AN ACCURATE METABOLIC SIMULATOR FOR INDIRECT CALORIMETRY SYSTEM VALIDATION

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ABSTRACT

A metabolic simulator capable of simulation of respiratory oxygen consumption (VO_2) and carbon dioxide production (VCO_2) for validation of indirect calorimetry systems is described. The metabolic simulator adds/removes respiratory gases by way of mass flow controllers to/from a physiologically realistic lung simulator (Michigan Instruments Inc. Training/Test Lung). The metabolic simulator and Michigan Instruments Training/Test Lung in combination are capable of simulating a wide range of metabolic and physiologic lung conditions. Simulation of VCO_2 is achieved by adding controlled amounts of carbon dioxide to the Training/Test Lung every (mechanical ventilator delivered) breath cycle. VO_2 simulation consists of adding controlled amounts of nitrogen and removing controlled amounts of inspiratory gas from the Training/Test Lung every breath. Real time monitoring of ventilation parameters is obtained from a Novametrix Cosmo+ respiratory profile monitor and control of gas flow through the simulator is achieved by way of a programmed IBM personal computer.

Key Words: VO_2,VCO_2, Respiratory Quotient, Indirect Calorimetry, Metabolic Simulation, Training/Test Lung, Cosmo+ Respiratory Monitor, EPLD.

Introduction

The monitoring of respiratory gas exchange (indirect calorimetry) in the medical field is used in the assessment of patient energy expenditure and substrate (fat, protein, and carbohydrate) utilization for determination of proper nutritional management of critically ill (ventilator dependent) patient populations. Caloric mismanagement has been associated with increased morbidity and mortality as well as increased hospital stay[1,2,3,4,5,6]. Further, improper management of substrate balance may produce ventilator weaning difficulties. The development of an indirect calorimetry system was previously described[8], this paper addresses an *in vitro* metabolic simulation system for validation of the accuracy of this indirect calorimetry system.

Indirect calorimetry systems measure the quantity of oxygen consumed (VO_2) and the quantity of carbon dioxide produced (VCO_2) in a patient. The ratio of VCO_2 to VO_2 is known as the respiratory quotient (RQ). The RQ varies according to substrate utilization with fats producing a low RQ (~ 0.70), carbohydrates a high RQ (~ 1.0), and protein falling in between (~ 0.80). Protein is generally a minor metabolic energy source and its rate of metabolic consumption can be either measured directly using

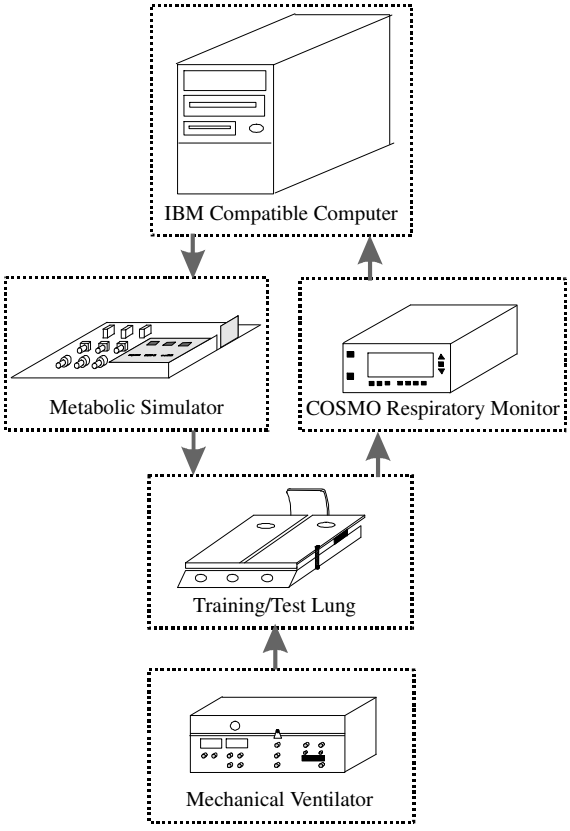

Figure 1. Diagram of the metabolic simulation system

urea nitrogen concentrations or simply estimated. Since protein consumption is typically small compared with fats and carbohydrates, the RQ can be used to estimate the proportionate amount of fat and carbohydrate metabolism. Further, once the VO_2 and VCO_2 values have been measured, the energy expenditure of the patient per unit time can be determined[9]. The information thus provided by the indirect calorimetry system empowers the physician to tailor the patient's nutrition support regimen.

