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Clinical non-invasive measurement of effective pulmonary capillary blood flow

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Abstract

Since traditional pulmonary function testing is centered on measurements of air flow and lung volume, a method to assess the pulmonary circulation might improve our ability to evaluate diseases that impact upon pulmonary hemodynamics. We have developed a PC based application that rapidly calculates pulmonary blood flow. Subjects rebreath a mixture of 10% argon and 3.5% freon for 20 seconds. Gas concentrations at the mouth are monitored by a clinical mass spectrometer and signals are acquired and processed with off-the-shelf hardware. To test the accuracy and reproducibility of this technique, patients with pulmonary artery catheters were assessed by standard thermodilution methods and the rebreathing test. Measurements using this non-invasive technology closely corellate with invasive thermodilution methods ($r = 0.980$) and show equivalent reproducibility (average standard error = 2.5%). This application of signal processing technology can extend the role of pulmonary function testing to include routine evaluation of the pulmonary circulation.

Abbreviations: Q_C – Pulmonary Capillary Blood Flow, Q_{TD} – Thermodilution Cardiac Output

Introduction

The measurement of non-shunted pulmonary capillary blood flow (Q_C) using a soluble inert gas was first described in 1912 by Krogh and Lindhard, who employed a single maximal breath of a gas mixture containing nitrous oxide [1]. In 1959, Cander and Forster described a modification of this method employing a series of breath holding maneuvers to quantify the rate of disappearance of a soluble inert gas in relation to an insoluble inert gas [2]. In the 80 years since the original technical description, scattered reports have appeared describing the application of this technique [3, 4, 5, 6, 7] and establishing its validity in various groups of subjects [8, 9, 10]. Although most reports have generally followed the analytic approach outlined by Cander and Forster, different authors have utilized minor modifications of this approach and no methodology has been accepted as a standard. The use of this technique has been hindered by cumbersome analysis methods that require visual determination of expired gas concentration plateaus from hard copy multichannel plots and manual digitalization for entry into a main frame computer for analysis [8, 9, 3, 10]. Some investigators have relied on complex instrumentation beyond the capabilities of most pulmonary function laboratories and difficult to apply in a routine clinical setting [7]. We have developed a straightforward personal computer supported method for acquisition and analysis of pulmonary blood flow data that performs calibration, data collection and analysis in less than one minute, thereby allowing the routine clinical application of this measurement. The purpose of this communication is to provide a detailed description of our methodology and its computer implementation and validation.

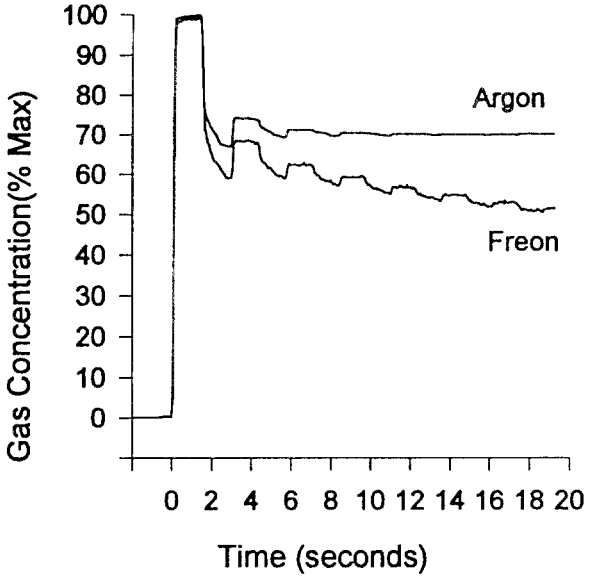

Fig. 1. Gas concentration changes during a typical 20 second rebreathing manuever. The argon plateau signifies complete mixing in the alveolar volume while the progressive decrease in Freon concentration reflects uptake into passing capillary blood.

Methodology

Apparatus and test procedure

The test protocol is performed in the pulmonary function laboratory on spontaneously breathing subjects in a sitting position with nasal occlusion. When the study is performed at the bedside in hospitalized patients, subjects are studied in a semi-recumbent position with the head of the bed elevated to approximately 30°. Test protocols were approved by the Norwalk Hospital Institutional Review Board and were performed after informed consent had been obtained from each patient. Prior to pulmonary blood flow testing, each subject has vital capacity measured using a set of forced expiratory maneuvers (Vitalograph, Lenexa, KS) and are then instructed to relax for 10 minutes prior to the first blood flow test in order to standardize tests done at different times in the same patient. Subjects are instructed to breathe quietly through a disposable mouth piece connected to a three-way rebreathing valve (3900C, Hans-Rudolph, Kansas City, MO). The three-way valve vents to room air in the closed position and, when opened, is connected to a standard anesthesia rebreathing bag (Series 6040, Hans-Rudolph, Kansas City, MO), which is filled with a gas volume equal to 80% of the subject's measured vital capacity. The test gas is composed of a mixture of 10% argon, 3.5% Freon, 35% oxygen and balance nitrogen (AGL Inhalation Therapy Co., Clifton, NJ). A Teflon mass spectrometer sampling line (0.0249 mm i.d.) is connected to the rebreathing circuit between the subject and the three-way valve and leads to a magnetic sector mass spectrometer (MGA 1100, Perkin-Elmer, Pomona, CA).

