SIMULATIONS OF PHYSIOLOGICAL RESPONSES TO EXERCISE

Parameter Estimation on the Computer Model -MACPUF-

GEORGE HAVENITH

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THEORETICAL BIOLOGY GROUP
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CONTENTS

PREFACE

Reaching the end of my work at the theoretical biology group, I would like to expres my gratitude to all those who helped making it enjoyable and fascinating for me; especially to Maarten Woerlee for his moral support, as well as for the many talks on topics from in and outside our field of work;
Also to Norman Jones and all the others at Mc. Master University, who made my stay there very enjoyable and fruitfull to me.
Finally I would like to thank the " Utrechts Universiteits Fonds " and prof. Jones for their financial support for my stay at Mc. Master University.

SUMMARY

In a twelve month project theoretical biology, an investigation was done on the possibilities of simulating the physiological responses to exercise in humans.
As a basis the computer model of human respiration and circulation " MACPUF " (Dickinson 1977) was used.
A large amount of time was spent on the study of literature, related to the physiological responses to exercise, with emphasis on literature concerning the transition from aerobic to anaerobic energy production in human exercise; often referred to as the anaerobic threshold.
Then results of model simulations were compared to the results described in literature, and by this means, any discrepancy between the models behaviour and realistic test behaviour could be determined.
The next phase of the investigation was the improvement of the model in order to eliminate the afore mentioned discrepancies.
Through this procedure, the following items were changed in or added to the program:

- A work rate-oxygen consumption relation (efficiency) was added, to allow the determination of the work rate (model input) in Watts external energy production.
- An error in the time delay of the blood circulation representation was corrected;
- The slope of the cardiac output-oxygen consumption relation was changed and improved;
- A program part concerning the regulation of the tissue respiratory quotient (related to oxygen consumption) was introduced, aiming at the simulation of short term exercise tests (less then 3/4 of an houre);
- The representation of the lactate metabolism was changed; putting great emphasis on the catabolism of lactate in the working muscle;
- The buffering ratio of lactate by bicarbonate was raised;
- The calculation of mean aleolar pCO2 was changed;
- A new program part was added, calculating heart rate and stroke volume.

After these changes and additions were made, simulations of several exercise conditions showed that the behaviour of several model variables (VCO2, Ve, lactate concentration, R.Q., bicarbonate concentration, respiratory rate, cardiac output) had improved significantly.
Further investigations pointed out the necessity of the incorporation of a seperated working muscle (lactate production) compartment for a realistic simulation of lactate distribution between muscle and blood, and of the behaviour of lactate concentration after the end of an exercise period.

Finally, it appeared from simulations of exercise in subjects with cardiac disease, that the oxygen saving effect of the anaerobic production of lactate as it is incorporated in the model has to be reconsidered.

I. INTRODUCTION

This paper presents the results of the last six months of my project theoretical biology, in which I worked with the computer model " MACPUF " (Dickinson 1977). The results of the first six months were presented in my paper: " THE TRANSITION FROM AEROBIC TO ANAEROBIC ENERGY PRODUCTION IN HUMAN EXERCISE " (anaerobic threshold); subtitle: parameter estimation on the computer model " MACPUF " (april 1981). As the title mentions, the main point of interest was the anaerobic threshold. For this I did a study of the relevant literature and adapted the model in order to get better results in the simulation of exercise. Changes were made in the models description of: work input, delay time in circulation, cardiac output, tissue respiratory quotient, lactic acid catabolism and buffering by bicarbonate. These changes resulted in improved exercise simulation results for carbondioxide production, respiratory quotient, blood lactate concentration and minor improvements in the results of minute ventilation, breathing frequency and blood bicarbonate concentration.

At that point (the start of the last six months of the project), I ran into a practical problem: the behaviour of several variables, which were important in exercise, is not very well documented in research literature. For the continuation of my work, I needed real data from exercise tests to compare them with the models simulation results, in order to give a qualitative, as well as a quantitative judgement of these results. For the first part of my project I used data from B.G.D./P.T.T.; but their quantity was limited and they did not measure lactate concentrations.

Then I wrote to several exercise physiology groups with a request for data. In this way I contacted prof. dr. N.L.Jones (Ambrose cardiorespiratory unit of Mc.Master University medical centre, Hamilton, Canada). Dr. Jones suggested that it would be more efficient if I would visit his exercise group and in this way make it possible to do some mutual work. For this purpose I visited Mc.Master university from October to December 1981. Considering Dr.Jones and my own field of interest, I decided to put more emphasis on the simulation of physiological responses to exercise in general than on the specific simulation of the anaerobic threshold. Besides the simulation of exercise in general, I was also going to do some work on the simulation of exercise in patients with cardiac disease. In this period at Mc.Master, I did less literature study than in the first part of my project, as I received an enormous quantity of information in discussions with Dr.Jones and his co-workers.

Although the subject of my work has slightly changed, all the changes and adaptations of the model, which have been discussed in my first paper are still relevant. For a good understanding of the suggested changes in the model which will be discussed in the next chapters, some knowledge of my first paper

will be usefull. In this paper I will first describe some of the suggested additional changes in the model. After this I will present and discuss some results of exercise simulations in several different circumstances; some of them compared to real exercise test data.

II. ARTERIAL AND ALVEOLAR CO2 PRESSURE AND VENTILATION

In my first paper I already mentioned the deviations of ventilation values between the model and real data. I also described the influence of rising body temperature on ventilation. As this could not alone account for the deviations which were found, I continued my study of the ventilation regulation mechanisms. When I was studying the influence of arterial CO2 pressure on ventilation, I noticed that these CO2 pressures were quite low in exercise. Then, calculating arterial CO2 pressures directly from the values of alveolar ventilation and VCO2 (minute carbon dioxide output) by the respiratory formula:

$$PaCO2 = \frac{VCO2 * 0.86}{V_A}$$ (Jones and Campbell 1982)

with: Va=Alveolar ventilation;
VCO2=minute carbondioxide production;
PaCO2=partial arterial carbondioxide pressure

which can be deducted from the formula:

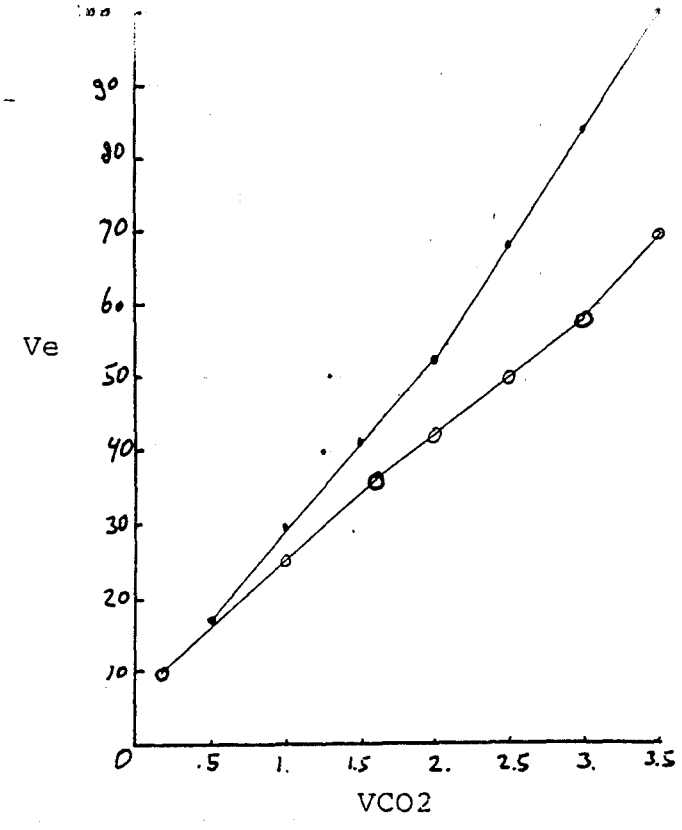
$$Ve = \frac{VCO2 * 0.86}{PaCO2} + (V_D * Fb)$$

with: Ve=Minute ventilation;
VD=dead space;
Fb=frequency of breathing.

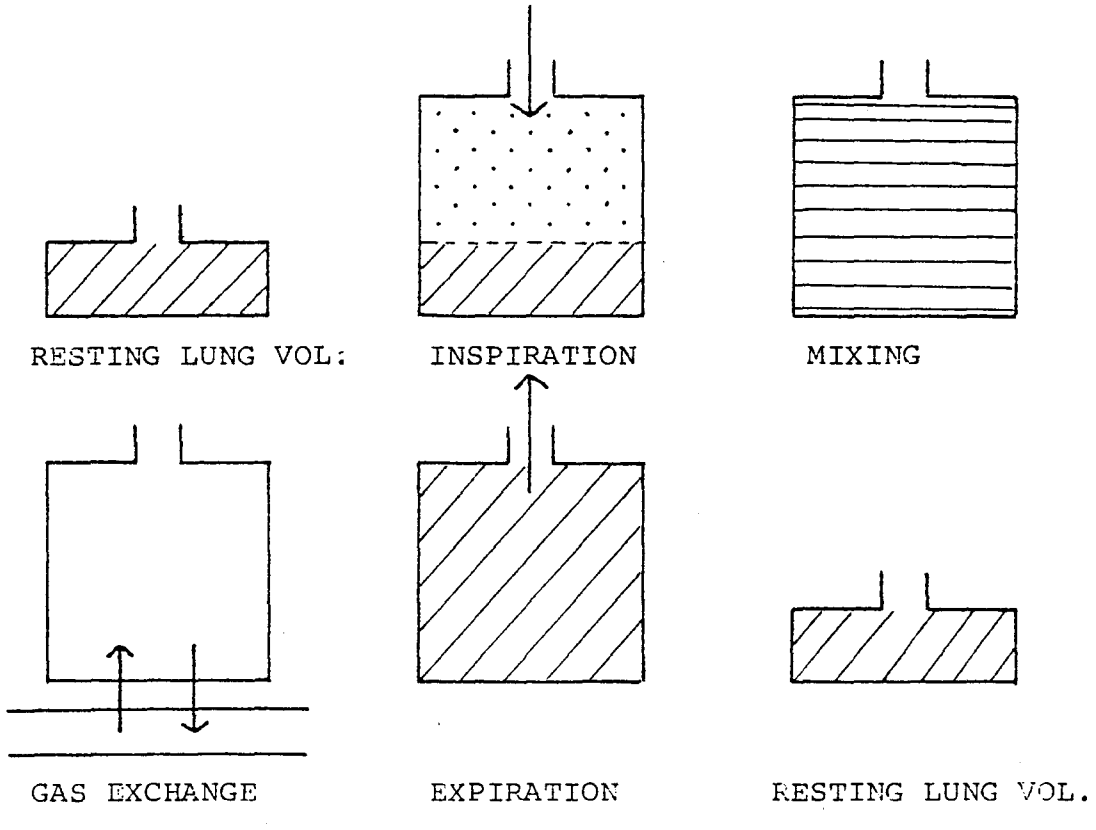
It appeared that the values calculated by MACPUF were not equal to these directly calculated values (see table 2-1).

