimize perfusion artifacts
- Drug injection pathway built directly into pulmonary perfusate stream
- Unique compensation system for vascular transmural pressure changes
- System dedicated option for continuous measurement of lung weight (edema)
- More measurement parameters than any other system

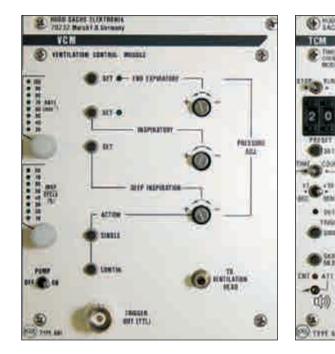
The IPL-4 Basic Consists of the Core System & Selections Among the Following Options

Core System: 73-4297 (115V) or 73-4296 (230V):

Basic IPL-4 System Includes:

- IPL-4 Base Unit for Isolated Rabbit to Fetal Pig Lungs
- Thermocirculator
- Analog Roller Pump & Tubing
- Perfusion Pressure Measurements
 - Low Range Pressure Transducer
 - TAM-D PLUGSYS Transducer Amplifier Module
- Perfusion Controller Module, SCP (for constant flow or constant pressure perfusion)
- PLUGSYS Basic System Case, 603
 - Utilizes 8 of 20 Available Slot Units*
- Respiratory Flow Measurement
 - Heated Pneumotachometer
 - Differential Low Pressure Transducer DLP
 - TAM-A PLUGSYS Transducer Amplifier Module
- Artificial Thorax Pressure
 - Differential Low Pressure Transducer MPX
 - TAM-A PLUGSYS Transducer Amplifier Module
- 6L Perfusate Reservoir
- Operating Table for Stable Perfusion Pressure
 During in-situ Preparation
 - Operating Table with Ball Mount
 - 2 Thorax Retractors
 - Plastic Trough for Collecting Waste
- * If your chosen options require more than 20 Slot Units you will need to add a case extension. See page 33.

For a working unit, the core system requires the addition of a selection of one of the option VCMR-4 or PPV-4 in combination with PPV-683 or PPV-Inspira.



Option VCMR-4: 73-4298

Negative Pressure Ventilation Controller with Regulator to Core IPL-4

* Requires pressurized gas supply from tank or house air in the range of 2-8 bar (29 – 116 PSI)

For both Positive- and Negative-pressure Ventilation

- VCM4-R PLUGSYS Ventilation Control Module for Rabbit Lung Respiration
- TCM PLUGSYS Timer Counter Module for introduction of periodic Sigh Breaths (hyperinflation)
- Utilizes 6 Slot Units

Option PFGS-4: 73-4309

Pressure Free Gas Supply for IPL-4 (Option PPV-4)

* For use when alternative gases are used

Includes:

Pressure Free Gas Supply Adapter

Option PPV-4: 73-4312

IPL-4 Adapter for Positive Pressure Ventilation

* Multiple Ventilator Options Available – Sold Separately

- Includes:
- Adapter to Connect to External Ventilator

Option PPV-683: 55-0000

683 Small Animal Ventilator

Note: For description see page 17.

Option PPV-Inspira:

Inspira Advanced Safety Ventilator

- 55-7058: Inspira Advanced Safety Ventilator Volume Controlled (ASVv)
- 55-7059: Inspira Advanced Safety Ventilator Pressure Controlled (ASVp)
- **55-7061:** Inspira Advanced Safety Ventilator with Inspiratory Hold Volume Controlled (ASVv-IH)

55-7062: Inspira Advanced Safety Ventilator with Inspiratory Hold Pressure Controlled (ASVp-IH)

Note: For description see page 16.



Option FLOW-4: 73-4281

Real Time Flow Measurement to Core IPL-4 System Includes:

- Flow Probe Type 4N
- TTFM PLUGSYS Transit Time Flowmeter Module
- Utilizes 4 Slot Units





Lung Weight Measurement

Option LW-4: 73-4299

Lung Weight Measurement to Core IPL-4 System Includes:

- HSE Weight Measurement System
- CFBA PLUGSYS Carrier Frequency Bridge Amplifier Module
- Utilizes 2 Slot Units



Option AG-4: 73-4310

Aerosol Nebulizer to Core IPL-4 System Includes:

- Multi-Gas Adapter and Connection Kit for IPL-4
- Pressure Free Gas Supply



D200 Fiber Oxygenator



Stand with Triangular Base Plate

Option DEOX200-4: 73-4311

Deoxygenation Unit to Core IPL-4 System

FEATURES & BENEFITS

- Deoxygenation of Blood or Buffers Containing Protein (e.g. Albumin) or Erythrocytes
- 54 ml Priming Volume
- MediSulfone[®] Membrane Material with 0.6 m² Deoxygenating Surface Area