At the start of the test, the subject is instructed to exhale to residual volume. When residual volume is reached, the three-way valve is rotated to place the subject in the rebreathing circuit, the computer data acquisition is initiated and the subject is instructed to repeatedly empty and fill the rebreathing bag while being coached by the investigator to breathe at a rate of approximately 15 to 20 breaths per minute. The rebreathing maneuver is continued for 20 seconds, after which the subject is allowed to resume breathing room air. Repeat test maneuvers are undertaken when the digital read-out of the mass spectrometer shows that the expired Freon concentration from the test subject is no greater than 0.01%, a time interval of three to four minutes in normal subjects. The final value represents the average of three successive determinations of pulmonary capillary blood flow. Voltage signals from the mass spectrometer are sampled at 60 hertz by an analog/digital converter (DAS-16, Metrabyte, Taunton, MA) installed in a personal computer (IBM AT, International Business Machines). Each data collection is copied to magnetic disc storage immediately following completion of a breathing maneuver. A typical rebreathing curve for a normal subject is shown in Figure 1.

In order to assess the variability of successive Q_C measurements, nine normal subjects were evaluated on at least two different days. At each sitting, subjects had three or more Q_C measurements. Reproducibility was evaluated by determining the standard error of the mean (SEM) for the multiple measurements [11]. This measurement was normalized for differences in the absolute magnitude of Q_C to yield SEM%.

Cardiac output was measured invasively in nine patients in whom pulmonary artery flow directed thermodilution catheters (Baxter Healthcare Corporation, Irvine, CA) had been placed for a variety of clinical indications. Thermodilution cardiac output (Q_{TD}) measurements were performed immediately prior to Q_C determinations. Q_{TD} was determined by standard methods [12] using a 10cc room temperature injectate and standard cardiac output instrumentation (COM-1

Cardiac output computer, American Edwards Laboratories, Irvine, CA). Thermodilution cardiac output (Q_{TD}) was taken as the average of at least three determinations.

Calibration

The clinical mass spectrometer is calibrated against standard test gases according to manufacturer recommendations [13]. This instrument has a response time to 90% of full scale of 100 msec and a sampling rate of 1.0 ml/sec. In addition, prior to each set of rebreathing tests, a two point calibration is performed using room air and the test gas mixture containing 10% argon and 3.5% Freon. Gas is sampled for a five second interval and the voltage signals corresponding to argon and Freon during the second, third and fourth seconds are averaged to yield calibration values. Referencing the argon concentration to air eliminates the necessity of accounting for ambient argon in the subsequent data analysis.

Analysis

Data handling and normalization

The source code for the data acquisition and analysis is written in Turbo Pascal (Borland International, Scotts Valley, CA) and found at Appendix 1. The incoming data are initially read into a one dimensional buffer array. Each point is then subjected to software calibration and the two vectors representing argon and Freon concentration over the acquisition period are placed in a two dimensional array. Each gas concentration vector is searched for a maximum value and every point is divided by this value to yield normalized gas concentration vectors with values lying between zero and one.

Analysis region

The program initially defines an analysis region in which argon mixing is complete by locating the plateau in the argon concentration signal. Analysis region definition is accomplished by searching the argon vector from the end of the acquisition back toward the beginning. Pairs of argon concentration points separated in time by one second are examined, looking for an argon concentration difference greater than a threshold of 0.10%. When the concentration difference between these points exceeds the threshold value, the start of the analysis region is defined. All data points from this analysis start point until the end of the 20 second rebreathing maneuver are included in the subsequent calculation and define the analysis array. The average of all argon concentration points in the analysis array defines the argon steady state value (AR_{SS}), which is used to calculate alveolar volume using the equation:

$$V_A = \frac{V_B}{A_{SS}} \times \frac{760}{(P_B - 47)} \times \frac{(273 + T_B)}{273} \qquad (1)$$

where V_A = alveolar volume, V_B = initial bag volume, P_B = barometric pressure, T_B = body temperature. The initial concentration of argon in the rebreathing bag does not appear in equation (1) since this value has been normalized to one.

Blood flow

In the next step, a ratio vector is developed as the value of Freon concentration divided by the corresponding argon concentration for each point in time. This ratio vector compresses the information in the two dimensional analysis array into a one dimensional vector of ratios. The points in the log transformed ratio vector are then fit to a straight line of the form:

$$\ln\left(\frac{Ar}{Fr}\right) = a \times \text{time} + b \qquad (2)$$

by the least squares method [14] to yield a slope of the log transformed ratio vector, which is represented by the coefficient a. This slope is then used in the solution of the pulmonary blood flow equation of the form described by Petrini and co-authors [15]:

$$Q_c = a \times \frac{V_A + \alpha_T \times V_{tissue}}{\alpha_B} \qquad (3)$$

where Q_C = pulmonary capillary blood flow, V_{tissue} = tissue volume and α_B = Bunsen solubility coefficient for Freon in blood or tissue (α_T) (ml gas/ml blood).

Tissue volume

In order to calculate V_{tissue}, which represents the volume of tissue water in which Freon instantaneously dissolves independent of blood flow, the ratio vector is extrapolated back to time zero. The difference between this value and the argon steady state plateau represents a change in Freon concentration that cannot be explained by mixing in the alveolar volume and must, therefore, be due to solution in lung water. Time zero is chosen as 100 msec after the argon concentration

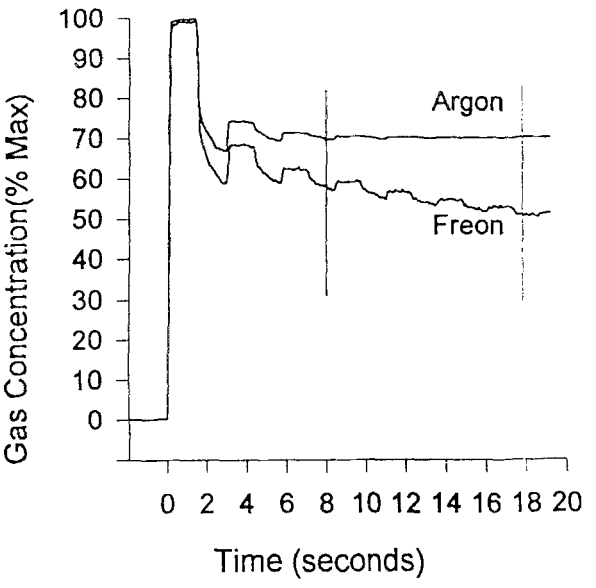

Fig. 2. A rebreathing curve demonstrating the analysis region defined by the vertical lines for determining pulmonary capillary blood flow.