Besides this I alsq found an important difference between MACPUF values and real data values (OHREN 1981), when I looked at the relation between Ve (minute ventilation) and VCO2 (see Graph 2-1). Where OHREN finds a steeper increase of ventilation values above a certain level of CO2 output, MACPUF shows a shallower increase.

The first program part I checked was the transportation of carbondioxide through the circulation. Carbondioxide transport through the different circulation compartments is calculated by the FICK-principle:



Graph 2-1;Relation between ventilation and carbondioxide production; dots:values from OHREN 1981; circles:values from MACPUF. Ve and VCO2 both in litres/minute.



Graph 2-2 Calculation of mean alveolar gas pressures.

LOAD %	$\dot{V}e$	$\dot{V}CO2$	PaCO2	$\dot{V}_A$	$\dot{V}_A$calc.	PaCO2 calc.
178	9.9	373	38.7.	7.9	8.2	40.6
400	21.0	864	36.5	17.8	20.3	41.7
800	39.9	1788	34.9	35.0	44.8	43.9
1200	82.8	3003	27.2	71.4	94.9	36.2

Table 2-1 Values from constant load test simulations; taken 15 min. after start of test. Load in % of resting metabolism Ve: minute ventilation in litres/minute; VCO2 minute carbondioxide output in litres/minute; PaCO2: partial arterial carbondioxide pressure in mm. Hg; Va: alveolar ventilation in litres/min.; calc.: values calculated through respiratory formula.

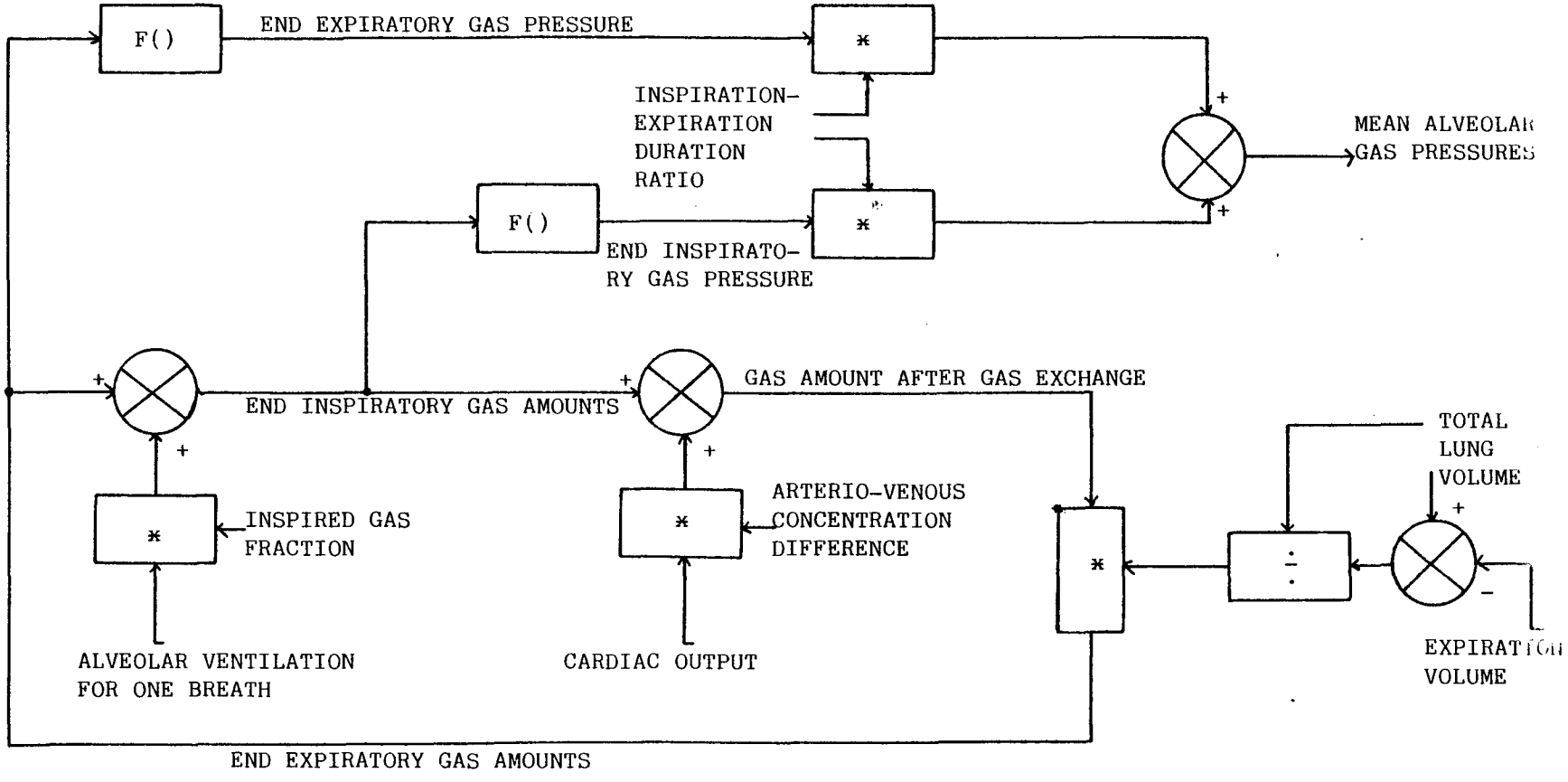
[] IN COMPARTMENT=FLOWin * []in - FLOWout * []out

in which [] stands for the concentration of the fluid.

As I did not find any errors in this description I concentrated on gas exchange in the lungs. Then I found that not only arterial pCO2 was rather low in exercise, but that also alveolar CO2 showed this behaviour. As arterial pCO2 in the model is deducted from the mean alveolar pCO2 (through pulmonary arterial pCO2 and the amount of venous admixture), the cause for the deviations might be located in the calculation of mean alveolar pCO2.

MEAN ALVEOLAR PCO2

How is the value of mean alveolar pCO2 calculated in the model? Starting with the resting lung volume (3000 ml.), room air is inhaled according to the value of alveolar ventilation for each breath (minute alveolar ventilation divided by respiratory rate). (Graph 2-2 and 2-2a). Inspired air contains known concentrations for each gas (FiO2=20.93, FiCO2=0.03, FiN2=79.04%). Inspired air and the residual air in the lungs are mixed and then the end inspiratory gas pressures are calculated.
After this, gas exchange between alveolar air and pulmonary capillaries takes place (according to cardiac output multiplied by arterio-venous concentration difference). The new amounts of gases are then reduced by the amount which is exhaled until resting lung volume is reached again. Then gas pressures in the resting lung volume (end expiratory gas pressures) are calculated. From end inspiratory gas pressures and end expiratory gas pressures, mean alveolar gas pressures are calculated, taking account of the relation between inspiration and expiration time (insp./exp. ratio). Finally these mean alveolar gas concentrations are used as values for idealized pulmonary capillary



GRAPH 2-2a: CALCULATION OF MEAN ALVEOLAR GAS PRESSURES

blood.

Of course this describes only the principles of the calculations as there are also several conversions from S.T.P.D to B.T.P.S. and vice versa, and, when itteration time is not equal to breathing time, everything is converted and calculated per itteration interval (time wheighting).

TIME WHEIGHTING AND INSP./EXPIR. DURATION RATIO.

To get an idea of the influences of changing the integration interval-respiration rate relation, I simulated an exercise test (load=800%) with constant respiration rate for three different integration times. The results are presented in table 2-2. From

Integration interval	Ve	VCO2	V_A	PaCO2	PaCO2 calc.	Respiratory Rate
4	25.5	1066	21.9	37.7	41.9	15.2
2	24.6	1023	21.1	36.2	41.7	15.0
1	24.5	1024	21.0	35.6	41.9	15.0

Table 2-2 Influences of changes in integration interval-respiration time relation. Work load 800% of resting value. Integration interval in seconds; other units see table 2-1.

this table we can conclude that changing the itteration time-respiration rate relation does influence the calculation of arterial CO2 pressures, but does not account for the total present deviation. I found a similar effect when I experimented with different values for the inspiration/expiration duration ratio. Lowering this ratio means lowering the influence of end inspiratory gas pressures and raising the influence of end expiratory gas pressures on the mean alveolar gas pressures. For carbondioxide, where end inspiratory gas pressures are lower then end expiratory gas pressures, lowering the ratio should increase the mean alveolar gas pressures. E.g.: reducing this ratio to .15 increased paCO2 only by 1.1 mm. Hg. instead of about 7. mm. Hg.

END INSPIRATORY GAS PRESSURES

One of the factors which could account for the too low arterial (and alveolar) pCO2 is a too low end inspiratory CO2 pressure. This in turn could be caused by the representation in MACPUF of gas exchange between alveoli and arteries. It takes place after the end of inspiration and before expiration, whereas in reality it is of course a continuous process, taking place during in and expiration. If a part of the carbondioxide is tranported from the blood into the alveoli before the calculation of the end inspiratory CO2 pressure, it will result in a higher end inspiratory gas pressure for CO2. This introduced in the model,

produced results as presented in table 2-3. We find that

% gas exch. inspiration	Ve	V_A	Paco2	Paco2 calc.	Respiratory Rate
0	58.3	51.7	31.7	44.2	18
40	67.1	58.9	33.0	39.1	20.6
70	74.1	64.5	33.4	35.8	22.8
90	78.5	68.0	33.7	33.9	24.1

Table 2-3 Influence of % of gas exchange taking place during inspiration; results from constant load test (200 Watt). Units see table 2-1.

calculated and simulated partial carbondioxide pressures converge when the amount of gas exchange during inspiration is raised. But to reduce the calculated-simulated pCO2 difference to less then 1 mm Hg., the amount of gas exchange during inspiration has to be raised above 85 %, which is hardly realistic.