- Stand Alone Fiber Oxygenator Holder
- D200 Fiber Oxygenator, Pack 5
- Triangular Stand w/ Clamp
- D200 Fiber Oxygenator Connection Kit

AVE



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CONSTANT FLOW INTEGRATED LUNG & PRESSURE WEIGHT MEASUREMENT Quick switch from constant Allows calculation of filtration coefficient flow to constant pressure for maximum application flexibility Track edema formation FULLY THERMOSTATED LUNG CHAMBER Keep lungs warm and moist 0.014 **a** o **BUILT IN RESERVOIR** SECONDARY Venous discharge returns to the reservoir, decoupling the circuit to HEAT avoid applying non-physiological **EXCHANGER** pressures to the lung vasculature Due to heat loss through the tubing after leaving the heater/oxygenator, perfusate is reheated by a heat exchanger located proximally to the PA Cannula.

IPL-16 Isolated Lung Perfusion System

(HSE) HUGO SACHS ELEKTRONIK

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ATED

LUNG

PERFUSION

SYSTEM



OXYGENATOR

Oxygenator holders for common heart-lung heater-oxygenators

REMOVABLE SURGERY CANNULATION PLATFORM

Allows continuous ventilation and perfusion during surgery



IPL-16 BASIC: The Newest Addition for Lung Perfusion in Translational Medicine





The IPL-16 system is designed for whole lung or single lung lobe perfusion of pig or human**. The unique cannulation system allows the researcher to remove the cannulation block and platform to cannulate the vasculature and trachea outside of the main chamber while maintaining constant perfusion flow and physiological pulmonary artery pressure, and continuous ventilation. The system is positive-pressure ventilationbased and has an integrated reservoir designed for recirculating perfusion. Perfusion can be performed on a single lobe through multiple arteries or via a single pulmonary artery, as well as to the full lung*. The basic system includes lung weight measurement and can easily be upgraded to add capability modules for virtually any ex-vivo pulmonary assay - with additions for a nebulizer, real-time flow measurement, and more. For detailed descriptions of system extensions and options see pages 29-33.

* For very large human lungs, a custom chamber lid may be desired, as well as a higher-flow capacity cannulation block.

For Research Use Only.

** Not for clinical use or transplant use unless proper investigational device regulations have been followed.

MEASURED SIGNALS & PARAMETERS ON AN IPL-16 BASIC SYSTEM:

The Following Signals are Recorded as Raw Data:

- Pulmonary Artery (Perfusion) Pressure
- Perfusion Flow
- Intrapleural (artificial thorax) Pressure or Tracheal Pressure
- Respiratory Flow

The Following Parameters can be Calculated From the Raw Data*:

- Tidal Volume, Minute Volume
- Respiratory Volume
- Peak Inspiratory and Expiratory Airflow
- Vascular Resistance
- Respiration Rate
- Inspiratory Time & Expiratory Time
- End Inspiratory and Expiratory Pressure
- Lung Compliance
- * Calculations are automatic when HSE PULMODYN software is used.

FEATURES & BENEFITS

- Positive Pressure Ventilation-based (only)
- Optimized temperature and humidity conditions for the isolated lung, unique jacketed thoracic chamber
- Continuous measurement of lung weight to monitor edema formation
- Very low flow resistance and minimal dead space volume virtually eliminate perfusion artifacts
- Drug injection pathway built directly into pulmonary perfusate stream for precision compound dosing and screening
- More measurement parameters with greater precision than any other system*

The IPL-16 Basic Consists of the Core System & Selections Among the Following Options

Core System: 73-4302 (115V) or 73-4301 (230V)

Basic IPL-16 System:

- IPL-16 Base Unit for Pig or Human Lung/Lung Lobe
- Thermocirculator
- Analog Roller Pump & Tubing
- Perfusion Pressure Measurements
 - Low Range Pressure Transducer
 - TAM-D PLUGSYS Transducer Amplifier Module
- Perfusion Controller Module, SCP (for constant flow or constant pressure perfusion)
- PLUGSYS Basic System Case, 603
 - Utilizes 10 of 20 available slot units*
- Respiratory Flow Measurement
 - Heated Pneumotachometer
 - Differential Low Pressure Transducer DLP
 - TAM-A PLUGSYS Transducer Amplifier Module
- Tracheal Pressure
 - Differential Low Pressure Transducer MPX
 - TAM-A PLUGSYS Transducer Amplifier Module
- Lung Weight Measurement
 - Weight Transducer Built into Chamber
 - TAM-A Transducer Amplifier Module
- * If your chosen options require more than 20 Slot Units you will need to add a case extension. See page 33.