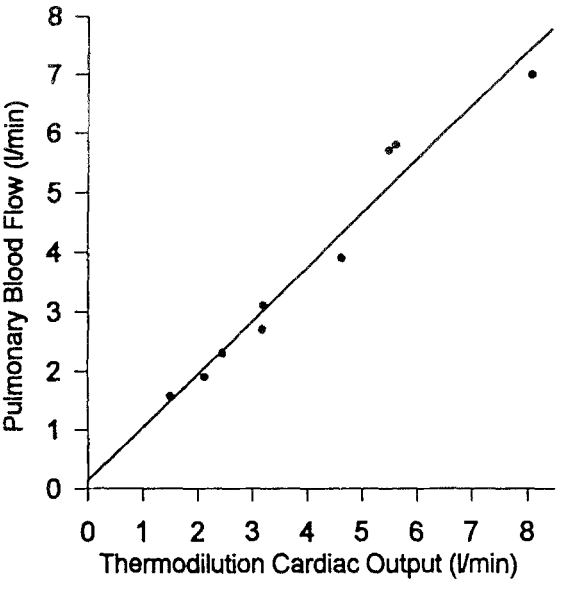

Fig. 3. The relationship between thermodilution cardiac output (Q_{TD}) and pulmonary capillary blood flow (Q_C) in ten patients ($r = 0.98$, $p < 0.001$).

reaches 90% of its peak value based upon theoretical considerations that suggest a 100 msec equilibration time for gas uptake into lung water [7]. This time is substituted into the regression equation (2) described above to yield a back projected log ratio of Freon to argon concentration at time zero. The exponential of the intercept value multiplied by 100 yields a Freon concentration as a percent of the argon concentration (incept) that may be substituted in the following equation to yield tissue volume by the relationship [15]:

$$V_{tissue} = \frac{V_A}{\alpha_T} \times \frac{100 - \text{incept}}{\text{incept}} \qquad (4)$$

Acquisition validation

After completion of calculations, the operator is presented with the interim results and a graphical display of the gas dilution curves with vertical bars showing the points which the program automatically chose to define the analysis region (Figure 2). The operator is given the opportunity to override these defined boundaries and relocate the analysis region boundaries. The overall procedure, including zeroing, data collection and analysis requires less than 60 seconds.

Results

In order to be a clinically useful examination, Qc must show agreement with an accepted standard and the test should be reproducible over multiple measurements. Q_C is effectively equivalent to non-shunted cardiac output because it is a measure of flow through the pulmonary circulation that comes into contact with alveolar gas. In the absence of significant right-to-left shunt, thermodilution cardiac output and Q_C should be in close agreement. To validate Q_C, comparison was made with simultaneously measured thermodilution cardiac output. Figure 3 shows the relationship between these methods of blood flow determination. The two methods are highly correlated ($r = 0.980$, $p < .001$) and Q_C predicts Q_{TD} with a high degree of accuracy.

The variability of the Q_C with repeated measurement at a single sitting is represented in Table 1. The SEM% of measurements averaged over each sitting ranged from 0.9% to 4.8% with an average of 2.5%. A review of 14 studies on the reproducibility of Q_{TD} determined as the average of three measurements showed an SEM% range of 2.1% to 4.3% in research studies using customized thermodilution apparatus and an SEM% range of 3.9% to 5.0% in a clinical environment with commercial equipment [11].

Table 1. Variability of Q_C measurement over multiple tests

Subject number	# of Q_C determinations	Mean Q_C	Standard error of the mean (SEM%)
1	15	3.97	3.0%
2	6	3.62	0.9%
3	11	3.56	1.8%
4	8	3.23	4.8%
5	9	5.66	2.1%
6	8	4.17	2.2%
7	10	3.25	1.5%
8	7	3.71	4.1%
9	8	3.92	2.2%

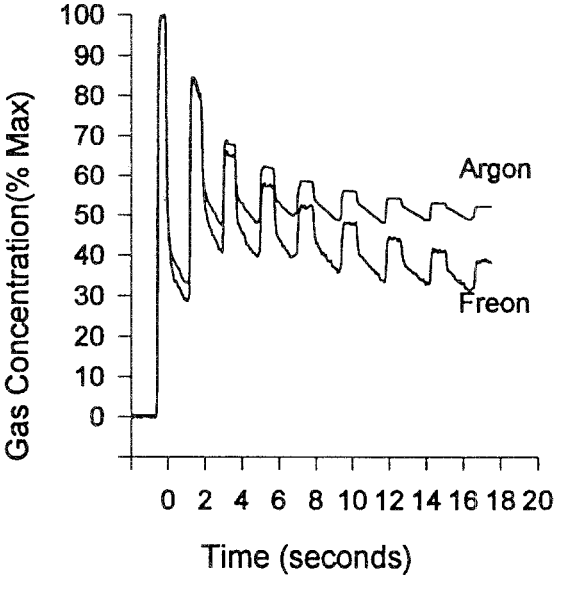

Fig. 4. A rebreathing curve for a patient with advanced obstructive airways disease. The large fluctuations in gas concentration with each breath and the failure of argon to reach a steady state concentration reflect a marked impairment in gas mixing.