Since indirect calorimetry systems measure VO_2 and VCO_2, validation of their accuracy can be estimated *in vitro* using a simulator or standard which generates known values of VO_2 and VCO_2. The metabolic simulator described here is designed to meet these objectives.

The indirect calorimetry system to be validated by this metabolic simulation system[8] is unique in that it uses on-airway oxygen and carbon dioxide sensors. Other existing indirect calorimetry systems siphon airway gas off to sensors located inside the housing of the device. However, in this indirect calorimetry system, the sensors are mounted at the inlet to the patients airway allowing a direct determination of the concentration (as well as flow) of airway gases. Thus, a determination of VO_2 and VCO_2 values is obtained by combining airway flow and gas concentration information. Therefore, in order to verify that the VO_2 and VCO_2 values generated by this indirect calorimetry system are accurate, a metabolic simulator capable of simulating a range of inspiratory and expiratory flow patterns (lung mechanics) for a mechanically ventilated patient is required.

Previous attempts at metabolic simulation have not included the effects of varying lung mechanics. These metabolic simulation strategies include alcohol burn[10,11,12] (methanol or butanol) which produce CO_2 and H_2O and consume O_2. These burns are typically done in a bottle or combustion chamber and lung mechanics cannot be varied. Other attempts at using flow controllers have input flow into bottles[13,14] and have also ignored the effects of lung mechanics. The metabolic simulator described here allows for a range of physiologically realistic lung mechanics settings due to the inclusion of a user settable test lung.

Figure 1 illustrates the complete metabolic simulation system designed. The system consists of an IBM personal computer which obtains breath information from a COSMO+ respiratory profile monitor (Novametrix, Inc.) and drives a metabolic simulation module which simulates gas exchange. Pulmonary mechanics simulation is provided by means of a Training/Test Lung (TTL, Michigan Instruments Inc.).

Methods

Metabolic Simulation Module

Simulation of respiratory gas exchange is provided by means of valve-modulated introduction and removal of respiratory gases from the test lung during the inspiratory phase of breath delivery. The timing of the introduction and removal of these gases is controlled ensuring that the quantities and concentrations of the gases are known. The gas removed is ventilator inspiratory gas and the gases introduced are carbon dioxide (CO_2) and nitrogen (N_2). Figure 2 illustrates the timing of gas introduction and removal from the test lung during a volume-cycled mechanical breath.

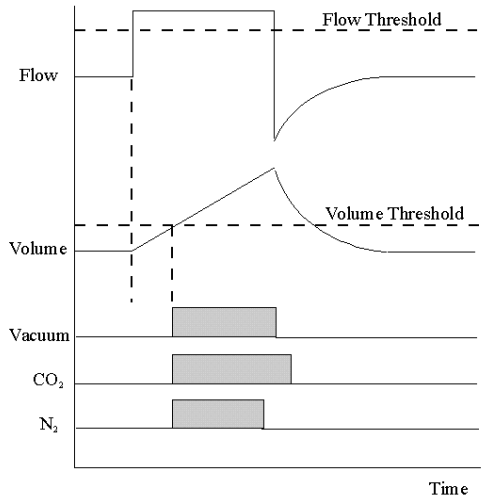

Figure 2. Timing of gas removal and introduction from metabolic simulator to test lung during one breath.