END EXPIRATORY CO2 PRESSURES

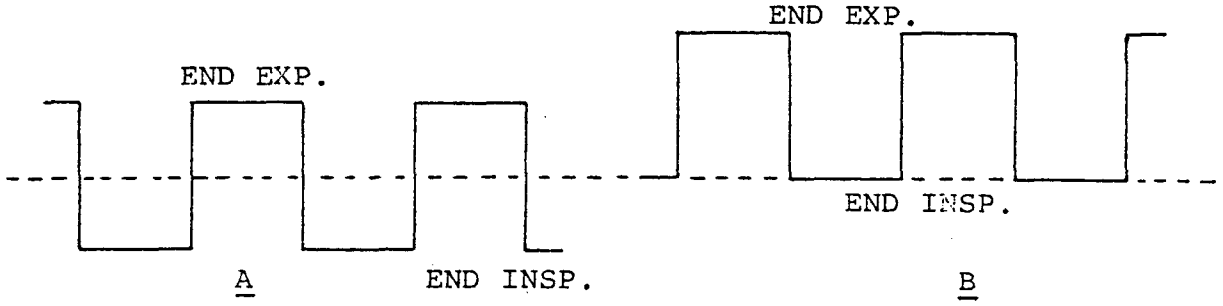
The results mentioned above lead us to the last factor directly influencing the calculation of mean alveolar CO2 pressure: the end expiratory CO2 pressure. When I did simulations with a seperated print-out of the values of end inspiratory, end expiratory, mean alveolar, arterial and calculated arterial (respiratory formula) partial carbon dioxide pressures, it struck me that values, calculated with the respiratory formula were very close to the simulated end expiratory values (difference ca. 1 mm. Hg.) This fact shows that it would never be possible to get realistic mean alveolar pCO2 values, only by changing end inspiratory pCO2; as the mean value will always stay lower as the end expiratory gas pressure.

What can be the cause of the resemblance of end expiratory gas pressure and calculated arterial gas pressure? Let us take another look at Graph 2-2 and look at the way in which the value of end expiratory CO2 pressure in the model is reached. At end inspiration all produced carbondioxide is added to the amount CO2 in the lungs, and then a part of it is exhaled according to alveolar ventilation. The concentration of the CO2 in the exhaled volume is equal to the concentration in the residual volume, as well as to the concentration in the total volume in which all CO2 (produced+inhaled+already present in residual volume) is present. For a steady state situation the concentration in the residual volume at end expiration will remain constant. This implies that all added CO2 (produced+inhaled) will be exhaled. This leads to the following equalities:

$$\frac{\text{Residual volume CO2 amount}}{\text{Residual volume}} = \frac{\text{Produced+inspired CO2 amount}}{\text{Exhaled volume}} =$$

$$\frac{\text{Total CO2 amount}}{\text{Total lung volume}} = \text{End expiratory CO2 pressure}$$

The term PRODUCED+INSPIRED CO2 AMOUNT/EXHALED VOLUME, which is the same as
EXHALED CO2 AMOUNT/EXHALED VOLUME
fits exactly into the respiratory formula (PaCO2=VCO2*.86/Va), as the exhaled CO2 amount is equal to VCO2*.86 (VCO2 in S.T.P.D.) and as exhaled volume equals (in this case) alveolar ventilation. This means that we were calculating mean alveolar CO2 as presented in Graph 2-3b, instead of the way presented in Graph 2-3a.



Graph 2-3 A and B; Calculation of mean alveolar CO2 pressures from end inspiratory and end expiratory CO2 pressures; dotted line is realistic mean alveolar CO2 pressure.

After locating the causes for the strange behaviour of mean alveolar CO2 in the model, the question is how to improve it. After several different attampts to do so, it appeared that Dr. Dickinson (personal communication) had already solved the problem in a later version of the model (81.5,22 july 1981). In this version end expiratory gas pressures are calculated by using partial gas pressures instead of gas amounts for the calculation of expired gas quantities. This is done both for CO2 and O2.
Although I concentrated on the improvement of calculated mean alveolar CO2 pressures (because of its influence on ventilation), most of the things I discussed are of course also applicable on the calculation of mean alveolar oxygen pressures. The changes are incorporated in the program between statement label 800 and 820.

III. RESPIRATION RATE

One of the variables which still showed deviations from data values after the change of several parameters (as described in my first paper) is the respiratory rate. Expressed against time in a stage 1 test (100 Kpm. per min. incremental test) we find much too low values (see Graph 9-4) As the respiration rate is related to the values of minute ventilation and tidal volume, I collected these values from tests done at B.G.D./P.T.T. and at Mc.Master, in order to compare them with values from the model. The averages of these test values for respiratory rate and tidal volume, expressed against Ve are given in Graph 3-2 and 3-3. When we draw in these graphs the values of the original MACPUF model (version 79.2) we see that MACPUF values for respiration rate are too low, and those for tidal volume are too high and reach their maximum too early. As tidal volume in MACPUF is deducted from minute ventilation and respiratory rate, we can alter both respiratory rate and tidal volume by changing the first.
In MACPUF respiratory rate is determined by the fomula:

```
RRATE=(C49+DVENT**.7*.37)*C50/(PJ+40)

C49=constant related to lung elastance;
C50=constant related to body temperature;
DVENT=minute ventilation (initial 6 litres/min.)
PJ=oxygen saturation of arterial blood (initial 97%);
```

and from this tidal volume as:

```
TVOL=DVENT*1000/RRATE
```

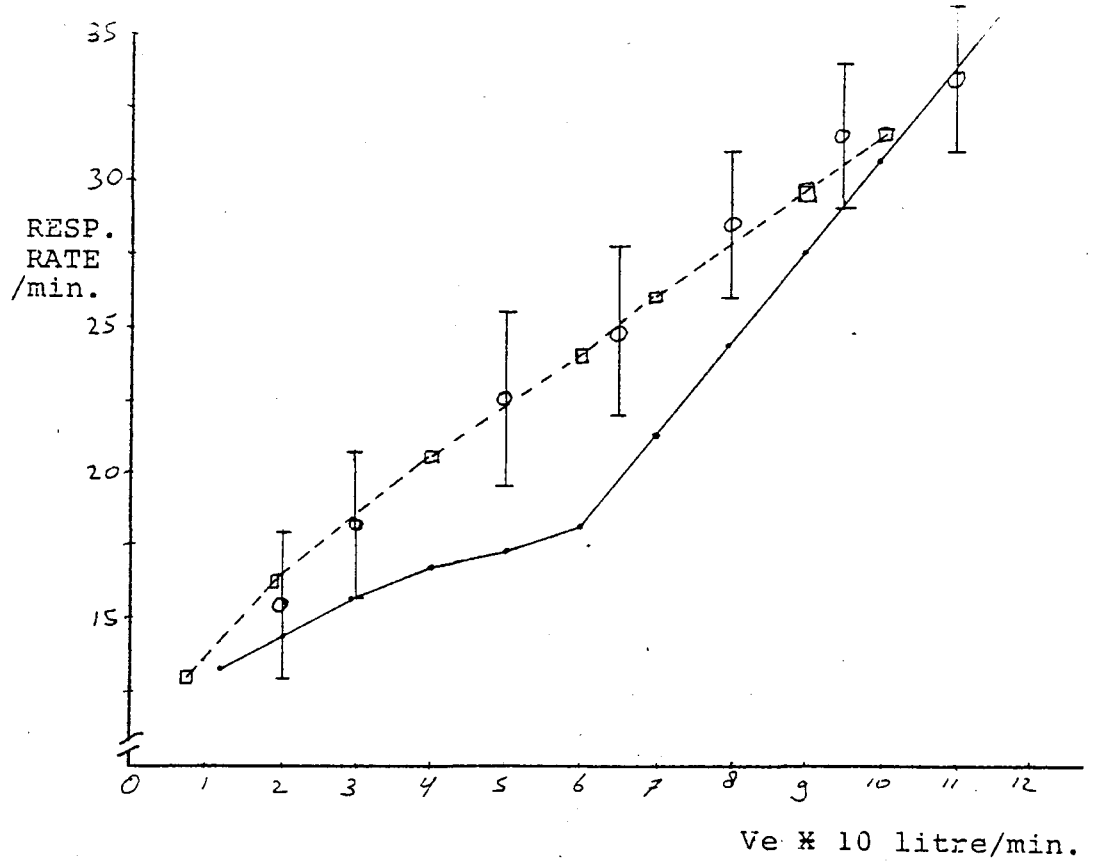
In the graph we see that this formula determines respiratory rate only up to a Ve value of 60 litres/minute. Above this value the maximal tidal volume is reached and respiratory rate is calculated by:

```
RRATE=DVENT*1000/TVOL
```

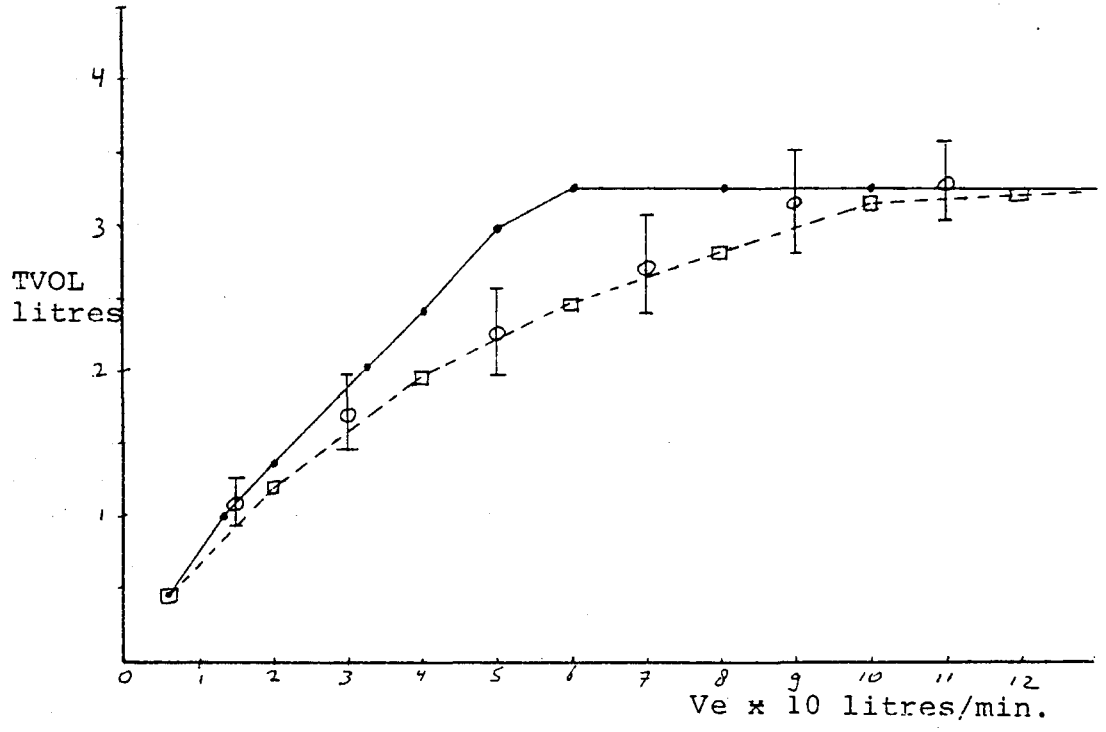
The aim of a change in the respiratory rate formula should be an increase of respiratory rate in relation to minute ventilation. Such a change will in turn lower tidal volume in relation to a certain minute ventilation. Maximal tidal volume will then be reached at higher Ve values, and so the range in which the formula for respiratory rate is working will be increased. If we rewrite this formula as:

$$RRATE = \frac{C49*C50}{PJ+40} + \frac{C50*DVENT**7*.37}{PJ+40}$$

and regard all parameters beside DVENT as (nearly) constant, it is easy to see that an increase in the respiratory rate-Ve



Graph 3-2;Relation between ventilation and respiration rate; circles:mean values (+/-SE) of real exercise tests, (n=6); dots: original MACPUF; squares: MACPUF results with new formula (see text).