For a working unit, the core system requires the addition of a large animal ventilator e.g. Option PPV16-613 or any ventilator for humans as well as an deoxygenator. See options on the next page.





Option FLOW-16: 73-4303

Real Time Flow Measurement to Core IPL-16 System

FEATURES & BENEFITS

- Direct Real-Time Flow Measurement using Ultrasonic Transit Time Technology
- Custom-Built Flow Through Probe Allows Visualization of Trapped Air Bubbles that Could Interfere with Measurement

Includes:

- Inline Adapter and Flow Probe 12AX
- TTFM PLUGSYS Transit Time Flowmeter Module



Option PPV16-613: 55-0715 (115V) or 55-0723 (230V)

Large Animal Volume Controlled Ventilator Model 613A

FEATURES & BENEFITS

- For animals from 1.5 to 50 kg (3.3 to 110 lb) in weight
- Volume adjustable from 30 to 750 cc/stroke
- Variable Inspiratory: Expiratory Ratio
- Direct input for alternative gases, both pressurized and atmospheric

Options for Deoxygenation of Blood or Alternative Perfusate

While Hugo Sachs Elektronik - Harvard Apparatus does not supply the deoxygenator for the IPL-16 system, researchers can use readily available oxygenators used in the heart-lung machines of their affiliated hospital/ translational research institute. Offered here are multiple custom oxygenator holders for use with the IPL-16 system. If you do not see a compatible holder here, please contact one of our support specialists to request a custom holder for your oxygenator (be prepared to supply a sample).



Option QUADROX: 73-4014

Base Platform for Quadrox Oxygenator



Option MEDTRONIC: 73-4004

Base Platform for Medtronic Minimax Plus PRF Oxygenator



Option MEDTRONIC-C: 73-4313

Base Platform for Medtronic Carmeda AFFINITY NT Oxygenator

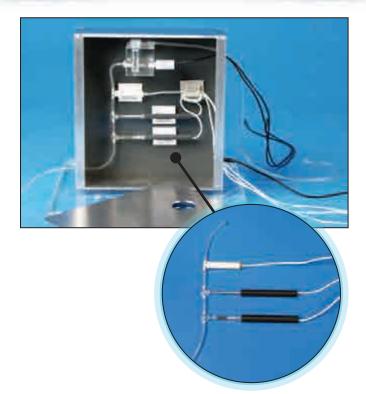


Option TERUMO: 73-2805

Base Platform for Terumo Capiox CX*SX10 Oxygenator

Common Package Additions to All IPL-Systems

The following add-on options are useful for any of the Hugo Sachs Elektronik - Harvard Apparatus IPL Systems. These include Metabolic Monitoring options (pH, pCO₂, pO₂) using traditional chemosensors or all-new optical biosensors, venous pressure measurement addition, data acquisition options as well as flow controlled drug addition, allowing you to create a complete isolated perfused lung system.



Option BIOSEN: 73-4304 (115V) or 73-4287 (230V)

Measuring System for pO_2 , pH, pCO_2 to Core IPL Systems - Chemosensors

The Universal Perfusion Solution Monitor permits precise continuous or discontinuous measurement in liquid media or perfusate of these three key parameters: $pO_{2^1} pH$, & pCO_{2^2} . The electrodes are all ion-sensitive chemosensor-based, side stream flow-through electrodes and require a pulsation-free roller pump to deliver constant flow of perfusate through the electrode at flow rates in the range of 0.5-2 ml/min. Because of the high impedance of these sensors, screening or shielding of the measuring circuit is required to protect against electrostatic discharges and other electrical disturbances.



FEATURES & BENEFITS

- Rugged Construction
- Noise-Free Design, No Channel Crosstalk
- High Sensitivity
- Good Linearity

Includes:

- Analog Roller Pump & Tubing for Side Stream Sampling
 Shielding Case and Mounting Plate for 3 Sensors
- Sensors not included, please choose from the following:

Option MO2: 73-4029

pO₂ Measurement Includes:

- Mini Flow-Through O₂ Electrode 1/16th"
- OPPM Oxygen Partial Pressure Measurement Amplifier
- pO₂ Zero Solution for Zero Calibration
- Utilizes 2 slot units

Option MCO2: 73-4031

pCO₂ Measurement

Includes:

- Mini Flow-Through CO₂ Electrode 1/16th"
- EMM Electrometer Amplifier
- Utilizes 2 slot units

Option MpH: 73-4030

pH Measurement

- Mini Flow-Through pH Electrode 1/16th"
- Reference Electrode
- pHMM pH Amplifier
- Utilizes 2 slot units

Common Packages: Polestar Fluorescence based Biosensors, detection of pH, CO_2 , O_2

Harvard Apparatus – Polestar Fluorescence-based Biosensors represent breakthrough technology in the measurement of typical blood gas parameters in tissue engineering, organ perfusion and general physiology applications.