Gas Removal. Ventilator gas is removed from the test lung by the metabolic simulation module during the inspiratory phase. The ventilator gas is of known concentration, humidity and temperature distal to the inspiratory valve of the ventilator. At a controlled point in the inspiratory phase, a vacuum source in the metabolic simulation module is enabled diverting ventilator gas into the metabolic simulation module. The activation of the vacuum path is controlled by an external software program which monitors ventilator inspiratory flow and volume and activates the vacuum path once a user defined flow and volume threshold have been exceeded (Figure 2). These

thresholds ensure that the gas being removed from the patient circuit is pure inspiratory gas from the ventilator and not mixed gas entrained from backflow or exhalation flow from the test lung.

Gas Addition. Two gases of known concentration and temperature (carbon dioxide and nitrogen) are introduced during the inspiratory phase concomitant with activation of the vacuum path. Carbon dioxide introduction is controlled to obtain a known flow of carbon dioxide per unit time, thus producing a known VCO_2. Nitrogen introduction is controlled in synchrony with inspired gas removal (21% or higher O_2 concentration) to dilute the oxygen concentration in the inspired gas, thus producing a known VO_2.

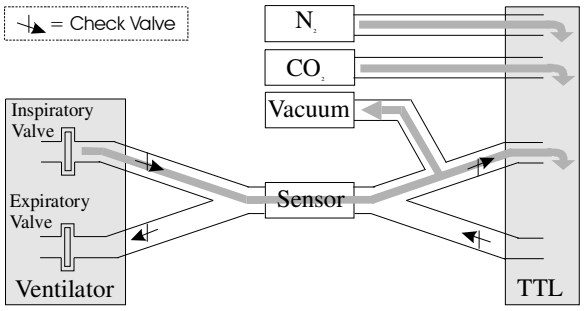

Figure 3. Gas flow during inspiratory breath phase.

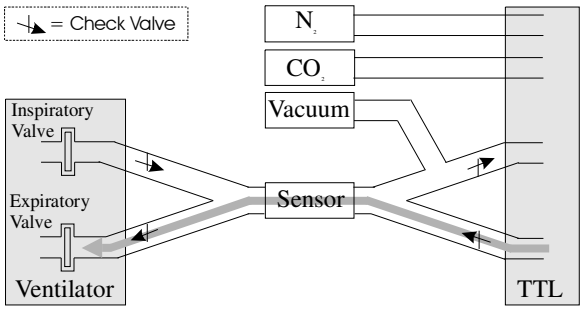

Figure 4. Gas flow during expiratory breath phase.

Gas Flow Control. The path of gas flow during the inspiratory and expiratory breath phases are shown in Figures 3 and 4. Both processes of gas addition and removal are regulated by mass flow controllers (MFCs). The MFCs provide closed-loop flow control which is highly independent of temperature and pressure variations. One MFC is used for nitrogen, one for carbon dioxide and one for vacuum removal of inspiratory gas. The MFC's have appropriate flow ranges allowing for simulation of VO_2 and VCO_2 at and about typical physiological ranges (0-240 and 0-192 ml/min respectively[15]). The upstream pressures of the nitrogen and carbon dioxide sources are controlled by pneumatic regulators and the vacuum source is wall vacuum and assumed to be adequately stable. Due to the limited response characteristics of the MFCs and the relatively short duration flow pulses necessary for
metabolic simulation, the MFCs are run in a steady state mode (flow is not varied with time). Rather, external flow diverter valves are used to direct gas flow into/out of the test lung (Figure 5). The flow diverter valves (XM-400, Evolutionary Concept, CA) are fast acting 3-way electrically activated solenoid valves. Their activation is modulated by an external programmable valve timer.

