

AFRL-SR-AR-TR-08-0166

REPORT DOCUMENTATION PAGE

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				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
				5d. PROJECT NUMBER	
6. AUTHOR(S) Dr. John F. Hunt, Principal Investigator 30-9-2005 to 29-9-2007 A. Rafi Baddour, PE, Lead Engineer 30-9-2005 to 29-9-2007				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Respiratory Research, Inc. 8711 Burnet Road Suite B-31 Austin, TX 78757				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) AF OFFICE OF SCIENTIFIC RESEARCH 875 NORTH RANDOLPH STREET ROOM 3112 ARLINGTON VA 22203 <i>Dr Howard Schlossberg/NE</i>				10. SPONSOR/MONITOR'S ACRONYM(S)	
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12. DISTRIBUTION/AVAILABILITY STATEMENT DISTRIBUTION STATEMENT A: UNLIMITED					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT All goals of this program were reached and are listed below: 1. Improve the efficiency of the Exhaled Breath Condensate collection system when attached to the exhaust port of a ventilator. 2. Implement a gas-standardization methodology for the continuous EBC pH monitoring system that is uniformly reliable, and does not depend on the availability of argon. 3. Assure that the EBC pH measurement system assures error-free removal of accumulated EBC from the pH assay chamber. Implement a simple system for pH probe calibration. 4. Development of the necessary electronics functionality for the continuous EBC pH monitoring system to be easily used in the clinical setting for the critical care management of war fighters and civilians.					
15. SUBJECT TERMS Exhaled Breath Condensate, Airway pH Monitoring, Oxidative Stress, Breath pH					
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August 31, 2005 to September 30, 2007

OBJECTIVES:

All objectives as outlined in the contract award have been met. These are:

1. Improve the efficiency of the Exhaled Breath Condensate collection system when attached to the exhaust port of a ventilator.
2. Implement a gas-standardization methodology for the continuous EBC pH monitoring system that is uniformly reliable, and does not depend on the availability of argon.
3. Assure that the EBC pH measurement system assures error-free removal of accumulated EBC from the pH assay chamber. Implement a simple system for pH probe calibration.
4. Development of the necessary electronics functionality for the continuous EBC pH monitoring system to be easily used in the clinical setting for the critical care management of war fighters and civilians.

A production-ready design which is now ready for commercial use. This design is now being fabricated to fulfill the first production-level purchase order from the University of Virginia for one unit. Additionally, pre-production prototypes are in use, one at the University of Virginia, and one at Brooke Army Medical Center. Col. Cancio at Brooke is using the device to study both blunt-force lung injury and chlorine-induced lung injury in intubated pigs, while UVA is conducting human studies in the OR to characterize and predict onset of ventilator-associated pneumonia.

Accomplishments/New Findings:

Substantial evidence has been accumulated with this device showing that airway pH is clearly seen to trend in association with and in advance of important clinical changes in humans. Animal models allow for precise knowledge of the time of injury preceding ARDS, and reveal correlation between induced lung injury in pigs and rapid downward trending of airway pH. This further supports the use of pH monitoring as a rapid measure of traumatic lung injury and biotrauma in field-deployed warfighters.

Other research highlights, their significance, their relationship to the original goals, their relevance to the AF mission, and potential applications in military/civilian technologies include:

- As of the date of this report, the recent prototypes have been validated while attached to 3 of the most commonly used ventilators, including the Maquet Servo I, Puritan Bennett 840, and Sievers high frequency Oscillator. The Sievers ventilator required special attachments to the PEEP value. The proven ability of the continuous pH condensimetry device to function robustly alongside technologically disparate ventilators helps to assure deployability in multinational cooperative deployments.
- Beyond simple testing of the technology, investigators using the device have been able to identify and investigate unique aspects of the biology of the lung. Using the device, evidence has been gathered showing that patients undergoing elective surgery (relatively healthy lungs) show a gradual decline in EBC pH during their procedure. This gradual decline is very common, but not evident in all subjects, and is found even in the complete absence of gastroesophageal reflux and aspiration as determined by concurrent esophageal pH/impedance studies and measurement of gastric pepsin in tracheal aspirates at end of procedure. These data support that gradual intrinsic airway acidification occurs in association with elective surgery in which patients are endotracheally intubated, and confirms that the lungs are exposed to acidic stress during such procedures.