Discussion

The development of powerful personal computer systems allows the application of complex processing tasks at the bedside. Measurement of pulmonary blood flow has previously been confined to specially equipped laboratories with complicated instrumentation. We describe one application of this new potential accomplished on a standard 80286 microprocessor based system equipped with 640 kilobytes of random access memory using an off-the-shelf analog/digital converter board that interfaces to a clinical mass spectrometer. The system is readily applied in a pulmonary function laboratory and at the bedside. Using a specially designed bag-in-box system interposed into a standard ventilator circuit, we have applied this methodology to mechanically ventilated patients in the ICU as well [16]. Direct data acquisition and processing avoids the time consuming process of setting up and calibrating multichannel chart recorders used by other investigators. The application of a point-by-point comparison of all data points avoids the labor intensive and error prone manual selection of end tidal gas concentration plateaus.

Because an underlying requirement of the rebreathing system is that adequate mixing of gases occurs between the lung and the rebreathing bag, advanced obstructive airways disease may limit the application of this test procedure. Even when using rapid rebreathing rates, this group of patients fail to achieve adequate gas mixing manifest as a quasi-steady state plateau in the argon concentration before the onset of blood recirculation (Figure 4). Furthermore, this same group of patients may have difficulty completing the rebreathing maneuver due to their marginal ventilatory status. Although there is insufficient experience with the rebreathing technique to define this group of patients by pulmonary function criteria, simple visual inspection of the rebreathing curves readily identifies tests in which gas mixing is inadequate. With this single exception, we have found the rebreathing technique for Q_C determination to be easily and reproducibility applied to cooperative patients in the clinical setting.

We elected to use a mixture of argon and Freon as the test gases because of our previous experience using this gas mixture in the study of pulmonary blood flow [16, 17]. The methodology is not linked to these particular gases in any fashion and other pairs of gases with similar solubility characteristics that can be easily detected, such as acetylene and helium, would also suffice.

In summary, we believe that this approach represents a new clinically applicable integration of PC based signal processing and basic lung physiology that may expand routine clinical pulmonary function testing to allow non-invasive evaluation of the pulmonary circulation.

References

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APPENDIX 1

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PROGRAM PBF;
{ rev. 1}
{ARGON/FREON EFFECTIVE PULMONARY BLOOD FLOW DETERMINATION}
{VERSION 2 FOR NEW DATA ACQUISITION AND ANALYSIS}
{S.M. WINTER, 2/90, NORWALK HOSPITAL}
{**************************************************************************
*       PROGRAM PULMONARY BLOOD FLOW(PBF) USES A MODIFICATION            *
* OF THE ARGON-FREON REBREATHING METHOD OF CANDER AND                     *
* FORSTER(JAP 14:541-551,1959) TO CALCULATE EFFECTIVE PULMONARY           *
* BLOOD FLOW. A MASS SPECTROMETER PROBE CONTINUOUSLY                      *
* MONITORS ARGON AND FREON CONCENTRATIONS AT THE MOUTH DURING             *
* A STANDARD 30 SECOND REBREATHING MANUEVER.                              *
*       THE PROGRAM STRUCTURE INVOLVES AN INITIAL TWO POINT ZERO          *
* AND CALIBRATION ROUTINE USING ROOM AIR AND A SPECIALCALIBRATION         *
* GAS. THE USER INPUTS INITIAL TEST CONDITIONS FOR THE SUBJECT AND        *
* WHEN THE SUBJECT BEGINS THE REBREATHING MANUEVER GAS CONCEN-            *
* TRATION SIGNALS FROM THE MASS SPECTROMETER ARE PASSED TO A 16           *
* BIT A/D BOARD THROUGH CHANNELS 1 AND 2. THE GAS CONCENTRATION           *
* SIGNALS ARE NORMALIZED AND RULES ARE APPLIED TO DETERMINE THE           *
* APPROPRIATE PORTIONS OF THE CURVES TO INCLUDE IN THE ANALYSIS           *
* BASED UPON ATTAINING A STEADY STATE ARGON CONCENTRATION.                *
* CALCULATIONS OF ALVEOLAR MIXING VOLUME, EFFECTIVE TISSUE                *
* VOLUME AND EFFECTIVE PULMONARY BLOOD FLOW ARE PERFORMED.                *
*       BEFORE FINAL RESULTS ARE DISPLAYED, PLOTS OF THE NORMALIZED       *
* ARGON AND FREON CURVES ARE DISPLAYED WITH A PLOT OF THE LOG OF          *
* DIFFERENTIAL GAS CONCENTRATIONS.  THESE CURVES ARE INSPECTED            *
* BY THE OPERATOR TO ASSURE THAT THE PROGRAM HAS SELECTED                 *
* A PROPER ANALYSIS REGION. THE OPERATOR MAY MODIFY THE ANALYSIS          *
* REGION AND REPEAT CALCULATIONS FOR AN ACCEPTABLE ANALYSIS.              *
*       THIS PROGRAM WAS DEVELOPED BY STEPHEN M. WINTER, NORWALK          *
* CONNECTICUT, JUNE 1990.                                                 *
**************************************************************************}

USES
  TP4D16,DOS,CRT,PRINTER,GRAPH;


CONST
   SETNPTS=3600; {TOTAL NUMBER OF DATA POINTS ACQUIRED FOR
      ARGON/FREON CURVES}
   SETACQPTS=1800; {NUMBER OF DATA POINTS ACQUIRED PER CHANNEL}
   NCHAN=2;  {NUMBER OF A/D DATA INPUT CHANNELS}
```

```
    LOCHAN=1; {FIRST A/D BOARD CHANNEL NUMBER}
    HICHAN=2; {LAST A/D BOARD CHANNEL}
    ACAL=0.0974; {CAL GAS INITIAL CONCENTRATION FOR ARGON}
    FRCAL=0.0489; {CAL GAS INITIAL CONCENTRATION FOR FREON}
    SMOOTHVAL=2; {NUMBER OF POINTS ON EACH SIDE OF SMOOTHED POINT}
    ARGONTHRESH=0.01; {THRESHOLD VALUE FOR VARIATION TO DEFINE
       ADEQUATE GAS MIXING}