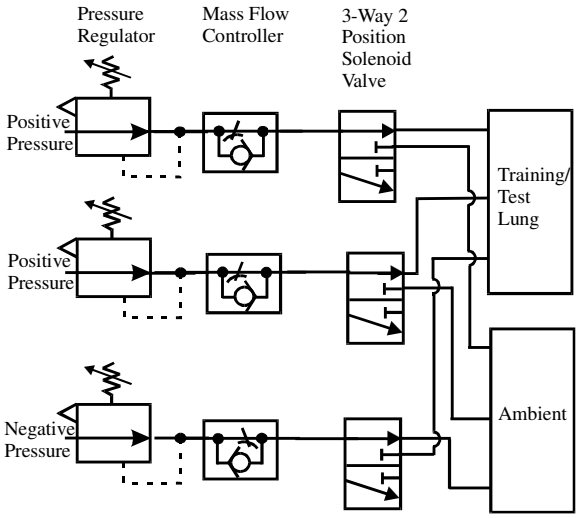

Figure 5. Pneumatic Schematic of Metabolic Module

Programmable Valve Timer Board. The programmable valve timer board consists of three erasable programmable logic devices (EPLDs) and associated support hardware which communicate with a software program running on an IBM personal computer. The EPLDs are the central processing element controlling the timing of valve activation. Each EPLD outputs valve activation time to a 7-segment display which updates in real time during valve activation (similar to a stop watch) and latches at the pre-programmed activation time. Both the valve activation time and the initiation of activation are controlled by the same external software program which monitors inspiratory flow and volume to command valve activation.

EPLD Design. The EPLDs were programmed using Altera Inc.'s Max+plusII (Version 9.3) development environment. This graphical programming environment allows for creation of programmable

logic devices using a number of design approaches (e.g. chip-based design, programming-based design, timing-based design). The design approach chosen was a chip-based design approach in which a graphical representation of existing TTL chips were used and interconnected to produce the desired digital output (See Appendix A for schematic). Three identical versions of the valve timer implementation as realized in the Max+plusII Baseline software were programmed on three 84-pin EPLD chips (Altera Inc. P/N EPM7128SLC84-15).

The inputs to the EPLD chips (Table 1) consist of a 20 kHz square wave (resulting from a 2 MHz crystal which is frequency divided in hardware to 20 kHz), +5 VDC/GND power supply, and 10 logic lines from the parallel port of an IBM personal computer. The 20 kHz square wave input is used by the chips to clock their internal logic. The +5 VDC power and ground lines are connected to a number of pins on the chips in order to supply an internal power circuit to the chips. Finally, the 10 input logic lines from the parallel port of an IBM personal computer are used by the chips for internal addressing issues and to initiate the valve timers.

TABLE 1. Valve Timer EPLD Inputs/Outputs

Input Line Description	Function
+ 5 VDC/GND	Chip Power
20 kHz Square Wave	Clocks Chip Logic
Parallel Port (25 Pin) Pins 2-5	Data Lines
Parallel Port (25 Pin) Pins 6-9	Selects Internal Latch Chip
Parallel Port (25 Pin) Pin 10	Strobes in Latched Data
Parallel Port (25 Pin) Pin 11	Initiates Timer
Output Line Description	**Function**
Valve On Line	Turns on Green LED to Signify Valve Activation
Valve Off Line	Turns on Red LED to Signify Valve Activation
(4) 7-segment LED outputs	Displays Elapsed Time Since Counter Activation

The EPLD design consists of four cascaded binary-to-decimal counters (SN7490). Each counter, once commanded to begin counting, counts from 0 to 9 repeatedly, incrementing on each successive clock pulse. When connected in cascade, these chips are capable of counting up to 10^n-1 with n being the number of cascaded chips. Thus, the four cascaded binary-to-decimal counters used in this design are capable of counting to 9,999. The output of the cascaded counters are sent to a comparator which determines whether a pre-programmed value has been reached. The pre-programmed value is sent to the comparator from the parallel port of an IBM personal computer running a communications program. In this way, the communications program running on the computer can dictate the value to which the cascaded binary-to-decimal counters will count. Once the target count has been reached, the cascaded binary-to-decimal counters stop counting until the PC once more commands (through another parallel port line) the counting to re-start.