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- With the development of higher efficiency condensers as part of this program, higher minute-to-minute resolution of EBC pH is obtained, allowing for recognition of sudden airway pH shifts as occur from gastric acid aspiration. Notably, this finding confirmed the need for the conversion to the planned higher efficiency condenser as outlined in the initial development plan.
- Gastric acid reflux and aspiration has been identified to occur commonly in mechanically ventilated patients, allowing establishment of the need for reflux precautions and medications in patients so identified.

Status of Effort and Continuation:

65 intubated subjects have been enrolled at the University of Virginia for 3 hours to 14 days of total monitoring duration. The purpose of enrolling these subjects was to test various prototypes of the evolving ALFA system. Modifications were made to the ALFA as indicated by these data. These studies continue under the funding already delivered to the University of Virginia, and Respiratory Research, Inc. has extended its relationship with the university until all studies are complete. These should continue through the first half of 2008.

The commercialization of the device, trademarked "ALFA Airway Lining Fluid Acidity Monitor" continues with the expected delivery of the first true production unit to the University of Virginia in early 2008. Also, as the studies at Brooke Army Medical Center progress, the prototype unit placed there will be swapped with a production unit to allow better utility of the device.

Airway acid stress remains the first identifiable alteration in biology that occurs in response to respiratory viral infections. It also has been identified in acute lung injury and ARDS. ALFA monitoring will be used to monitor impending deterioration of lung status in patients on mechanical ventilators. More importantly, there is currently a development effort to treat airway acid stress directly with inhaled compounds. When these drugs are available, ALFA monitoring will be an intimate part of the diagnostic strategy to determine how to dose these drugs in individual patients with lung disease.

Respiratory Research, Inc., plans to promote the ALFA to research institutions within its current customer network and encourage research into these areas. Additionally, the University of Virginia continues to actively investigate these areas. As research use increases, it is expected that new investigational utility will be independently developed by the research community.

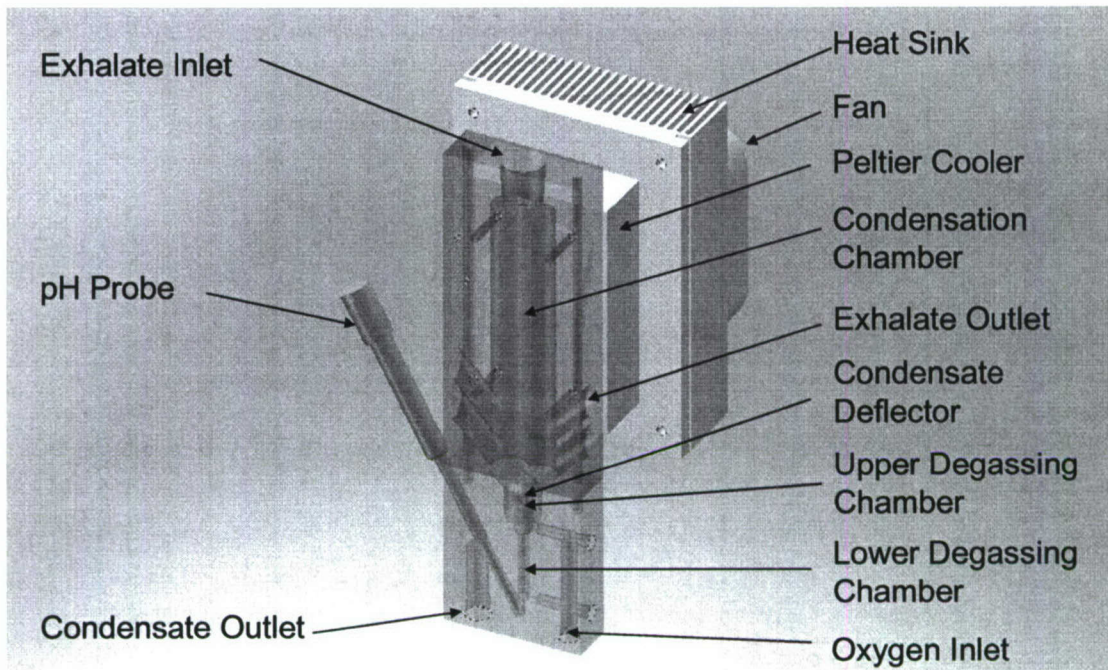
All of the money budgeted has been spent by the Company per the contract plan, and funding of continuing efforts is proceeding primarily from commercial sale of the ALFA device. Subsequent grant monies will be considered and applied for as a leading path for clinical implementation of this technology and device emerges.