Graph 3-3;Relation between ventilation and tidal volume; dots, squares and circles as in graph 3-2.

relationship can be accomplished by a rise in the power of DVENT (**7) or in the multiplication factor *.37. Simulations with several different combinations of these factors showed that best results were achieved with the formula:

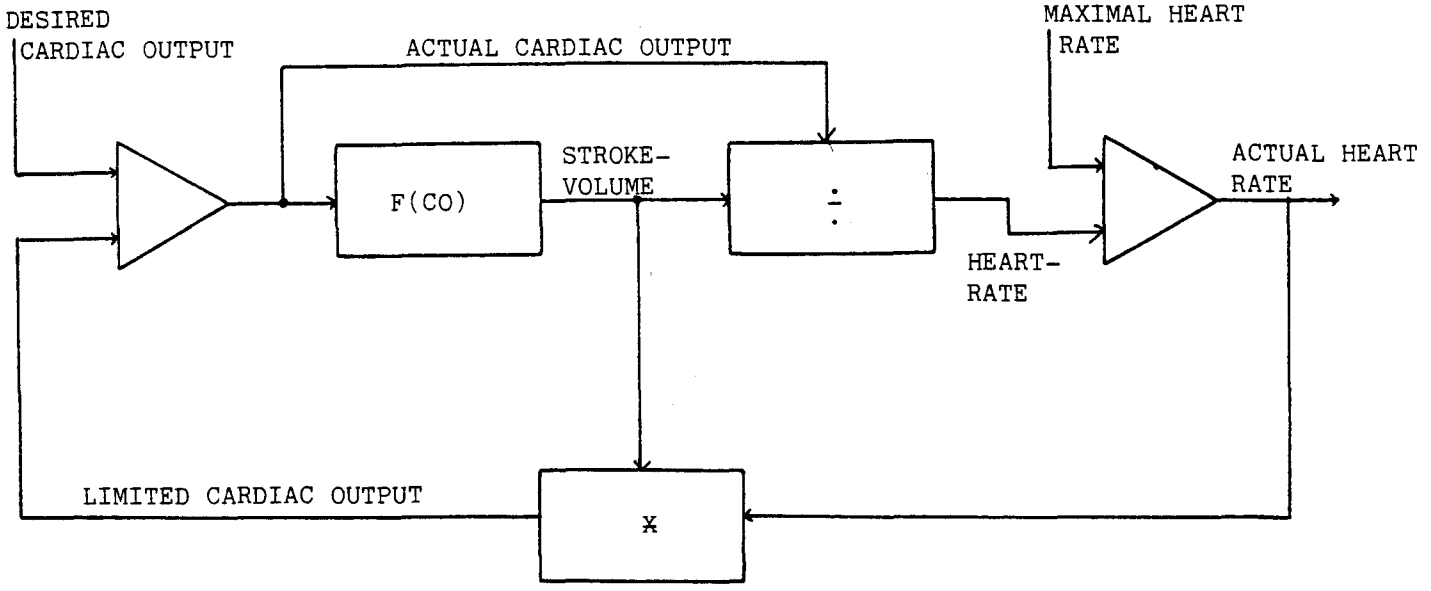
```
RRATE=(C49+DVENT**.865*.37)*C50/(PJ+40)
```

Results of this formula for the relation between RRATE and TVOL against Ve are shown in graph 3-2 and 3-3. Results of these variables expressed against work load will be presented at the end of this paper.

IV. HEART RATE

One of the factors which limits the value of MACPUF as an educational tool for the simulation of work in general and especially for work in cardiac disease is the absence of a representation of the heart rate. In the model we do find a representation of cardiac output (litres/minute), which of course can easy be related (translated to a value of heart rate. However, when we want to simulate cardiac disease (e.g. mitral valve stenosis or insufficiency, both limiting strokevolume; Holmgren 1958) in MACPUF by reducing cardiac output (factor 3), the results are very unrealistic. Reducing factor 3 results in an always insufficient cardiac output in this simulation. This results in an oxygen shortness in the tissues even at very low work loads and at rest. The patient will not be able to compensate for this insufficiency (except by a higher arterio-venous concentration difference).
In reality a patient will compensate for his disease by rising his heart rate. Oxygen delivery to the tissues will then become limited when the patient reaches his maximal strokevolume and his maximal heart rate, which then will result in a rapidly increasing lactate concentration and fatigue.

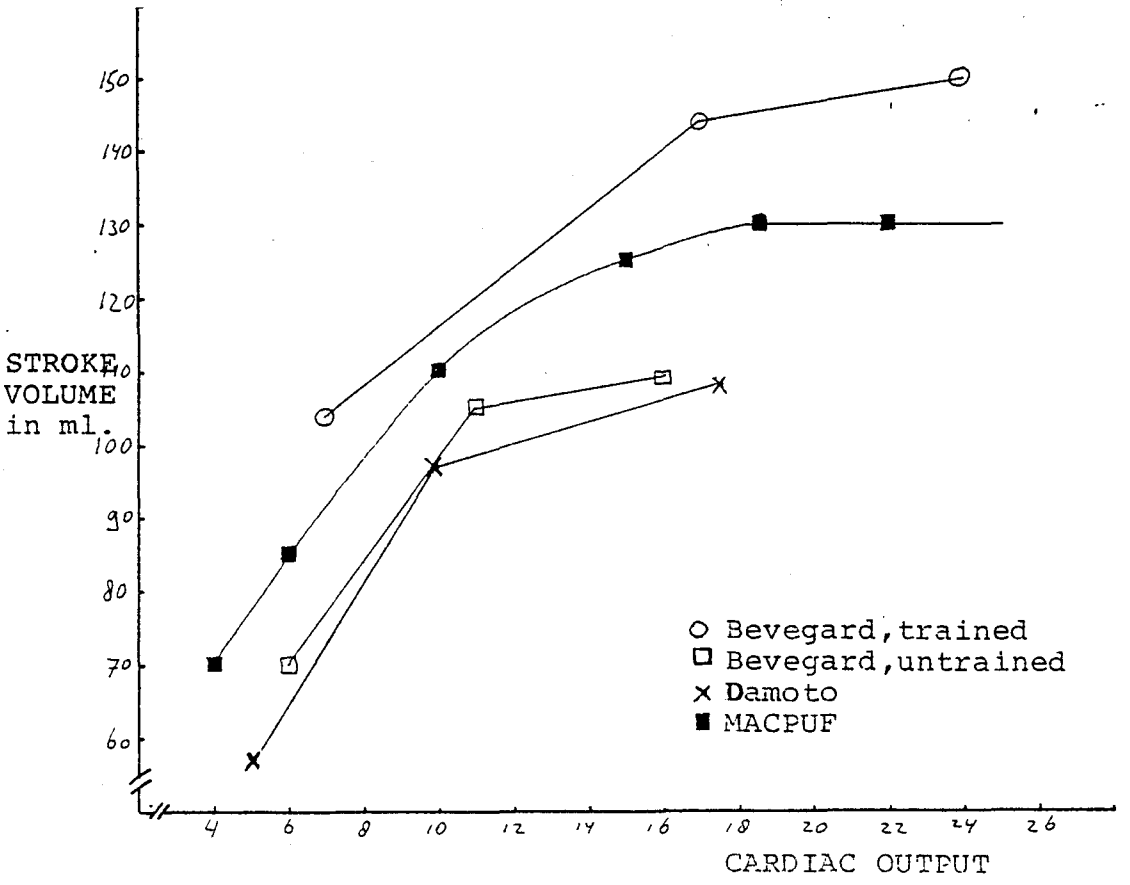
In order to create the possibility of simulating this phenomenon, I decided to introduce strokevolume and heart rate in the model. I chose for a deduction of strokevolume from cardiac output and in turn of heart rate from strokevolume and cardiac ouput. In case the limits for heart rate and strokevolume are reached, these will influence (limit) cardiac output by a feedback mechanism (graph 4-0).



Graph 4-0 Relation between cardiac output, stroke volume and heart rate; influenced by maximal heart rate (see text).

STROKE VOLUME

In graph 4-1 we see a cardiac output-strokevolume relation as found by Bevegard and Damoto (1963). With increasing cardiac



Graph 4-1 Cardiac output-stroke volume relation; cardiac output in litres/minute; stroke volume in millilitres.

output strokevolume increases fast and reaches quite soon values close to maximum. As the data provide values for persons of different fitness, I had to find a way to choose the wright data for the model. For MACPUF I aimed at a subject with a VO2max of 3.5 litres. Damoto's values are averages for subjects with VO2max of 2.9 litres. Bevegards values for untrained persons are averages for a subject with VO2max of 2.6 litres, and the values for trained persons for a subject with VO2max of 4.1 litres. (All these VO2max values deducted from given heart rate, estimated maximal heart rate and given oxygen uptake). Other research literature suggests maximal strokevolumes between 120 ml. for young sedentary subjects (Marshall-Shepherd 1968) and 135 ml. (Astrand 1970, fitness unknown). All this information

indicated that the maximal strokevolume in MACPUF should be ca.130 ml., and that the shape of the curve should be as drawn in graph 4-1. This resulted in the formula:

```
STRV=-.3*Q**2=11.*Q+30.
```

And

```
IF (Q.GE.18.) STRV=130
```

STRV=strokevolume, Q=cardiac output litres/minute

FACTORS INFLUENCING STROKEVOLUME

Maximal strokevolume shows interindividual differences (Marshall-Shepherd), which can be related to several factors:
-Fitness
-Sex
_Body weight

If maximal strokevolume is expressed in ml./kg., we find a range as follows;

	MINIMUM	AVERAGE	MAXIMUM
MALE	1.2	1.6	2.0
FEMALE	1.0	1.4	1.8

Variations in these values are caused by differences in sex and fitness. In MACPUF fitness is present as factor 25 with a normal value of 33. This represents the value of TO2PR (tissue oxygen pressure) below which anaerobic metabolism starts to increase. In earlier simulations (paper 1) it appeared that differences in fitness between atletes and unfit persons could be realized in the model using a fitness range of 29-36. The difference in strokevolume related to sex differences amounts .2 ml/kg. These considerations led to a maximal strokevolume representation (in ml./kg.) of:

```
STRVMAX=(1.4+XMALE*.2+(33-FITNESS)/10)
```

STRVMAX=maximal strokevolume
XMALE=sex, if male =1., if female =0.