The IBM PC programs the value to which the cascaded counters are allowed to count to by sending a binary representation of a decimal value (0–9) to a bank of four addressable latches (SN7475). The latched or target value of each latch chip is then compared (using a comparator, SN7485) to the value of an associated counter chip. When the values of each of the counters matches the values of each of their respective latches, a bit is set by a master comparator which terminates the counting process. In this way, all possible counter outputs from 0 to 9,999 are sequentially compared to preprogrammed values which can also range between 0 and 9,999. Thus, the counting process can be stopped at any value between and inclusive of 0 and 9,999.

The programming of the latches requires 9 parallel port lines (pins 2-10). Four lines (pins 6-9) select the latch chip to be programmed (since there are 3 valve timer EPLDs there exist 12 latch chips in total). The latch chip is selected by means of a dedicated selection bit of which 16 are available from a 16-bit demultiplexer (given the four input lines from the parallel port). This selection bit is sent to a 2-bit AND gate for comparison with a parallel port strobe line (pin 10) which, when high, produces a logical high at the AND gate output. The AND gate output is connected to the enable line of the latch. When the dedicated selection bit for a particular chip is high and the parallel port strobe line is high, data is allowed to flow into the latch chip. When the parallel port strobe line is subsequently set low, the data is latched into the latch chip. Data to be latched is presented at four input pins on the latch chip. These pins are directly connected to four parallel port lines (pins 2-5) which send a binary representation of a decimal value between 0 and 9 to be latched. In this manner, every counter chip can be compared to an associated latch chip containing a programmable value between 0 and 9.

The counting is stopped once there is a match between the latch chip values and the counter chip

values. This match produces a high logic level at the output of the master comparator. The master comparator output is then inverted and ANDed with the clock input. A high logic level at the master comparator then, effectively removes the clock pulse from the output of the AND gate. The output of the AND gate is sent to the counter chips to strobe the counter chips. Thus, removal of the clock pulse by a logical high output at the master comparator removes the clock pulse from the input to the counter chips which terminates counting.

A final parallel port line (pin 11) is used for restarting the counting process once the counting process has been stopped by the master comparator. This line resets all of the counter chips to zero reinitiating the counting process.

The 20 kHz clock which is input to the EPLD chips is frequency divided by 20 to 1 kHz via two cascaded counters (SN7490) configured to divide by 10 and divide by 2 respectively. The resulting 1 kHz clock cycle is used by the counters. Therefore, each clock pulse represents 1 msec. In this way, pre-programmed values represent elapsed msecs and the valve timer can time valve intervals up to 9.999 seconds with 1 msec resolution.

The final EPLD design (See Appendix A) was programmed into three 84-pin EPLD chips (Altera Inc. P/N EPM7128SLC84-15) using the Altera Max+plusII programmer (Version 9.3).

Valve Timer Board Level Design. Board level support of the three valve timer EPLD chips is constructed on a large (17"X8") prototype board. This support consists of a 20 kHz square wave generator, 7 segment LEDs, valve timer activation status LEDs (green and red), a +5VDC power supply, a valve driver (amplifier) stage, and a parallel port connector.

The outputs of each MAX 7128 EPLD are sent to 7-segment displays located external to the valve timer EPLD chip for display of elapsed time (Figure 6). In addition, a bit signifying that counting is in progress is sent to an external green LED and a bit signifying that counting has been terminated is sent to an external red LED.

The 20 kHz square wave generator consists of a 2 MHz crystal connected is series with two cascaded counters (CD4017BCN) configured as frequency (divide-by-ten) dividers.