Device Details:

The core of the ALFA is a high-efficiency condenser/degasser module shown below. Exhaust from the ventilator is channeled to the Exhale Inlet in the device where it is condensed. A solid-state Peltier cooler is utilized to cool the condensation chamber. The heat taken from the chamber is removed through a large fan-cooled heat sink. The dried exhalate is channeled out of the circuit through the four Exhale Outlets, and the condensate is gravity-fed into the Upper Degassing Chamber. Degassing allows for the removal of carbonic acid from the condensate and greatly improves both the signal-to-noise ratio and the reproducibility of the pH measurements. The degassed condensate then flows past a Ross pH probe for pH measurement.

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Two complexities which were solved in this development program were the selection of an optimized pH probe and the implementation of a continuous real-time degassing process. Eight alternative probes were evaluated for the ALFA application. The pH probe selected uses the Ross electrode technology and is highly accurate in low ionic strength solutions, such as condensate. Also, it was rigorously tested to ensure a minimal and predictable drift over time. The high accuracy and low drift of this probe makes it uniquely suited to this application.

The degassing system is an evolution of the diffusion-based apparatus used for fixed-volume specimens. As a carbon dioxide-free gas is bubbled through the condensate, the carbon dioxide diffuses into the gas medium and is removed from the sample. For the ALFA, the degassing required that some measure of "first-in-first-out" fluid management be applied to the continually-flowing condensate stream. Yet the degassing process necessitated a dynamic, violent interaction across the boundary between the condensate and the diffusion medium, inevitably creating a mixing and disturbance of the fluid flow. This problem was solved by approximating a FIFO system through the use of a waterfall system in which condensate is degassed in stages using two separate pools of condensate. As the upper pool fills, condensate is gravity-fed to the lower pool, where degassing continues. A small orifice allows fluid to move from the lower pool to the measurement chamber as hydrostatic pressure demands, making the system less prone to the randomizing effect of turbulence in the motion of the condensate. The two-stage degassing also improves consistency by impeding condensate droplets from racing through the system without sufficient exposure to the degassing process.

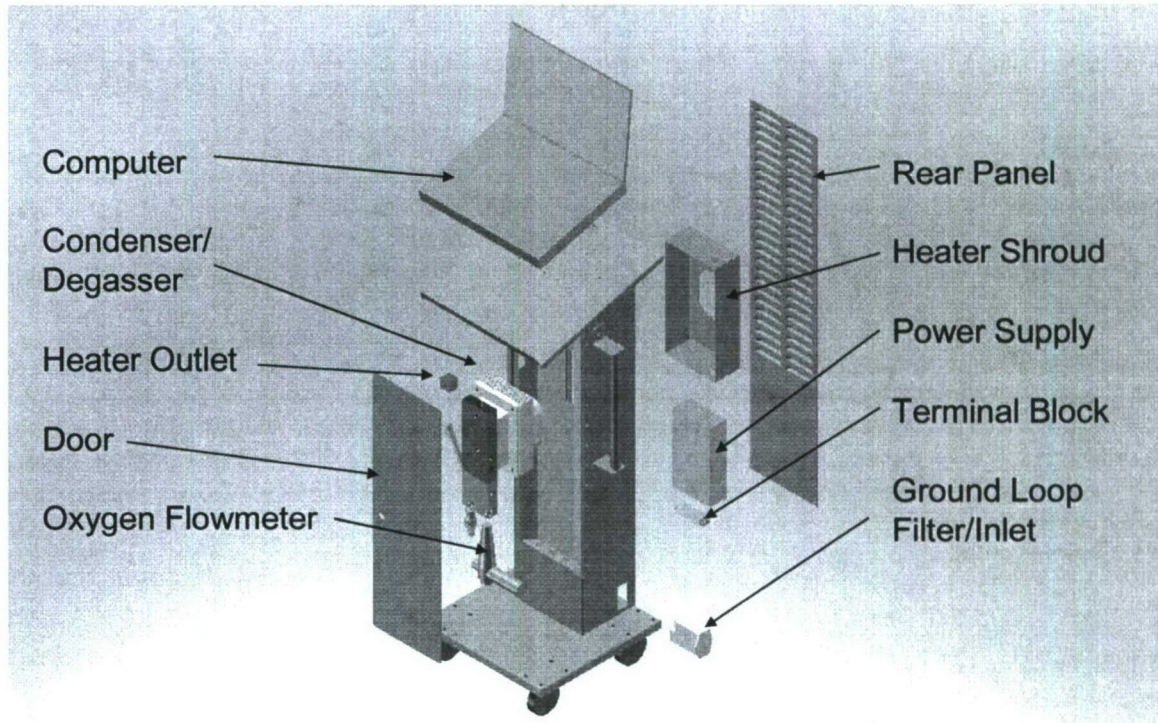
Medical-grade oxygen was selected as the degassing medium due to its easy availability from wall outlets throughout the hospital. With a specification of no more than 300 ppm of CO₂, this gas provides a predictable level of CO₂ concentration for the condensate. This freed the system from the need of maintaining its own supply of bottled gas and greatly improves both the utility and economics of the device.