Then total maximal strokevolume can be calculated by multiplication with bodyweight:

```
STRVMAX=STRVMAX*WT
```

WT=body weight

Now we have to combine this calculated maximal strokevolume with the function relating strokevolume to cardiac output. This function was aiming at a max. strokevolume of 130 ml. A

combination results in:

```
X=CO/100*(1.4+XMALE*.2+(33-FITNESS)/10)*WT
STRV=X*(-3*COADJ**2+11*COADJ+30)/130000
COADJ=cardiac output
```

Factor CO (initial 100 %) provides the possibility to limit strokevolume in order to simulate cardiac disease. Factor CO is in the model available as factor 3.

HEART RATE

Finally, the existing heart rate can be calculated by dividing cardiac output by strokevolume:

```
HR=COADJ/STRV
```

However, heart rate cannot increase without limit. Predicted maximal heart rate is usual related to age (Guyton) by the formula:

```
HRMAX=210-.65*AGE
```

In MACPUF I used this formula to limit heart rate. But whenever maximal heart rate is reached (as well as maximal strokevolume), cardiac output should also reach its limit. For this I added:

```
      IF (HR.LE.(210-.65*AGE)) GOTO 10
      HR=(210-.65*AGE)
      COADJ=HR*STV
  10  CONTINUE
```

adding all these parts together the representation in MACPUF is:

In subroutine CONSTANT:

```
C++++++++++++++++++++++++++++++++++++
C two added constants for maximal heart rate:C(74) and
C maximal strokevolume:C(75)
      C(74)=210-.65*AGE
      C(75)=(1.5+XMALE*.2(33.-FITNESS)/10.)*WT*C(16)
      c(16)=CO*.01
C++++++++++++++++++++++++++++++++++++
```

In the MAIN PROGRAM:

```
C++++++++++++++++++++++++++++++++++++
C incorporation of heart rate and stroke volume
      X=(-.3*COADJ**2.+11.*COADJ+30.)
      IF (COADJ.GE.20.) X=130.
```

```
C strokevolume in litres
      STRVL=C75*X/130000.
      HRATE=COADJ/STRVL
C limit cardiac output through stroke volume and heart rate
      IF (HRATE.LE.C74) GOTO 242
      HRATE=C74
      COADJ=HRATE*STRVL
 242  CONTINUE
C if heart stops make output and rate zero
      IF (CO-3.) 250,260,260
 250  COADJ=E
      HRATE=E
      GOTO 280
 260  CONTINUE
C
C++++++++++++++++++++++++++++++++++
```

V. WORKING MUSCLE COMPARTMENT

During the first part of my project, I paid much attention to the representation of lactate production and catabolism in the model. The result was an improved lactate model; especially by the incorporation of the working muscle lactate catabolism, which appears to be much more important than originally suggested. (Dickinson 1977). This model produced fairly realistic results, but in some tests (steady state) the results still could use some improvement. This might be achieved by the change of the time constants of lactate production and catabolism. For this I studied some mathematical descriptions of lactate metabolism (Freund and Zouloumian 1981). Unfortunately these were not applicable on MACPUF, as they only discussed the situation after exercise. In my first paper I already suggested the incorporation of a seperated working muscle compartment for the improvement of the simulation of lactate metabolism and distribution over the body.

Lactic acid concentration in the muscle and in the blood are not always equal. The transport of lactate from the muscle, where it is produced, into the blood is limited (Johrfeldt 1978) This limitation can be caused e.g. by a limited diffusion surface between muscle cells and blood capillaries and/or by a limitation of the active transport mechanism over the cell membrane.
This limitation can account for the different blood lactate concentrations at exhaustion, in different types of exercise tests (10 Watt/min., 50 Watt/min.). Although blood lactate concentrations differ, muscle lactate concentrations (and pH) can be approximately the same. In short tests with steep increases in work load, muscle lactate can increase very fast, whereas the increase in blood lactate is limited by the limited transport from muscle to blood.

In longer tests with smaller increases in work load, muscle lactate concentration will increase much slower, and the concentration gradient will remain rather low (Hultman and Sahlin 1980). The introduction of a seperate muscle (lactate production) compartment should allow us to simulate this phenomenon. I decided to use a part of the total lactate pool (35 litres in the model) for the new compartment. Then I arbitrarely chose for a compartment volume of 15 litres. This leads to initial values of a lactate amount 15 mmols and a pH of 7.075 (Hultman and Sahlin 1980) for the compartment at rest. Then the total remaining lactate pool is reduced according to this value to 20 litres with an initial lactate amount at rest of 20 mmols.

What are the parameters, influencing lactate transport from the muscle compartment to the blood and vice versa?

1. CONCENTRATION GRADIENT

If lactate transport takes place by diffusion, it will be dependant on the concentration gradient over the cell membrane.

Even in case of active transport over the membrane, the process will be influenced by the concentration gradient (Kruyt and Overbeek). Therefore one of the parameters in the transportfunction of lactate between muscle and blood has to be the concentration difference between the two compartments.

2. EXTRACELLULAR pH

A second parameter which has been shown to influence the transport of lactate from muscle to blood is the extracellular pH. Hirche et al (1978) showed in dogmuscle a three times higher lactate efflux from muscle in alkalosis (pH=7.5) than in acidosis (pH=7-7.1). Johrfeldt (1970) showed in a study using lactate infusion, a decrease of lactate release from the forearm muscle, from .48 mmol/min. at an arterial lactate concentration of 1.1 mmol/litre to .18 mmol/min.; at an arterial lactate of 3.55 mmol/litre. This shows that lactate efflux from muscle is influenced by the extracellular concentration of lactate, and therefore is related to extracellular (tissue in the model) pH.

3. ADDITIONAL FACTORS

Besides the concentration gradient and the extracellular pH, there might be several other factors influencing lactate transport from the muscle to the blood (e.g. blood flow through muscle). But as there is little information available on such influences, and as I primarily wanted to investigate the effect of a seperated lactate production compartment in general, I chose to start with a lactate transport equation, governed by the concentration gradient and the extracellular pH.

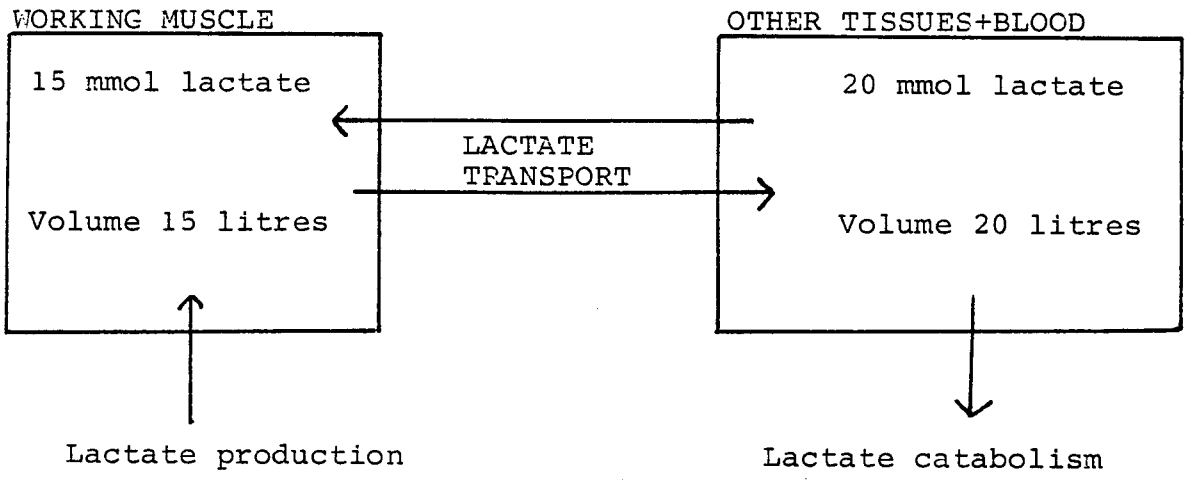
REPRESENTATION IN MACPUF (graph 5-1)

The amount of lactate in the " working muscle compartment " is determined by:

-the initial lactate amount (15 mmol) in the compartment,
-the amount of lactate production
-the lactate transport to or from the body lactate pool.

The Lactate amount in the body lactate pool (20 litres) is determined by:
-the initial amount of lactate (20 mmol)
-the transport of lactate to or from the working muscle compartment
-the amount of lactate which is catabolized.

Lactate concentrations can be calculated from total lactate amounts and compartment volumes. Working muscle pH is calculated with the formula:



Graph 5-1; Representation of a separated lactate production compartment in MACPUF. Values are initials.

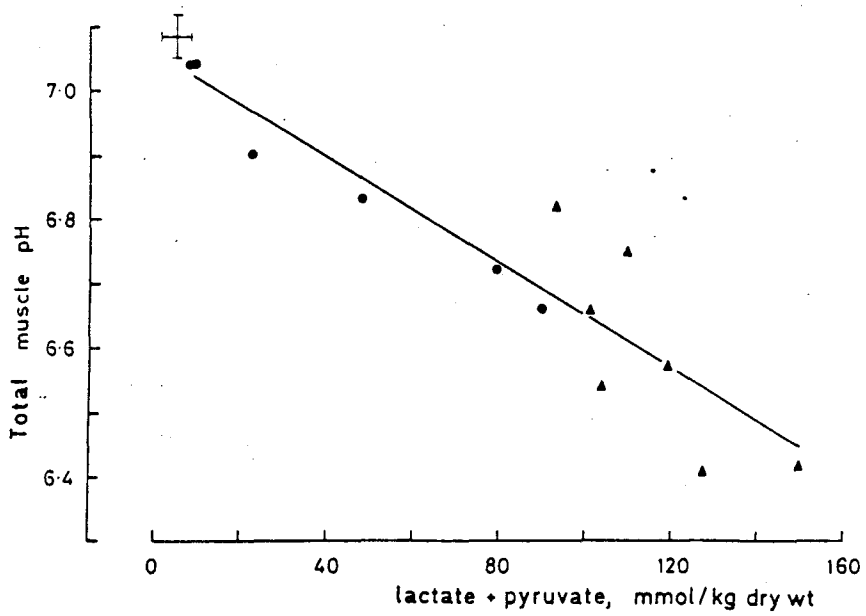
pH=7.1-.025*LACTATE CONCENTRATION

This formula is taken from Hultman and Sahlin (1980) (see graph 5-2). The transport of lactate from muscle to blood and vice versa is governed by the formula:

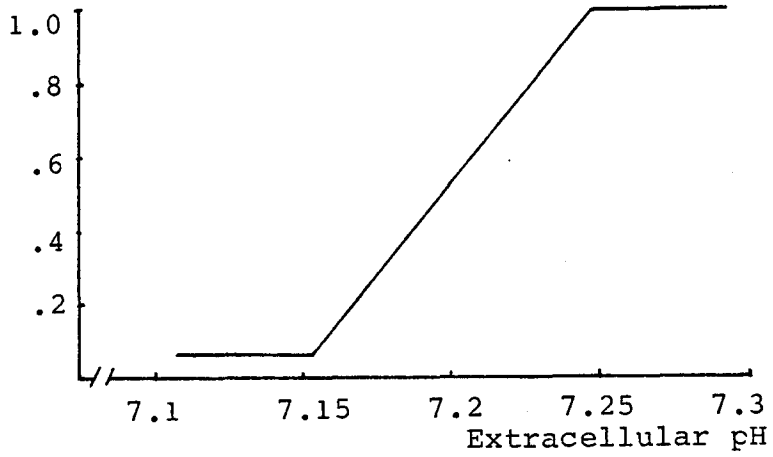
DLACT=(MLACT-BLACT)*MVOL*.1*Z*FT/.016667

DLACT=lactate transport per itteration interval
MLACT=muscle lactate concentration
BLACT=blood lact. conc.
MVOL=muscle volume
FT=itteration time

The influence of extracellular pH is incorporated by factor Z, which is related to tissue pH (which for the seperated muscle compartment represents extracellular pH) as shown in graph 5-3 (N.L.Jones, personal communication). The constant .1 has been arbitrarely chosen and can be changed to influence the transport speed.



Graph 5-2 Relationship between *p*H and content of lactate + pyruvate in muscle samples taken from quadriceps femoris muscle of man immediately after short-term bicycle exercise (Sahlin *et al*, 1976).
1 kg. dry muscle equals 4.3 kg wet muscle.



Graph 5-3; Relation between extracellular pH and transport speed of lactate over cell membrane;represented by parameter z in diffusion formula (N.L.Jones, personal communication).

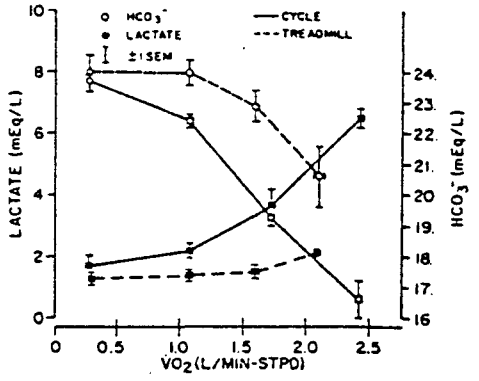
VI.BICARBONATE

In Macpuf, the relation between increase in lactate amount and the decrease in bicarbonate, which functions as a buffer, is originally 1 to .4.
I already suggested a change of this relationship (first paper) to 1 to .65, when I discussed results found by Wasserman (1973) and Bouhuys (1979). Results from Koyal (1976) as presented in graph 6-1, even suggest a 1 to 1.5 relation. The reason for the original description in the model was that a part of the buffering of lactate was accounted for by non-bicarbonate buffers (proteins, haemoglobin, (Dickinson 1977)). This approach implies that, after lactate enters the blood the following reaction takes place:

$$CH3CH2COO^-H^+ + HCO3^- <-> CH3CH2COO^- + H2CO3$$

$$H2CO3 <-> H2O + CO2$$

A different approach (Jones and Ehrsam 1981) is that lactate- and H+ transport from muscle to blood is not strictly equimolar. If H+ crosses the cell membrane in a higher rate than lactate- (Cechetto and Mainwood 1978), and this H+ is buffered by HCO3-, it will result in an imbalance of ionic charges in the plasma. The balance of the ionic charges can be restored by the transport of lactate- from the muscle into the plasma in an equimolar rate to HCO3- removal. An other possibility is that lactate- leaves the muscle in exchange for HCO3- (Roos 1975), which would also result in a 1 to 1 relation between lactate entry in the plasma and HCO3- decrease (Jones and Ehrsam). These considerations made me decide to change the factor .4 in the original description of the bicarbonate buffering system (TC3MT=TC3MT+...+.4* V) to 1.0, in order to create a 1 to 1 effect of lactate increase and bicarbonate decrease. In the model with a seperated muscle muscle compartment, I even had to raise this factor above 1.0 to account for the changed relations between compartment volumes (lactate pool and bicarbonate space).



Graph 6-1; Arterial lactate and bicarbonate concentrations during cycle ergometer and treadmill work at several levels of oxygen uptake (KOYAL 1976).

VII. LIMITATION OF OXYGEN UPTAKE BY CARDIAC OUTPUT LIMIT

When a person reaches his maximal cardiac output in an exercise test, this will also limit the amount of oxygen transported to the tissues.

OXYGEN TRANSPORT=BLOOD FLOW*OXYGEN CONTENT

The only possibillity to increase oxygen consumption any further is to increase the amount of oxygen which is extracted from a certain quantity of blood. This can be measured as a raised arterio-venous difference in oxygen content.

In the simulation of mitral valve disease (by a limitation of strokevolume), I found that in a 15 Watt/min. test, the simulated subject could maintain the exercise for 6 work loads after reaching its maximal heart rate (see graph 7-1). Compared to what we find in real patients (Holmgren 1958, Jones personal communication) this seems unrealisticly long.
Can this be explained by the arterio-venous oxygen difference?

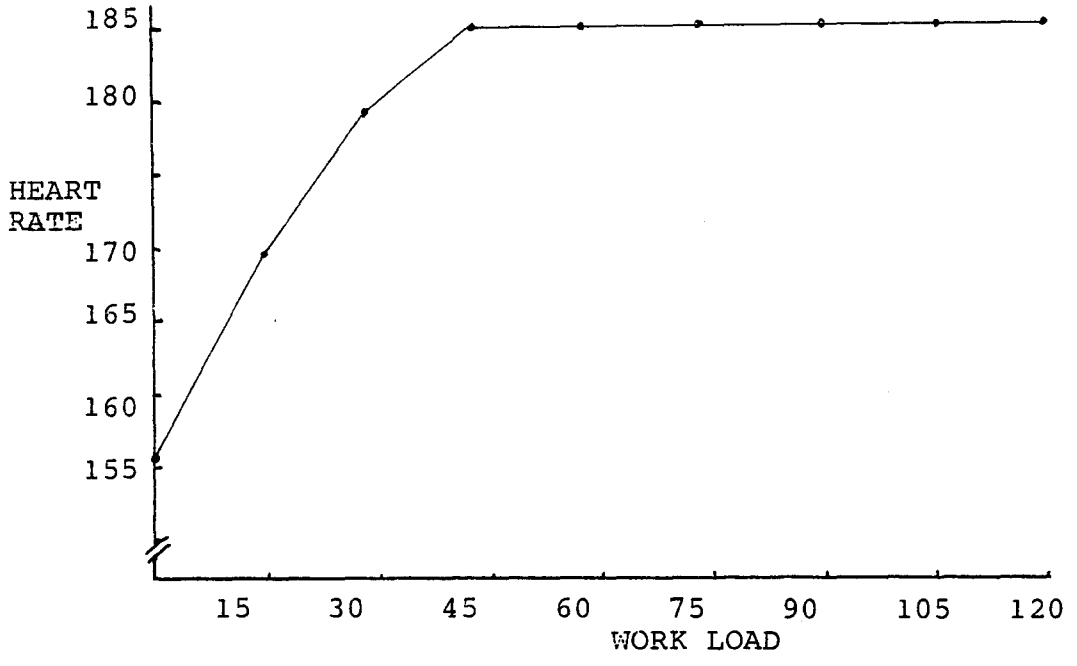
When the subject reaches its maximal cardiac output, his oxygen consumption is 913 ml. (model results). At exhaustion, his oxygen consumption is 1456 ml. This would imply that he could increase his oxygen consumption with more than 50 %, only by extracting a higher percentage of the oxygen from the blood. Is this possible?

In the simulation I used, cardiac output was limited to ca. 9 litres/min. The amount of oxygen which can be extracted from this blood flow is determined by the maximal possible arterio-venous oxygen difference. In graph 7-2 (Holmgren 1958) the maximal measured arterio-venous oxygen difference is circa 170 ml/litre. Dr.Jones (pers. comm.) suggested an absolute maximum of 160 ml/litre. (Astrand: 170 ml/litre for well trained males). Accordig to these values, the amount of oxygen which could be taken up by the tissues would be:

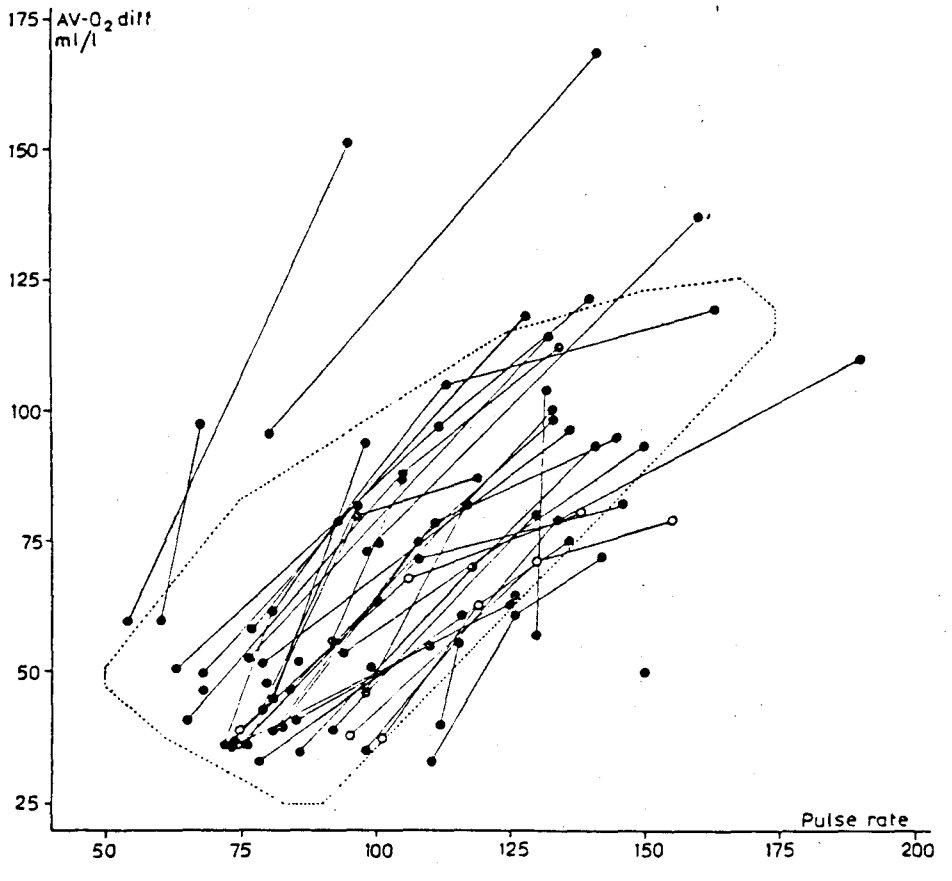
VO2=CARDIAC OUTPUT*MAXIMAL A-V O2 DIFFERENCE

which equals 9*160=1440 ml./min.. So the value of 1456 ml maximal oxygen uptake would be realistic.