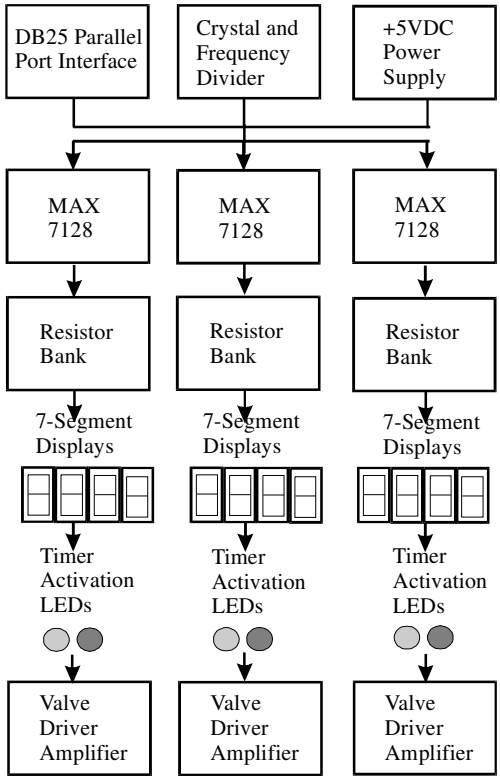

Figure 6. Functional Arrangement of Valve Timer Board

The power supply consists of an external +12VDC wall adapter interfaced with a +5VDC voltage

regulator (7805) thus generating +5 VDC power to the board.

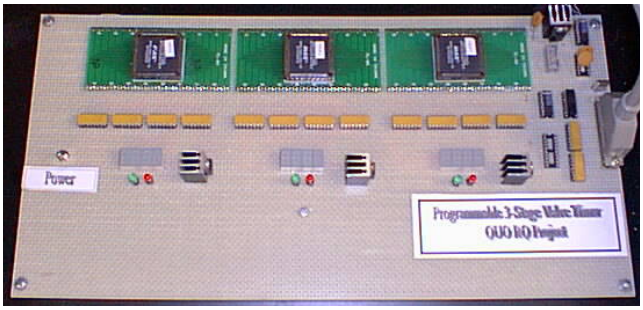

Figure 7. Picture of programmable valve timer board

the valve driver stages consist of TIP120 darlingtons configured to drive the valve load upon activation of the timer, and to terminate valve activation once the programmed elapsed time period has passed. A picture of the programmable valve timer board is shown in Figure 7.

Metabolic Simulator Software Program. A program which runs on an IBM personal computer has been developed to control the metabolic simulator. This program uses input received from the COSMO+ respiratory profile monitor as well as internal algorithms to command both valve activation and valve timing in order to achieve desired values of VO_2 and VCO_2.

The software program, was developed in the C++ programming language in the Borland C++ Builder 3 programming environment. The program is currently capable of controlling valve on-time and activation. User input of valve timing information, flow and volume thresholds for valve activation, and mass flow controller settings is presently required. Figure 8 shows the user interface for this program in which settings changes can be made.

Data is collected by the software program from the COSMO+ monitor by way of a serial port card on the IBM PC. Critical data such as airway flow and

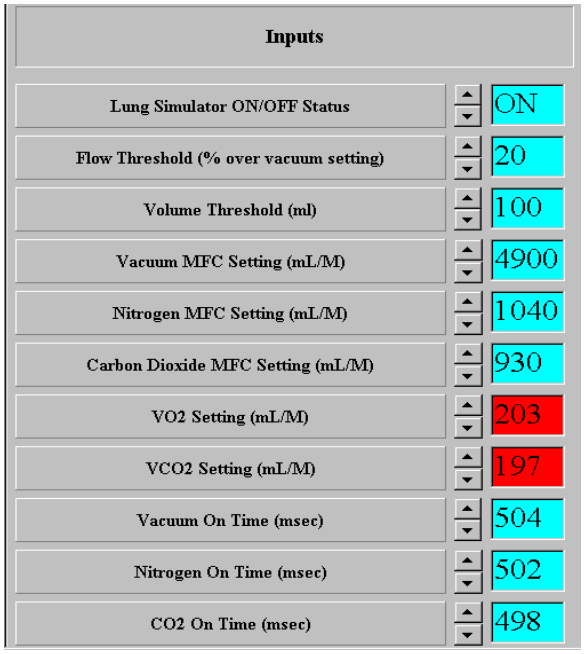

Figure 8. User interface of metabolic simulator software

pressure are obtained by the software program 100 times per second. Data is sent from the software program to the metabolic simulator by way of both a second serial port and a parallel port. The second serial port is used to communicate with the mass flow controllers which are commanded to a fixed flow rate on program launch. The parallel port is used, as described earlier, to both program the duration of, and to initiate valve activation.