    ALPHAB=0.83; {BUNSEN SOLUBILITY COEFF OF FREON IN BLOOD}
    ALPHAW=0.83; {BUNSEN SOLUBILITY COEFF OF FREON IN WATER}

LABEL 100,400,500,600;
TYPE
   {DEFINITION OF ARRAYS FOR DATA HANDLING.  THOSE STARTING WITH 'Z'
 ARE THE TARGET ARRAYS FOR THE A/D BOARD. THESE ARE TRANSFERRED
INTO ARRAYS ZVECTOR AND VECTOR WHICH HAVE A FULL SET OF A/D
CHANNELS PER LINE AND ARE OF LENGTH ACQPTS. EACH LINE IS DEFINED BY
AN ARRAY NAMED ZDATAPT OR DATAPT. TFLOW IS A TEMPORARY ARRAY
USED TO HOLD DATA DURING THE SMOOTHING ROUTINE AND DELTAAF HOLDS
THE DIFFERENCE BETWEEN THE ARGON AND FREON SIGNALS. EACH ARRAY IS
ASSOCIATED WITH A POINTER VARIABLE TO ALLOW DYNAMIC ALLOCATION OF
STORAGE}

    TPTR1=^INDATA;
    INDATA=ARRAY[0..SETNPTS] OF REAL;
    TPTR2=^VECTOR;
    DATAPT=ARRAY[1..NCHAN] OF REAL;
    VECTOR=ARRAY[0..SETACQPTS] OF DATAPT;  {DATA ARRAYS}
    TPTR3=^TFLOW;
    TFLOW=ARRAY[0..SETACQPTS] OF REAL;
    TPTR4=^DELTAAF;
    DELTAAF=ARRAY[0..SETACQPTS] OF REAL;


VAR
   {ALL VARIABLES WITH 'PTR' AS PART OF THEIR NAME ARE POINTER
   VARIABLES ASSOCIATED WITH ARRAYS DEFINED ABOVE}
   INPTR:TPTR1;
   PTR:TPTR2;
   TEMPPTR:TPTR3;
   AFPTR:TPTR4;
   TESTTIME:REAL;
   NPTS:INTEGER;
```

```
  ACQPTS:INTEGER;
  DATAFL:FILE OF REAL; {FILE TO WRITE NEW DATA FROM A/D BOARD}
  SAMRATE:REAL; {SAMPLING INTERVAL IN DATA POINTS/SECOND}
  GRAFSPACE:INTEGER; {SPACING OF GRAPHED POINTS TO STAY WITHIN 600 PT
      LIMIT}
  I,J,K,L,M:INTEGER;
  SIZE:INTEGER;  {SIZE OF SECTION OF GAS CURVES SUBJECTED TO ANALYSIS}
  ITIME,ETIME:INTEGER; {INITIAL AND END POINTS OF ANALYSIS SECTION}
  err_code:INTEGER; {RETURN CODE FOR A/D BOARD FUNCTIONS}
  SUM1,SUM2,SUM3,SUM4,FSUM,ACOEF,BCOEF:REAL;
  XBAR,YBAR:REAL;
  FLAG:BOOLEAN;
  GRAPHDRIVER,GRAPHMODE:INTEGER; {GRAPHICS INITIALIZATION
      VARIABLES}
  XX,YY,YY1:INTEGER;
  GMAX:ARRAY[1..NCHAN] OF REAL; {MAX GAS VALUES FOR SCALING
      GRAPHICS}
  MAXAF:REAL; {MAX ARGON-FREON RATIO VALUE FOR SCALING GRAPHICS}
  FNAME:STRING[30]; {NAME OF DATA INPUT FILE}
  FNAME1:STRING[10];
  FNAME2:STRING[2];
  RATIO,SCALE,ARMIX:REAL;
  CENTER,CYCLE:INTEGER;
  QT,VAO,VAOPRIME,VT,VTISSUE:REAL;
  QTAVE,VAOAVE,VAOPRIMEAVE,VTISSUEAVE:REAL;
  MODIFY:CHAR;
  SHIFTL,SHIFTR:INTEGER;
  RSHIFTL,RSHIFTR:REAL;
  ZTIME,INTERCEPT:REAL;
  INCHAR:CHAR;
  IERATIO:REAL;
  NEXT:CHAR;
  ZZERO:ARRAY[1..NCHAN] OF REAL; {ARRAY FOR ZERO OFFSET BIAS}
  ZMAX:ARRAY[1..NCHAN] OF REAL;  {ARRAY FOR MAX VALUE VOLTAGE}
  GCAL:ARRAY[1..NCHAN] OF REAL; {INPUT GAS CONCENTRATION VALUES}
  OUTVAL:REAL;
  RT,BT,BP:REAL;

{GRAPHICS INITIALIZATION PROCEDURE}
PROCEDURE GINIT(HEADER:STRING);

    BEGIN;
    SETTEXTJUSTIFY(CENTERTEXT,TOPTEXT);
```

```
      SETTEXTSTYLE(3,HORIZDIR,2);
      OUTTEXTXY(GETMAXX div 2,0,HEADER);
      END;