In contrast to traditional ion-sensitive chemosensors, these optical biosensors use a controlled optical source that emits light signals at specified frequencies which excite an ion-specific sensor spot in contact with the test medium. Changes in the parameter of interest are reported as a proportional change in some characteristic (intensity, phase shift, etc.) of the fluorescence. Because they are inherently self-referencing, this detection technology eliminates the potential for measurement error arising from changes in sample properties (i.e. flow rate, viscosity, etc...) over the duration of an experiment. This ensures stable, drift-free calibration and hence reliable measurements throughout the lifespan of a sensing element. For small animal lungs with low effluent flow rate, the included flow cell can be placed in-line or the included pump can be used for side-stream sampling. For larger lungs the included pump is used for side stream sampling.

Option POL: 88-0252

Measuring System for pO₂, pH, pCO₂ to Core IPL Systems – Fluorescence-Based Optical Biosensor

FEATURES & BENEFITS

- Rugged Sensors with Stable Readings over Full Sensor Lifespan
- Automatic Gain Control Ensures Optimum Measurement Reliability
- Sensors and System is Shipped Pre-Calibrated
- Non Ion-Consumptive Detection
- No Electrolyte Solution or Storage Solutions Needed – Low Maintenance
- Autoclavable/Sterilizable USP Class VI-Certified Sensors





Includes:

- DSP4000 4 Channel Optical Process Monitor with Cables
- Tri-fold Flow Cell for pH, pO₂, pCO₂ with 1/16" Barbed Connectors for Monitoring Effluent
 - Can be used in-line or as side stream sample, depending on effluent flow rate
- pO₂ Flow Cell for pre-lung O₂ measurement
- Analog Peristaltic Pump with Tubing for Side-Stream Sampling

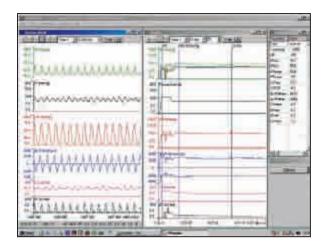


Option VPM: 73-4295

Venous Pressure Measurement for Core IPL Systems Includes:

- nciuues.
- Venous Pressure Transducer
- TAM-A PLUGSYS Transducer Amplifier Module*
- Dual Clamp for Mounting
- * Utilizes 2 Slot Units

Common Packages: Data Acquisition & Drug Addition



Option DAQ-HSE: 73-4284

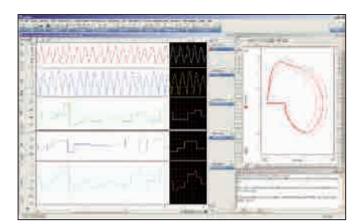
HSE Data Acquisition System with PULMODYN Software

FEATURES & BENEFITS

- Dedicated for Isolated Lung Experiments
- Easy Data Reduction and Export
- Fully Pre-Configured Out of the Box for All Measurements and Analysis
 - Tidal Volume, Minute Volume
 - Peak Inspiratory & Expiratory Airflow
 - Vascular Resistance
 - Respiration Rate
 - Inspiratory Time & Expiratory Time
 - End Inspiratory & Expiratory Pressure
 - Dynamic Resistance & Compliance

Includes:

- HSE Standalone USB Analog to Digital Conversion Hub
- PULMODYN Software



Option DAQ-PWL: 77-0243 (United States) 73-4285 (International)

FEATURES & BENEFITS

- Intuitive Setup and Operation
- Advanced Automated Analysis Routines
- Online and Offline Analysis
- Automation of Experimental Protocols
- Proven Track Record

Includes:

- 16 Channel Powerlab
- LabChart Software

Option C-EX: 73-4288

PLUGSYS Case Expansion for Additional 20 Slot Units

This option should be chosen when the number of amplifiers included in the options chosen exceed the base system case capacity of 20 Slot Units. Please add up the number of slot units required by each option in order to determine if you will require the case expansion option.

Includes:

- PLUGSYS 603 Case
- Link Module for Connecting Two 603 Cases

Option DA-FLC: 73-4289

Flow-Controlled Drug Addition (Requires DAQ-HSE Option)

- Pump 11 Plus Syringe Pump
- Connection Tubing
- RS232 Cable
- Software Option

IPL-1 References Continued:

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