Training/Test Lung. The lung model used (Training/Test Lung, Michigan Instruments Inc. Grand Rapids MI) is capable of simulating of a wide range of pulmonary conditions and pathologies. This test lung is a well accepted industry standard for lung simulation and meets appropriate ISO and ANSI standards for ventilator testing. It is therefore considered to be acceptable for the metabolic simulator described here from the standpoint of acceptability of lung mechanics simulation. The test lung consists of a spring tensioned bellows to simulate lung compliance and precision orifice restrictors to simulate airway resistance. The lung compliance can be set independently of airway resistance. The lung compliance modeled by the test lung is linear due to the linear force vs. displacement (volume) characteristic of the spring and bellows mechanism used. Actual physiologic lung compliance has a sigmoidal pressure vs. volume relationship. The airway resistance through the precision orifice restrictors produces a parabolic pressure vs. flow relationship representative of true physiologic airway resistance. Finally, the bellows resting volume produces a typical adult functional residual capacity. Table 2 gives applicable specifications for the test lung.

TABLE 2. Applicable Training/Test Lung Specifications

Test Lung Characteristic	Specification
Compliance Range	10 –150 mL/cmH_2O
Compliance Accuracy	+/- 5% at 150 mL/cmH_2O
Restrictors	Rp5, Rp20, Rp50
Lung Capacity	0 – 2000 mL

COSMO+ Respiratory Profile Monitor. Monitoring of ventilator delivered breath patterns is performed by a COSMO+ Respiratory Profile Monitor (Novametrix Inc, Wallingford CT). The monitor is configured to communicate with the software program. The COSMO+ is a non-invasive monitor generally used in a critical care setting for management of ventilator-dependent patients. Data obtained from the monitor, which is used here as a basis for control of the metabolic gas flows, includes such real-time information as airway flow, breath volume, and breath timing. The data generated by the monitor are obtained from an on-airway sensor located distal to the endotracheal tube (or airway

resistor). Applicable specifications for the COSMO+ are listed in Table 3 below:

TABLE 3. Applicable COSMO+ Specifications

COSMO+ Characteristic	Specification
Flow Range	0.25 - 180 L/Min
Flow Accuracy	> of ±3% reading or 0.5 L/min
Volume Range	1-3000 mL
Breath Timing Resolution	0.01 sec

Discussion

System Calibration

The system is being readied for calibration and test. In the calibration phase, the volume of gas delivered though each of the timed valves will be measured using a mercury-sealed spirometer. In this way, the on-time vs. volume curve for each of the valves can be determined. Once this determination is made, an algorithm can be designed and incorporated into the software which determines the appropriate valve timing for user selectable VO_2 and VCO_2 values. Thus, the user will simply select the desired values of VO_2 and VCO_2 and the software will control the metabolic simulator valve timing so that these values are correctly delivered to the test lung.

System Accuracy

Anticipated system accuracy is +/- 2% for VO_2 and +/- 1% for VCO_2. These values are obtained from the full scale flow accuracy of the MFCs (2 MFCs are used for VO_2 so each contributes a +/- 1% error to the delivered VO_2). The timing of the valves is controlled to 1 msec (or 0.1% of a 1 second valve on-time) thus, the contribution of valve timing resolution errors to system accuracy is considered to be negligible when compared to anticipated MFC flow errors.