{GAS DATA GRAPHICS}
PROCEDURE GRAPHER(DEX:INTEGER;SCALE:REAL);
      BEGIN;
      J:=1-GRAFSPACE;
      WHILE J<(ACQPTS-GRAFSPACE-3) DO
        BEGIN
        INC(J,GRAFSPACE);
        YY:=300-TRUNC((PTR^[J,DEX]/SCALE)*250);
        YY1:=300-TRUNC((PTR^[J+1,DEX]/SCALE)*250);
        L:=(J+(GRAFSPACE-1)) div GRAFSPACE;
        LINE(L,YY,L+1,YY1);
        END;
      READLN;
      END;
{GAS DATA RATIO GRAPHICS}
PROCEDURE RGRAPHER(SCALE:INTEGER);
      BEGIN;
      J:=ITIME-GRAFSPACE;
      WHILE J<ETIME-GRAFSPACE-2 DO
        BEGIN
        INC(J,GRAFSPACE);
        YY:=300-TRUNC((AFPTR^[J]/MAXAF)*250);
        YY1:=300-TRUNC((AFPTR^[J+1]/MAXAF)*250);
        L:=(J+(GRAFSPACE-1)) div GRAFSPACE;
        LINE(L,YY,L+1,YY1);
        END;
      READLN;
      END;


 {*******SMOOTH GAS DATA*****************************************}
 {(2*SMOOTHVAL+1) POINT NEIGHBORHOOD SMOOTH}
PROCEDURE SMOOTH(DEX:INTEGER);
     BEGIN;
     NEW(TEMPPTR);
      FOR I:=(SMOOTHVAL+1) TO (ACQPTS-SMOOTHVAL) DO
      BEGIN
        FSUM:=0;
```

```
        FOR J:=(I-SMOOTHVAL) TO (I+SMOOTHVAL) DO
          FSUM:=FSUM+PTR^[J,DEX];
          TEMPPTR^[I]:=(FSUM/(2*SMOOTHVAL+1));
      END;
      FOR I:=(SMOOTHVAL+1) TO (ACQPTS-SMOOTHVAL) DO
      PTR^[I,DEX]:=TEMPPTR^[I];
      DISPOSE(TEMPPTR);
      END;


PROCEDURE REGRESS;
BEGIN;
    SUM1:=0;SUM2:=0;SUM3:=0;SUM4:=0;
    FOR I:=ITIME TO ETIME DO
       BEGIN
       SUM1:=SUM1+I;
       SUM2:=SUM2+AFPTR^[I];
       END;
       XBAR:=SUM1/SIZE;
       YBAR:=SUM2/SIZE;
       FOR I:=ITIME TO ETIME DO
       BEGIN
       SUM3:=SUM3+(I-XBAR)*(AFPTR^[I]-YBAR);
       SUM4:=SUM4+(I-XBAR)*(I-XBAR);
       END;
       ACOEF:=SUM3/SUM4;
       BCOEF:=YBAR-XBAR*ACOEF;

    END;



BEGIN
   SAMRATE:=120.0;

   GCAL[1]:=ACAL;
   GCAL[2]:=FRCAL;
   BT:=37.0; {BODY TEMPERATURE OF SUBJECT FOR BTPS CORRECTION}
   RT:=23.0; {ROOM TEMPERATURE FOR BTPS CORRECTION}
   BP:=760.0; {ATMOSPHERIC PRESSURE CORRECTION}

{***WRITE LOGO TO SCREEN AND ENTER CAL DATA****}
   GRAPHDRIVER:=DETECT;
```

```
   INITGRAPH(GRAPHDRIVER,GRAPHMODE,'C:\DRIVERS');
   SETTEXTJUSTIFY(CENTERTEXT,CENTERTEXT);
   SETTEXTSTYLE(1,HORIZDIR,4);
   SETCOLOR(12);
   YY:=GETMAXY div 2;
   OUTTEXTXY(GETMAXX div 2,YY,'EFFECTIVE PULMONARY BLOOD FLOW');
   INC(YY,TEXTHEIGHT('EFFECTIVE'));
   OUTTEXTXY(GETMAXX div 2,YY,'  BY ARGON/FREON UPTAKE');
   INC(YY,TEXTHEIGHT('BY ARGON'));
   SETTEXTSTYLE(1,HORIZDIR,2);
   SETCOLOR(5);
   OUTTEXTXY(GETMAXX div 2,YY,'    STEPHEN M. WINTER  ');
   INC(YY,TEXTHEIGHT('STEPHEN'));
   SETTEXTSTYLE(1,HORIZDIR,2);
   OUTTEXTXY(GETMAXX div 2,YY,'   NORWALK,CONNECTICUT  ');
   DELAY(400);
   SETTEXTJUSTIFY(CENTERTEXT,BOTTOMTEXT);
   SETTEXTSTYLE(3,HORIZDIR,1);
   SETCOLOR(11);
   OUTTEXTXY(GETMAXX div 2,GETM    .Y,'PRESS RETURN TO CONTINUE...');
   READLN;
   CLOSEGRAPH;
{*************************************  **********************}
{*************************************  **********************}
{SPECIFY DATA FILE TO BE REVIEWED}

 400:WRITELN;
   WRITELN;
   TEXTCOLOR(10);
   WRITELN('BASE NAME FOR NEXT DATA FILE YOU WISH TO VIEW (eg.
SMW05150)?  ');
   READLN(FNAME1);
 500:WRITELN;
   WRITELN;
   WRITELN('TYPE FILE SUFFIX FOR NEXT FILE YOU WISH TO VIEW (eg. S1 ) ');
   READLN(FNAME2);
   FNAME:='a:'+FNAME1+'.'+FNAME2;
   WRITELN;
   WRITELN;
   TEXTCOLOR(12);
   WRITELN('CURRENT FILE  NAME= ',FNAME);
   WRITELN;
   WRITELN;
```