In MACPUF the (working) tissues can extract oxygen from the total amount of circulating blood. In reallity, only a part of the total blood flow will go to the working tissues (muscle), as the other part is used for oxygen delivery to the organs, the brain and the not working tissues.
If we assume that this second part amounts for a blood flow of ca. 4 litres and an oxygen consumption of about 200 ml. (N.L.Jones, pers. comm.) (Astrand: 3.73-4 litres/min. at a cardiac output of 5 litres and 3.75-5 litres/min. at a cardiac



Graph 7-1 heart rate related to work load in a simulated 15 Watt/min. incremental exercise test.



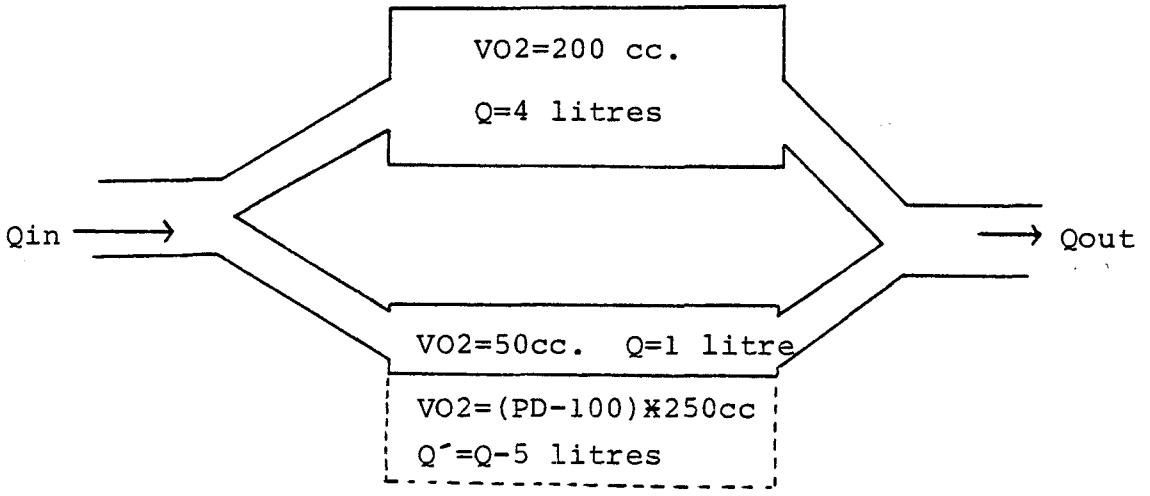
Graph 7-2;Arterio-venous oxygen difference (ml/litre), in relation to pulse rate, at rest and during exercise, in cases of mitral stenosis; the dotted lines indicate the normal variations from different series (HOLMGREN 1958).

output of 25 litres/min.) the working tissues can only use 9-4=5 litres of blood per minute. This leads to the following calculation:

RESTING TISSUE:	4 LITRE BLOOD	VO2=200 ML.
WORKING TISSUE:	5 LITRES BLOOD,	VO2MAX=5*160=800 ML
TOTAL: BLOOD FLOW:	9 LITRES/MIN,	VO2MAX= 1000ML

This indicates that in our simulation of mitral valve disease the subject should only be able to continue exercising for about two extra loads after reaching its maximal cardiac output.

In order to get the model to produce such results I have split up the blood flow as presented in graph 7-3.



Graph 7-3 Blood flow split in working tissue and non-working-tissue compartment. VO2: minute oxygen consumption, Q: cardiac output, PD: metabolic rate.

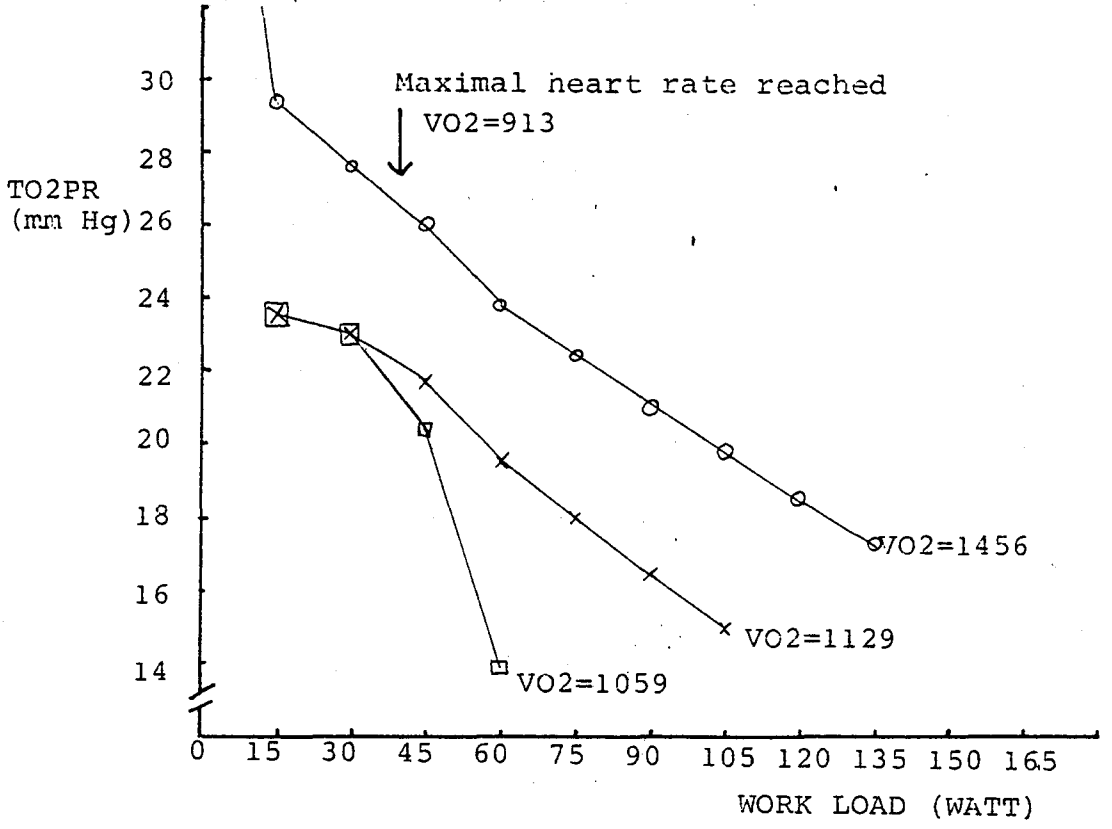
A part of the blood supplies the tissues which are not involved in the exercise (4 litres blood, VO2=200 ml/min., metabolic rate accounts for 80 % of resting value) and the other part supplies the working muscles (VO2 rest 50 ml/min., blood flow 1 litre). In exercise, this blood flow will equal total blood flow minus 4 litres, and metabolic rate equals total metabolic rate minus 80 %. After both blood flows have passed the tissues, they are mixed again and form the venous blood flow.

Simulations with this model (with several versions of changed blood flow divisions) resulted indeed in a more realistic maximal oxygen uptake: 1129 ml/min. Also the number of loads which are performed after reaching the maximal cardiac output is reduced from six to four.
This value is unfortunately still quite high.

ACCUMULATION OF LACTIC ACID

The remaining reason why it takes such a long time after reaching maximal cardiac otput before our simulated subject is exhausted is that it takes this long before lactate accumulates to an amount, which limits work performance. Although this was improved by the incorporation of a seperate working muscle compartment, it appears in this pathological situation that this was not sufficient.

Why does it take so long before lactate accumulates? Lactate production is dependant on tissue oxygen pressure. If we put Tissue oxygen pressure in a graph against work load (graph7-4) for the simulation with limited cardiac output, we see



Graph 7-4; Relation between work load and tissue oxygen pressure (15 Watt/min. test); o: original model, x: split blood flow, ◘: split blood flow with oxygen saving effect reduced to zero.

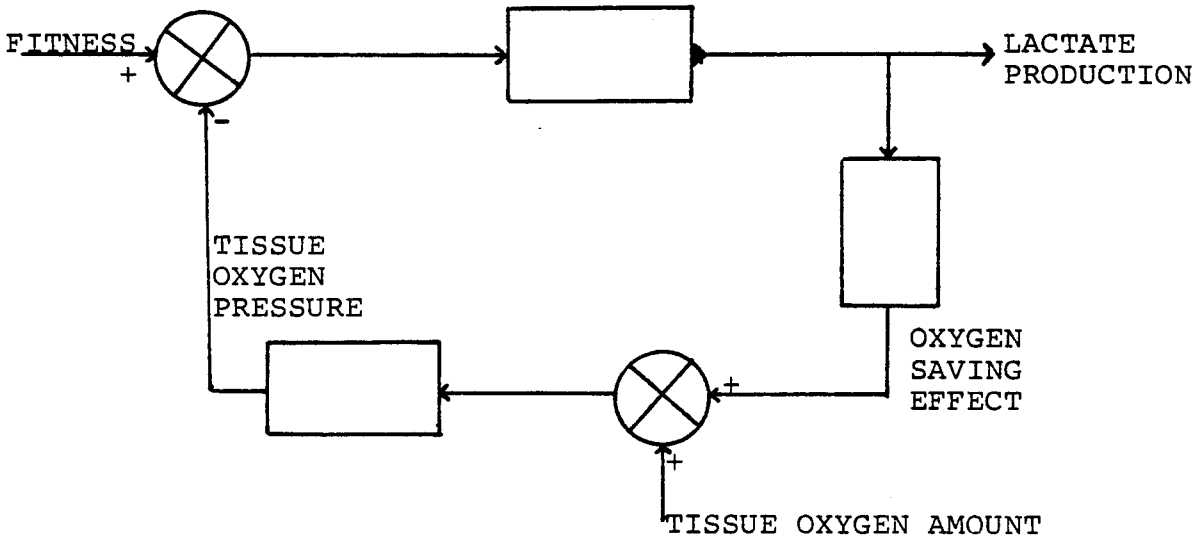
that in the model with a split blood flow, tissue oxygen pressure falls stronger when work load increases than it did in the old model. It also decreases stonger after maximal cardiac output has been reached. Nevertheless I was quite astonished, when I

noticed how litlle the difference in the angle of decrease of tissue oxygen pressure in both models was.
I expected a sharp drop of tissue oxygen pressure, starting at the moment where maximal cardiac output is reached, because of the relatively low increase of oxygen consumption over the last four work loads (VO2=876 at 45 Watt, and 1129ml at 105 Watt).