Acknowledgements

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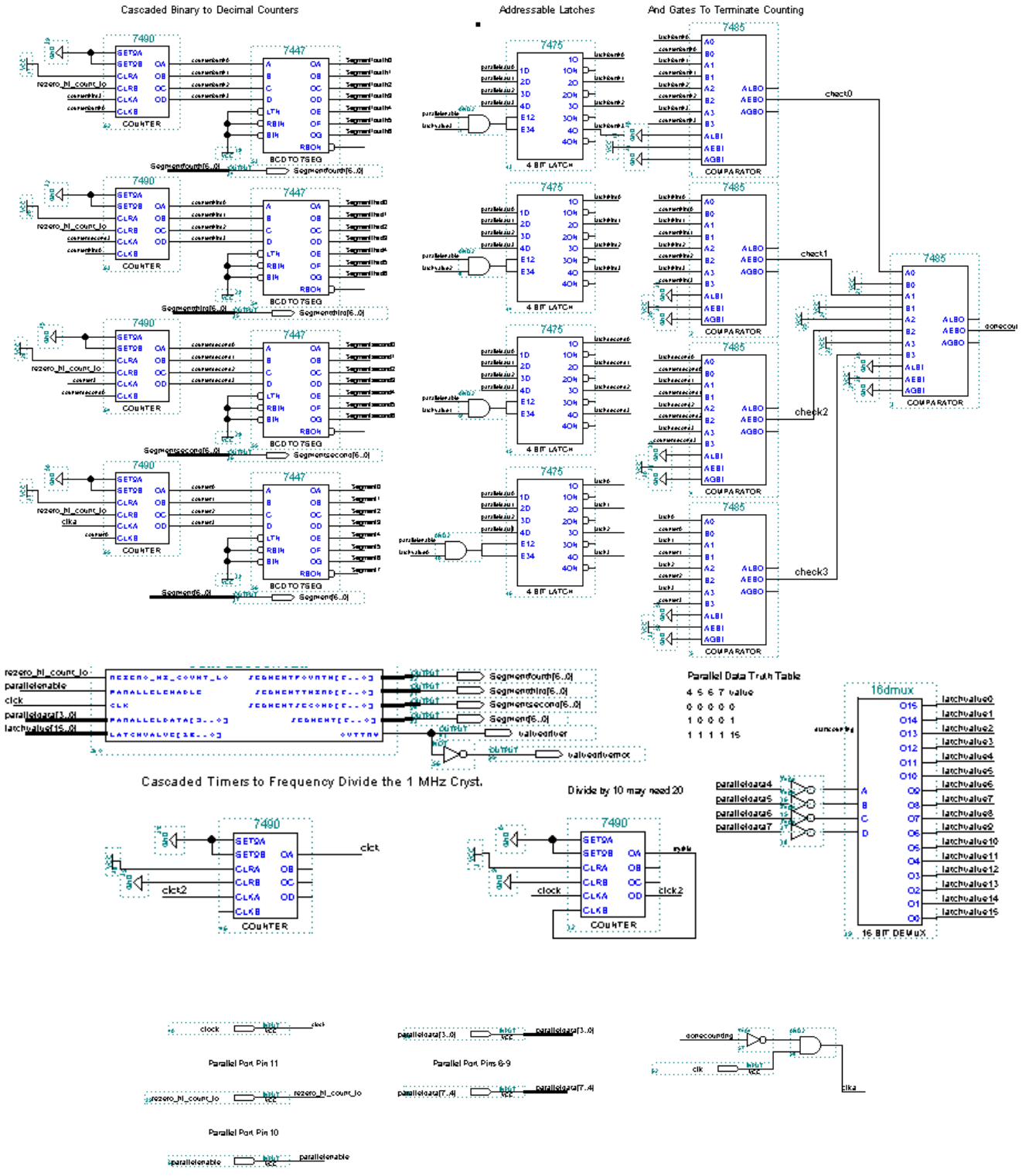
APPENDIX A


Cascaded Binary to Decimal Counters
Addressable Latches
And Gates To Terminate Counting
7490
7447
7475
7485
COUNTER
BCD TO 7SEG
4 BIT LATCH
COMPARATOR
check0
check1
check2
check3
donecount
Parallel Data Truth Table
4 5 6 7 value
0 0 0 0 0
1 0 0 0 1
1 1 1 1 15
Cascaded Timers to Frequency Divide the 1 MHz Cryst.
Divide by 10 may need 20
16dmux
16 BIT DEMUX
Parallel Port Pin 11
Parallel Port Pins 6-9
Parallel Port Pin 10