```
   WRITELN('HOW LONG WAS THIS REBREATHING TEST RUN IN SECONDS?');
   READLN(TESTTIME);
   NPTS:=ROUND(TESTTIME*SAMRATE);
   ACQPTS:=NPTS DIV NCHAN;
   GRAFSPACE:=ACQPTS div 600; {FREQUENCY OF POINTS PLOTTED WHEN
      ACQPTS>600}
   ASSIGN(DATAFL,FNAME);
   RESET(DATAFL);
   TEXTCOLOR(14);
   CLRSCR;
   WRITELN;
   WRITELN;
   WRITELN('READING INPUT FILES....');
   WRITELN;
   WRITELN;
   NEW(INPTR);
   FOR I:=1 TO NPTS-2 DO
   READ(DATAFL,INPTR^[I]);
   CLOSE(DATAFL);
{*******************************************************}
{*******************************************************}
     CLRSCR;
     WRITELN;
     WRITELN('********INPUT VARIABLES**********');

{****SPECIFY TIDAL VOLUME OF TEST SUBJECT*****}
     TEXTCOLOR(14);
     WRITELN('PLEASE INPUT TIDAL VOLUME OF SUBJECT IN LITERS?');
     READ(VT);
     TEXTCOLOR(12);
     WRITELN;
     WRITELN;
     WRITELN('BAROMETRIC PRESSURE IS ASSUMED AT 760mmHg(100.1kPa)');
     WRITELN('BODY TEMPERATURE AT 37 degC AND ROOM TEMPERATURE AT');
     WRITELN('     23 degC---TYPE Y TO ACCEPT OR N TO CHANGE');
     INCHAR:=READKEY;
     INCHAR:=UPCASE(INCHAR);
     IF INCHAR='N' THEN BEGIN
       WRITELN('TYPE VALUE FOR BAROMETRIC PRESSURE(mmHg)?');
       READLN(BP);
       WRITELN;
       WRITELN('TYPE VALUE FOR BODY TEMPERATURE(deg C)?');
       READLN(BT);
```

```
      WRITELN;
      WRITELN('TYPE VALUE FOR ROOM TEMPERATURE(deg C)?');
      READLN(RT);
      WRITELN;
      END;
    WRITELN;
    WRITELN('*******VARIABLE INPUT COMPLETED********');
    DELAY(500);
    CLRSCR;

{************PLACE DIGITIZED DATA IN 2-DIMENSIONAL ARRAY**************}
{***************OF LENGTH ACQPTS AND WIDTH NCHAN************************}

    NEW(PTR);
    I:=1;
    J:=1;
    FOR K:=1 TO NCHAN DO
    GMAX[K]:=0;
    WHILE I<NPTS-2 DO
     BEGIN
     FOR K:=1 TO NCHAN DO
      BEGIN
      PTR^[J,K]:=INPTR^[I+(K-1)];
      IF PTR^[J,K]>GMAX[K] THEN GMAX[K]:=PTR^[J,K];
      END;
    INC(J);
    INC(I,NCHAN);
    END;
    DISPOSE(INPTR);

{*****************************************}


{***************GRAPH RAW DATA*******************}
   INITGRAPH(GRAPHDRIVER,GRAPHMODE,'C:\DRIVERS');
     SETCOLOR(13);
     GINIT('ARGON/');
     GRAPHER(1,GMAX[1]);
     SETCOLOR(14);
     GINIT('                    FREON SIGNALS');
     GRAPHER(2,GMAX[2]);
     CLOSEGRAPH;
 {*******SMOOTHING ROUTINES*****}
```

```
WRITELN('WORKING....');
{SMOOTH ARGON AND FREON CURVES}
FOR K:=1 TO 2 DO
SMOOTH(K);

{*********FIND START OF ADEQUATE ARGON MIXING*******}
      J:=ACQPTS-60;
      FLAG:=TRUE;
      WHILE (FLAG) DO
      BEGIN
      IF ABS(ABS(PTR^[J,1])-ABS(PTR^[J-30,1]))>ARGONTHRESH THEN
        BEGIN
        ITIME:=J;
        ETIME:=ACQPTS-4;
        FLAG:=FALSE;
        SIZE:=ETIME-ITIME;
        END
        ELSE
        DEC(J);
      END;


      {NORMALIZE CURVES SUCH THAT MAX VALUE=1}
      FOR J:=1 TO ACQPTS-1 DO
      BEGIN
      PTR^[J,1]:=PTR^[J,1]/GMAX[1];
      PTR^[J,2]:=PTR^[J,2]/GMAX[2];
      END;

      {FIND TIME WHEN ARGON CONCENTRATION FIRST EXCEEDS 90% OF
       MAXIMUM ARGON CONCENTRATION--ADD 6 TIME UNITS(100 msec)
       FOR DETERMINATION OF TIME ZERO, ZTIME}
      J:=1;
      WHILE(PTR^[J,1]<0.90) DO
      INC(J);
      ZTIME:=J+6;

{DETERMINE FREON/ARGON RATIOS}
   100:WRITELN;
      NEW(AFPTR);
      MAXAF:=0;
      FOR J:=ITIME TO ETIME DO
      BEGIN
```

```
      RATIO:=PTR^[J,2]/PTR^[J,1];
      AFPTR^[J]:=LN(100*RATIO);
      IF AFPTR^[J]>MAXAF THEN MAXAF:=AFPTR^[J];
      END;

{FIND AVERAGE PLATEAU VALUE FOR ARGON, AR(MIX)}
     ARMIX:=0;
     FOR J:=ITIME TO ETIME DO
     ARMIX:=ARMIX+PTR^[J,1];
     ARMIX:=ARMIX/SIZE;

     REGRESS;