A significant issue with prior prototypes was the tendency of the exhalate to condense in the tubing connecting the ventilator with the ALFA. This has been solved with a modified off-the-shelf concentric breathing circuit in which the annulus between the inner and outer tubes is heated with

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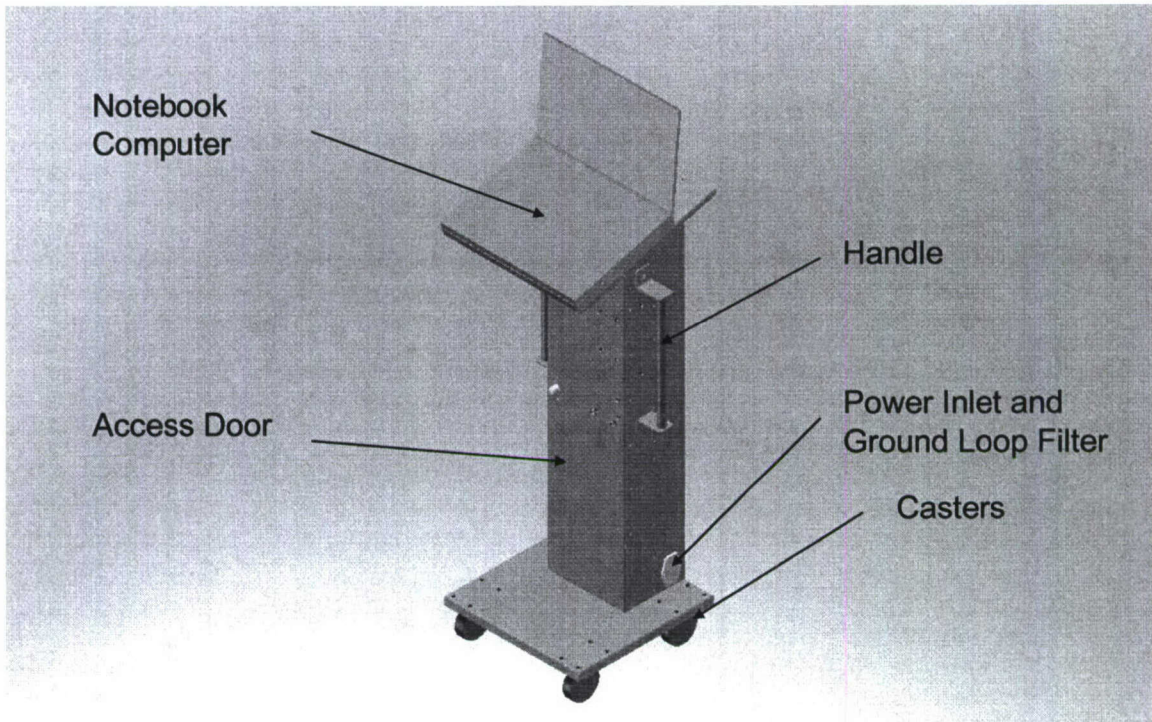
warm air. This warm air is channeled through the circuit from the ALFA by blowing waste heat from the Peltier cooler back through the circuit. The exhalate and the warm air stream never mix, yet enough heat is transferred to the exhalate to prevent condensation in the tubing.