     VAO:=VT/ARMIX;
     INTERCEPT:=ACOEF*ZTIME+BCOEF;
    {CORRECT TO BTPS}
     VAOPRIME:=VAO*(BP-20)*(273+BT)/((BP-47)*(273+RT));
    {DETERMINE TISSUE VOLUME}
     VTISSUE:=VAOPRIME*((100/EXP(INTERCEPT))-1)/ALPHAW;
     QT:=ABS(ACOEF*(VAOPRIME+VTISSUE)*60*60/ALPHAB);
     CLRSCR;
     WRITELN;
     TEXTCOLOR(3);
     WRITELN('*********INTERIM RESULTS*******************');
     TEXTCOLOR(7);
     WRITELN('REGRESSION EQUATION FOR
LN[FREON/ARGON]=',ACOEF:8:6,'*t+',BCOEF:4:3);
     WRITELN;
     WRITELN('INTERCEPT ',INTERCEPT:5:3,'
INTERCEPT%=',EXP(INTERCEPT):5:3);
     WRITELN('ARGON(MIX)=',ARMIX:5:3,'%');
     WRITELN;
     TEXTCOLOR(10);
     WRITELN('ALVEOLAR VOLUME(BTPS)=',VAOPRIME:3:2,'liters','  TISSUE
       VOLUME=',VTISSUE:3:2,'liters');
     WRITELN;
     WRITELN('EFFECTIVE PULMONARY BLOOD FLOW=',QT:5:3,'l/min');
     WRITELN;
     INCHAR:=READKEY;


    INITGRAPH(GRAPHDRIVER,GRAPHMODE,'C:\DRIVERS');
      SETCOLOR(3);
```

```
      GINIT('ACCEPT GRAPH');
      SETCOLOR(4);
      GRAPHER(1,1);
      SETCOLOR(5);
      GRAPHER(2,1);
      SETCOLOR(7);
      RGRAPHER(1);
      SETCOLOR(6);
      LINE(ITIME div GRAFSPACE,50,ITIME div GRAFSPACE,250);
      LINE(ETIME div GRAFSPACE,50,ETIME div GRAFSPACE,250);
      READLN;
      CLOSEGRAPH;
{**********ACCEPT OR REJECT***********}
    WRITELN;
    WRITELN;
    TEXTCOLOR(13);
    WRITELN('TYPE CARRAIGE RETURN TO ACCEPT THESE RESULTS');
    WRITELN;
    WRITELN;
    TEXTCOLOR(10);
    WRITELN('TYPE M TO MODIFY CURSOR POSITION AND RERUN THE
       ANALYSIS');
    READ(MODIFY);
    WRITELN;
    IF UPCASE(MODIFY)='M' THEN
      BEGIN
      WRITELN;
      TEXTCOLOR(11);
      WRITELN('TYPE THE NUMBER OF SECONDS TO MOVE THE LEFT
        CURSOR...');
      WRITELN('A POSITIVE NUMBER MOVES RIGHT, A NEGATIVE NUMBER
        MOVES LEFT.');
      READ(RSHIFTL);
      SHIFTL:=ROUND(RSHIFTL*SAMRATE/NCHAN);
      ITIME:=ITIME+SHIFTL;
      WRITELN;
      IF ITIME <= 0 THEN
      BEGIN
      ITIME:=120;
      TEXTCOLOR(15);
      WRITELN('YOU HAVE ASKED TO MOVE THE LEFT CURSOR BEFORE THE
        BEGINNING OF');
```

```
WRITELN('THE DATA. THE CURSOR POSITION HAS BEEN DEFAULTED TO
  TWO SECONDS');
WRITELN('FROM THE START.');
WRITELN('RETURN TO CONTINUE...');
INCHAR:=READKEY;
END;

TEXTCOLOR(12);
WRITELN('NOW TYPE THE NUMBER OF SECONDS TO MOVE THE RIGHT
  CURSOR ...');
READ(RSHIFTR);
SHIFTR:=ROUND(RSHIFTR*SAMRATE/NCHAN);
ETIME:=ETIME-SHIFTR;
IF ETIME>ACQPTS-1 THEN
BEGIN
ETIME:=ACQPTS-1;
TEXTCOLOR(15);
WRITELN('YOU HAVE ASKED TO MOVE THE RIGHT CURSOR BEYOND THE
  END OF');
WRITELN('THE DATA. THE CURSOR POSITION HAS BEEN DEFAULTED TO
  THE END.');
WRITELN('RETURN TO CONTINUE...');
INCHAR:=READKEY;
END;
SIZE:=ETIME-ITIME;
DISPOSE(AFPTR);
GOTO 100;
END;
CLRSCR;
WRITELN;
WRITELN;
TEXTCOLOR(11);
WRITELN('******FILE NAME=',FNAME,'************************');
TEXTCOLOR(12);
WRITELN('*************************************************');
WRITELN('***************FINAL RESULTS*********************');
WRITELN('*************************************************');
TEXTCOLOR(14);
WRITELN('*************************************************');
WRITELN('    ALVEOLAR MIXING VOLUME=',VAOPRIME:4:2,'liters            ');
WRITELN;
WRITELN('    EFFECTIVE TISSUE VOLUME=',VTISSUE:4:2,'liters            ');
WRITELN;
```

```
      WRITELN('    EFFECTIVE PULMONARY BLOOD FLOW=',QT:4:2,'liters/min  ');
      WRITELN('**************************************************');
      TEXTCOLOR(12);
      WRITELN('**************************************************');
      WRITELN('**************************************************');
      WRITELN('**************************************************');
      READLN;

DISPOSE(PTR);
CLRSCR;
WRITELN('TO RUN TEST ON A NEW PATIENT, TYPE 1');
WRITELN;
WRITELN('TO CONTINUE WITH ANOTHER TEST FOR THE SAME PATIENT, TYPE
2');
WRITELN;
WRITELN('TO QUIT, TYPE 3');
WRITELN;
NEXT:=READKEY;
CASE NEXT OF
   '1': GOTO 400;
   '2': GOTO 500;
   '3': GOTO 600;
    END;
600:WRITELN;
  END.
```