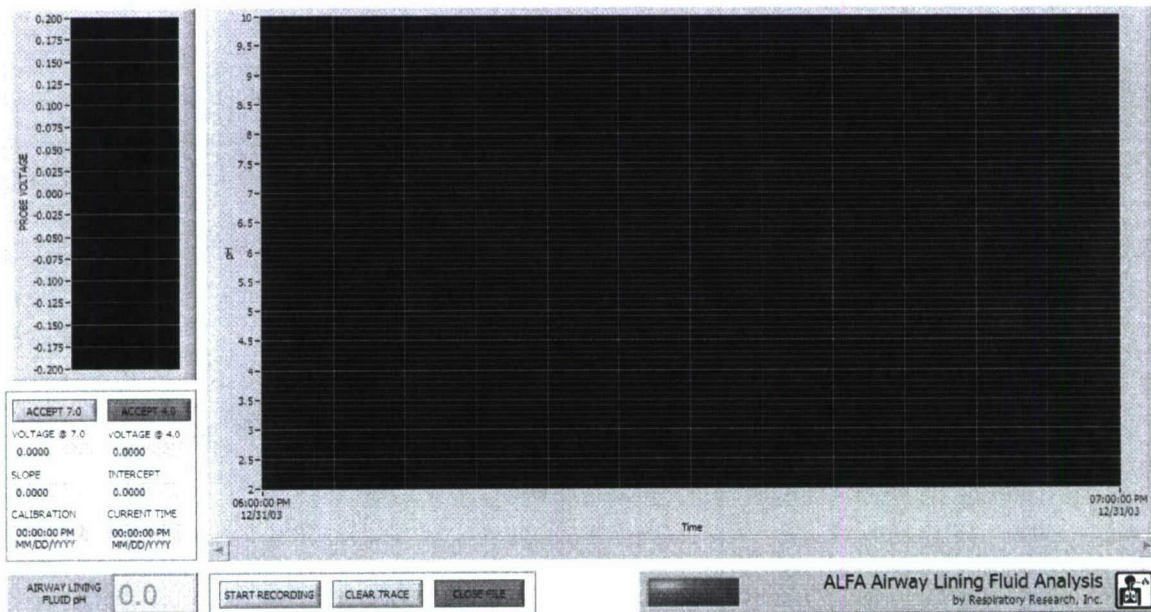
To complete the device, all components are packaged in a custom-designed mobile cabinet. Key considerations in the design of this cabinet were minimizing footprint, maintaining stability, and dealing with a high thermal load. Also, provisions were made to allow for waste condensate collection/storage, calibration solution storage, and general ergonomics. The Heater Shroud and Heater Outlet comprise the tube heating system and allowed RRI to avoid UL and other commercialization concerns regarding the use of electric heating wire, as is commonly done for breathing circuits.

The device presents in a simple, user-friendly manner as shown below:

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The Notebook Computer is the control as display center for the pH measurements. The initial plan was to use an off-the-shelf data acquisition unit, and indeed the original prototypes used such a unit. However, the high cost and inflexibility of the user interface forced a mid-course correction to a PC-based system using a USB-connected data acquisition device from National Instruments and the highly-flexible LabView® programming environment.



Not only did this reduce cost substantially, it allowed RRI to create a very simple and useful display, implement datalogging, and simplify the calibration procedure for the probe. The user interface is shown offers the following functions:

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- Calibration: this is performed very simply by placing the probe in the calibration solution and clicking the yellow or purple buttons to effect a two-point calibration
- Datalogging: all data is saved to a text file set up by the user. This data can be imported into Excel to create graphs, charts and analysis
- A real-time pH display and one-hour strip chart: pH is displayed numerically and updated every second. A strip chart is actively maintained in memory and can be easily scrolled through as the device is collecting data to review events occurring prior to the last hour.
- Probe Voltage: This is a diagnostic feature to allow the user insight into the actual probe measurement as a way of validating probe function

This system has been very well-received in the pre-production units, and the design is now the production design. Notably, since noise issues are endemic in this type of fine mile volt measurement, the software also cancels noise mathematically by rapidly averaging 1,000 voltage values per second to cancel out the effect of sinusoidal ground-loop and EMI noise from building lighting and power systems. This simple approach has proven very effective.

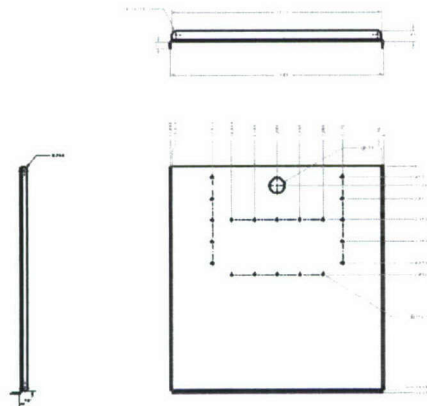
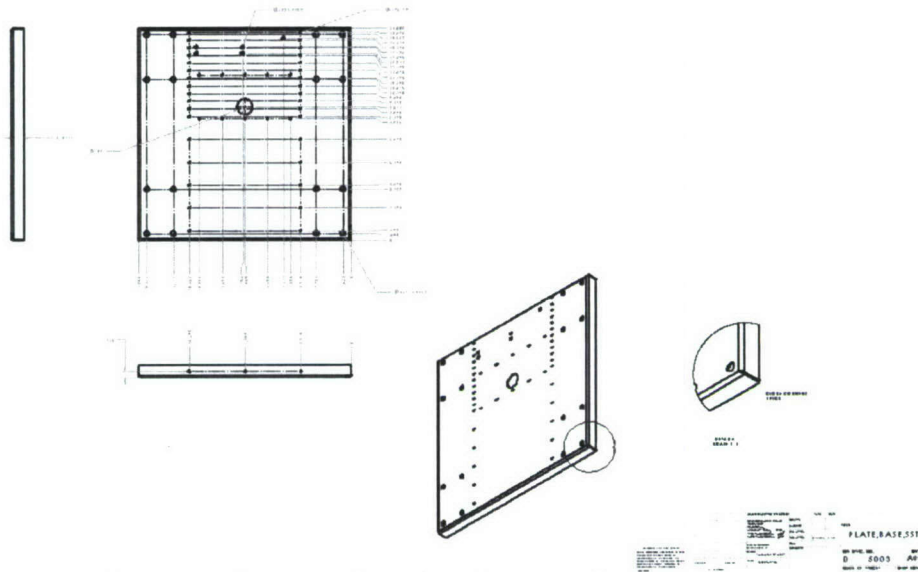
Costed BOM and Design Documentation:

The ALFA components total about \$6,000 allowing a sub-\$25k device price for the end users at a 75% margin for the Company. This is consistent with the perceived value of the device. A cursory costed Bill of Material is presented below:

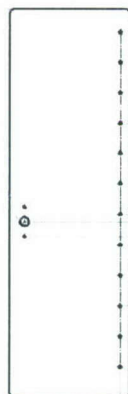
File Name/Part Name	Name	Part Number	Revision	Manufacturer	Distributor	Price	QTTY	COST
Main Body	BODY,MAIN,SST	5001	A00	EVS Metal		\$250.00	1	\$250.00
Door	DOOR,SST	5002	A00	EVS Metal		\$100.00	1	\$100.00
Ballast Plate	PLATE,BASE,SST	5003	A00	EVS Metal		\$150.00	1	\$150.00
Rear Column	PLATE,COLUMN,SST	5004	A00	EVS Metal		\$250.00	1	\$250.00
Block 2	BLOCK,COOL,SST	5005	A00	Birchfield Machining		\$950.00	1	\$950.00
New Continuous	BLOCK,DEGASS,DLRN	5006	A00	Birchfield Machining		\$511.63	1	\$511.63
Top Hat	INSRT,DEGAS,SST	5007	A00	Birchfield Machining		\$50.00	1	\$50.00
Top Plate	PLATE,TOP,SST	5008	A00	EVS Metal		\$100.00	1	\$100.00
Removable Panel	PANEL,RMVBLSST	5009	A00	EVS Metal		\$150.00	1	\$150.00
Heater Block	BLOCK,HTR,DEL	5010	A00	EVS Metal		\$75.00	1	\$75.00
Shroud	SHROUD,HTR,SST	5011	A00	EVS Metal		\$100.00	1	\$100.00
Mirror/Steel Angle	BRACE,ANGLE,SST	5012	A00	EVS Metal		\$100.00	1	\$100.00
Caster	CASTER,BRAKE,3"	03-SRP-3-WB	A00	Magnus Motion Control Solutions	N/A	\$9.18	4	\$36.72
Flowmeter	MTR,FLOW,OX,200CC	FM-200UO-DN	A00	Amvex	MedGas Components	\$197.00	1	\$197.00
DISS M Bulkhead Fitting	FTNG,DISS,M,BLKHD,OX	BA-O-BLK	A00	Amvex	MedGas Components	\$26.00	1	\$26.00
Flowmeter Adapter	ADPTR,MTR,FLOW	BA-O-M2	A00	Amvex	MedGas Components	\$5.00	1	\$5.00
Oxygen Hose	HOSE,24",DISS/DISS	HS-02UO-DHDHNA	A00	Amvex	MedGas Components	\$15.00	1	\$15.00
Power Filter/Inlet	MOD,PWR,RFI,6A,FUSED	562-864-0777	A00	Qualtek	Mouser Electronics, Inc.	\$24.93	1	\$24.93
Power Fuse	FUSE,6.3A	693-0034.3125	A00	Schurter	Mouser Electronics, Inc.	\$0.24	1	\$0.24
Power Cord	CORD,PWR,8',HOSP	562-233002-06	A00	Qualtek	Mouser Electronics, Inc.	\$5.50	1	\$5.50
Terminal Block	TERM,12POS,PHEN	538-38780-0106	A00	Molex/Beau	Mouser Electronics, Inc.	\$2.61	1	\$2.61
Hole Jumper	JMPR,TERM,12POS	538-38002-0331	A00	Molex/Beau	Mouser Electronics, Inc.	\$0.20	3	\$0.60
Power Supply	PWR,SPLY,24V,6.5A	PS-24-6.5	A00	TE Technology, Inc.		\$74.00	1	\$74.00
Cooling Plate	COOLER,THERM,65W	CP-065	A00	TE Technology, Inc.		\$261.00	1	\$261.00
Temp. Cotroller	CONTR,TEMP,PID	TC-24-10	A00	TE Technology, Inc.		\$109.00	1	\$109.00
Laptop	CMPTR,NTBK,XGAWS		A00	Dell		\$487.50	1	\$487.50
pH Probe	PROBE,PH,ROSS		A00	Fisher Scientific		\$450.00	1	\$450.00
A/D reader USB-6009	CNVTR,A/D,USB	779026-01	A00	National Instruments		\$269.00	1	\$269.00
Amplifier	AMP,UNI GAIN,BATT	PHTX-21	A00	Omega Engineering		\$59.00	1	\$59.00
Coaxial Respiratory Circuit	CRCT,COAX,BREATHING		A00	King Systems		\$25.00	3	\$75.00
Miscellaneous						\$500.00	1	\$500.00
Labor	Assy/Test			8 hours @ 75/hour		\$75.00	8	\$600.00
						Cost		\$5,984.73

Fabrication drawings of the key custom components are also shown over the next few pages:

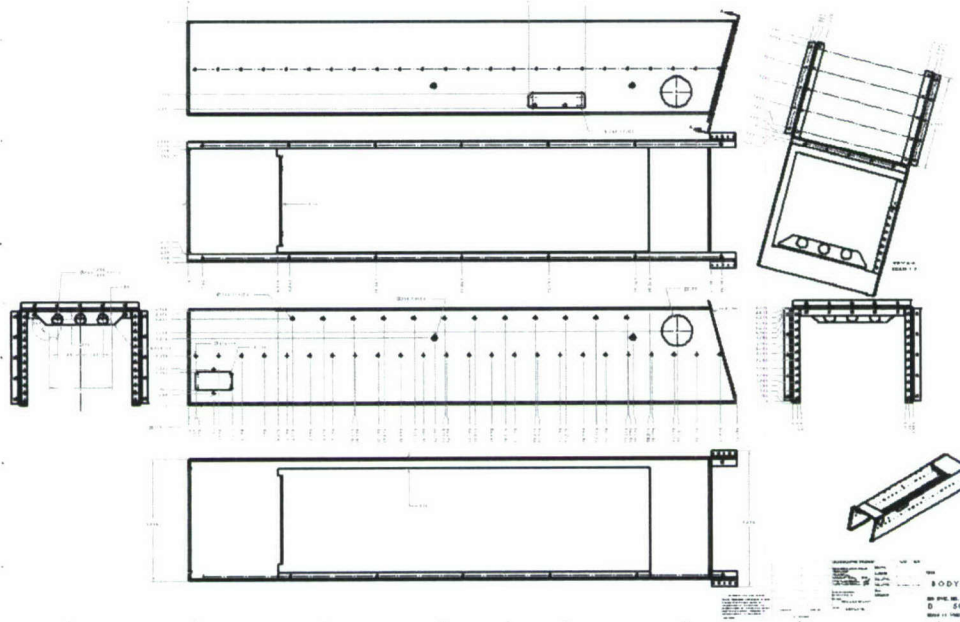
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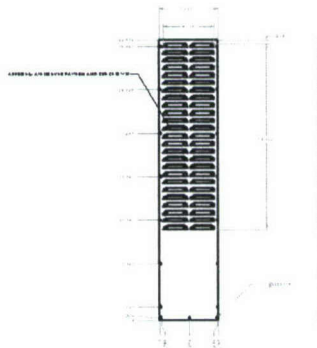
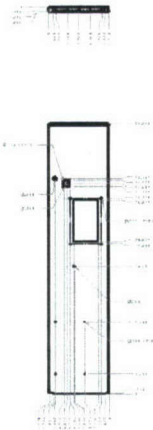
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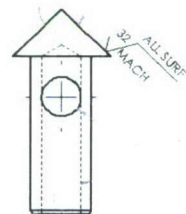
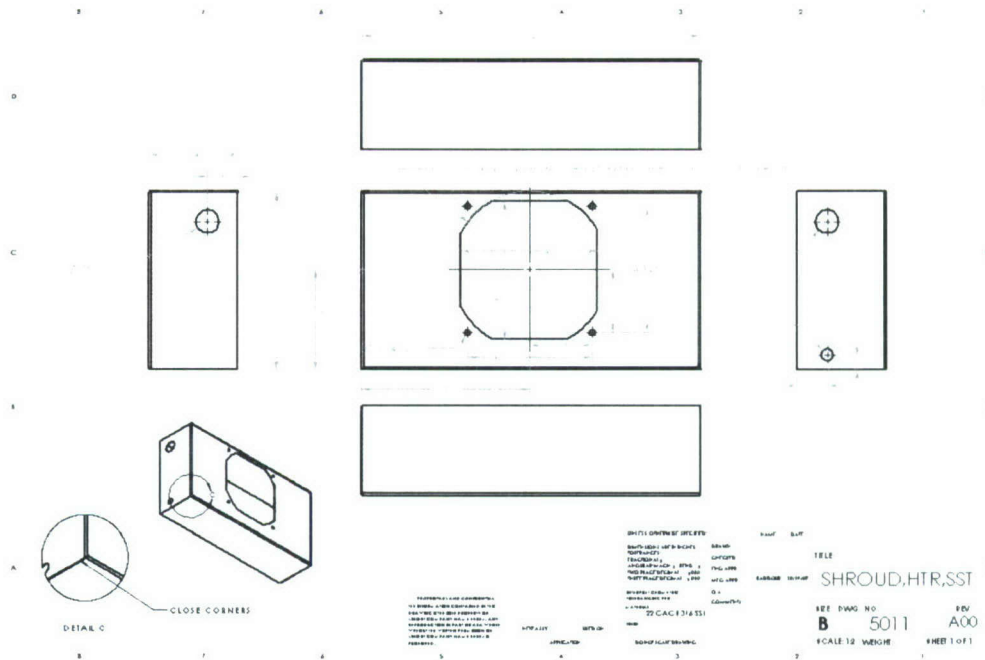
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Personnel Supported:

- John F. Hunt, MD – Principal Investigator for duration
- A. Rafi Baddour – Engineering, Development, and prototype fabrication for duration
- Brian Walsh – Validation, ICU application of technology, design guidance for duration
- Linda Baddour – Accounting, contract administration for duration

This staffing was the equivalent of 3 FTE.

Publications:

List peer-reviewed publications submitted over the duration of the program:

1. Paget-Brown A, Ngamtrakulpanit L, Smith A, Bunyon D, Hom S, Nguyen TA, Hunt J. Normative data for pH of exhaled breath condensates, *Chest* 2006, 129(2): 426-30.
2. Hunt J, Yu Y, Burns J, Gaston B, Ngamtrakulpanit B, Bunyan D, Walsh B, Smith A, Hom S. Identification of acid reflux cough using serial assays of exhaled breath condensate pH. *Cough* 2006, 2:3 (11 April 2006).
3. Walsh BK, Mackey D, Pajewski T, Yu Y, Gaston B, Hunt JF. Exhaled breath condensate pH can be safely and continuously monitored in mechanically ventilated patients. *Respiratory Care*. (in press).
4. Gaston B, Kelly R, Urban P, Liu L, Henderson E, Doctor A, Teague WG, Fitzpatrick A, Erzurum S, Hunt J. Buffering airway acid decreases exhaled nitric oxide in asthma. *J Allergy Clin Immunology* 2006 (in press).
5. Walsh BK, Chronic Cough Associated with Laryngopharyngeal Acid Reflux Disease (LPRD), Why Should a Respiratory Therapist Care? *AARC Times*, 2007 (in press)

Interactions/Transitions:

The continuous pH condensimetry has been presented in poster and oral formats at the American Academy of Allergy, Asthma, and Immunology in March 2006, the American Thoracic Society Annual meeting in May 2006, and the European Respiratory Society in Sep 2006.

New Inventions, Discoveries, Patent Disclosures:

There have been no new inventions, discoveries, or patent disclosures over this period. However, substantial know-how of a commercially-valuable nature has been accumulated enabling Respiratory Research, Inc. to uniquely serve the needs of the research community in the field of acute lung injury, airway acidification, and prognostic lung health assessment.

Honors/Awards:

Respiratory Research, Inc. received the Virginia Piedmont Technology Council's "Rocket Award" for the most rapid movement of product from concept to commercialization—this award was given for the company's acid reflux diagnostic system, based on technology involving gas-standardized pH measurement in exhaled breath condensate, akin to the continuous pH condensimetry system.