OXYGEN SAVING EFFECT

The only factor that can prevent tissue oxygen pressure from falling when VO2 does not increase in relation to work load is the oxygen saving effect of lactate production (factor XLACT in the model).

When tissue oxygen pressure falls below a reference value (fitness) lactate is produced. This lactate indicates that energy has been produced anearobically, which saves oxygen. Tissue oxygen amount is therefore increased with the amount of oxygen saved by anaerobic metabolism. This in turn, influences tissue oxygen pressure. This mechanism is based on a feed-back machanism (graph 7-5)



Graph 7-5 Feedback effect of lactate production on tissue oxygen pressure.

How big is the influence of this feed-back system? The most simple solution to be able to answer this question is opening the feed back loop. In other words, make the oxygen saving effect zero. The result of this action is presented in graph 7-4. The simulated subject is just able to perform one work load after

maximal cardiac output is reached. Tissue oxygen pressure drops very fast, and lactate accumulates very quickly. This behaviour of the model, which is much more in accordance with the behaviour of real patients, indicates that the oxygen saving effect in this situation is too high. (In order to produce extra work power when maximal oxygen uptake is reached, a person will produce for each 100 kpm increase in load, an amount of lactate equivalent to ca. 200 ml. of oxygen.

200 ml/min. O2 = 200/22.4 = 9 mmol/min. O2

1 mmol O2 = 6 mmol ATP = 4 mmol Lactate

Thus 9 mmols O2 per minute is equivalent to 36 mmols Lactate. These 36 mmols in a (muscle) lactate pool of 15 liters produce an increase in lactate concentration of 2.5 mmols/litre/minute (Dr. Jones, pers. comm.)).

In lack of time I have not been able to do any more work on this item. It is not yet clear if the oxygen saving effect is also too high in the simulation of normal, healthy subjects. It is clear that in this pathological situation, with relatively low oxygen uptakes every influence on this oxygen uptake will work out much stronger than it would at " healthy " high oxygen uptakes. As the oxygen saving effect is related to the absolute value of lactate production, it is also questionable how realistic this absolute value is.
Although the lactate concentrations in the model seem to be quite realistic, this is only a reflection of the quality of the lactate production/catabolism ratio, and this does not give any information on the validity of the quantitative representation of lactate production itself.

VIII. FINAL SIMULATIONS

In order to give a qualitative as well as a quantitative judgment of the validity of the model I did the following simulations:

A 15 Watt/minute incremental test, with a model including changes described up to chapter V.

B Influence of inspired oxygen fraction on the response to exercise (15 Watt/minute incremental test)
Simulations were done with three different percentages of oxygen in the inspired air: 12 %, 20.93 % (normal) and 32 %. For these situations, graphs are plotted for ventilation, lactate and heart rate.

C Reduction of the strokevolume:
Introduction of heart rate and strokevolume in the model, created the possibility to simulate cardiac disease by the reduction of strokevolume. Results are plotted for heart rate, ventilation and lactate. The simulated reductions of strokevolume were: 100%, 70 % and 60 % of normal strokevolume. The test was a 15 Watt/minute incremantal test.

D Working muscle compartment:
To show the effect of the incorporation of a seperated lactate production compartment, I simulated a 15 Watt/minute incremantal test with such a model. I continued the simulation after the end of the exercise period to show lactate behaviour during and after the test.

PERFORMANCE INDEX:	OLD	NEW
VO2	96.1	95.4
VCO2	81.7	94.9
Ve	78.3	88.2
Resp.Rate	69.2	91.9
R.Q.	85.3	94.9
Lactate	56.2	75.4

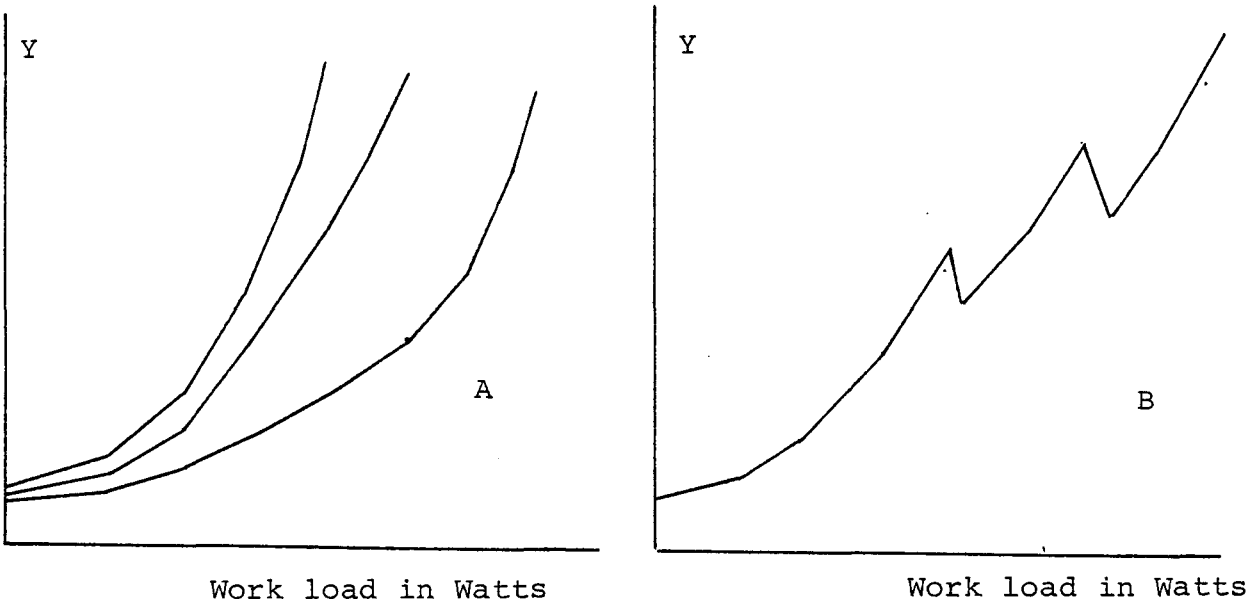
Table 9-1 Values of the performance index for the 15 Watt/min. incremental test. These values are averages of the performance indices, which were calculated from simulations compared to individual test data (as previously described in the first paper).
For these simulations (in opposition to those presented in the graphs) antropometric data (age,weight) and fitness were adjusted to those of the individual subject in the real test.

IX. RESULTS AND DISCUSSION

Concluding my work with MACPUF, I would like to present some simulation results. In my first paper I already presented results of a model, incorporating changes which are still present in the latest model. Therefore, the results of the variables related to these changes: VO2, VCO2, and RQ are still relevant. The additional changes, (made since april 1981) have had their main influences on minute ventilation, respiratory rate and heart rate.

A

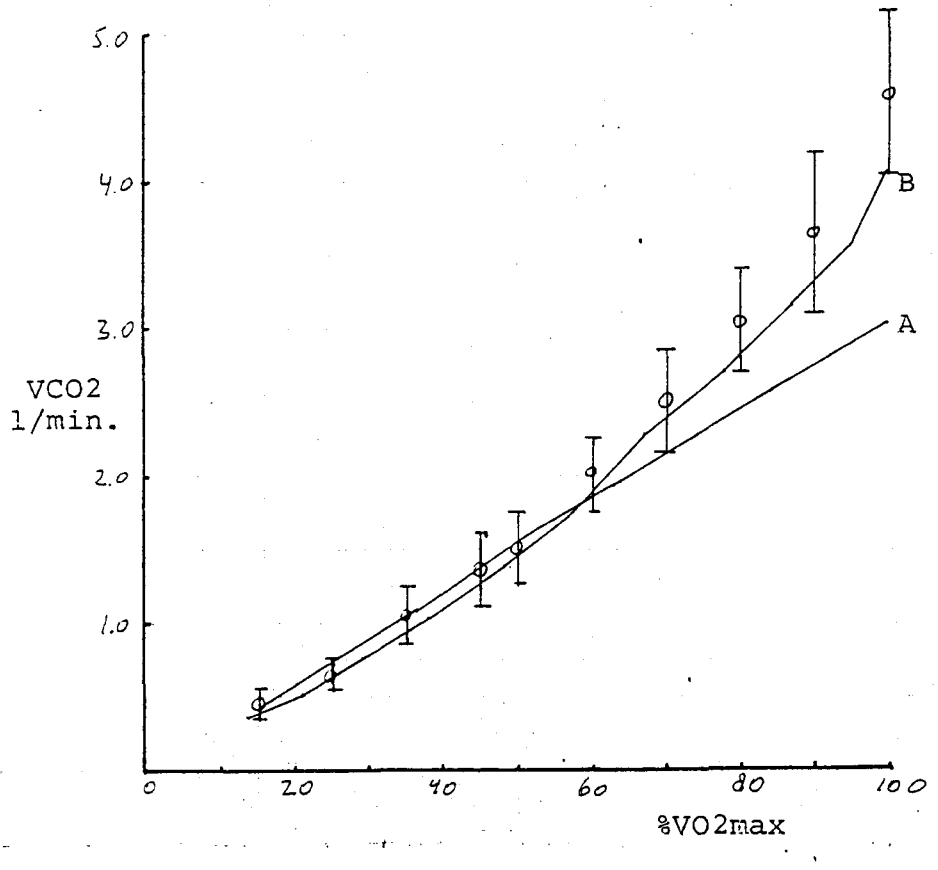
In the first paper I compared simulated results to individual exercise test results. As I had more data available, I now chose to compare the models results with " averages " of six individual (for lactate four) exercise test results (data from BGD/PTT and Mc.Master univ.). The data were plotted against the percentage of maximal oxygen consumption, as plotting (and calculating) against absolute oxygen consumption will produce unrealistic " average " curves, caused by the interindividual differences in maximal work loads (see graph 9-1). For these data, I calculated mean values and standard deviations. The standard deviation gives us another tool (besides the performance index) to estimate the goodness of fit (see chapter four, first paper.



Graph 9-1; A:Results for variable Y in three individual exercise tests, related to absolute values of work load.
B:Results for variable Y represented as averages from the tests as presented in A; related to absolute values of work load.

VCO2: (graph 9-2)

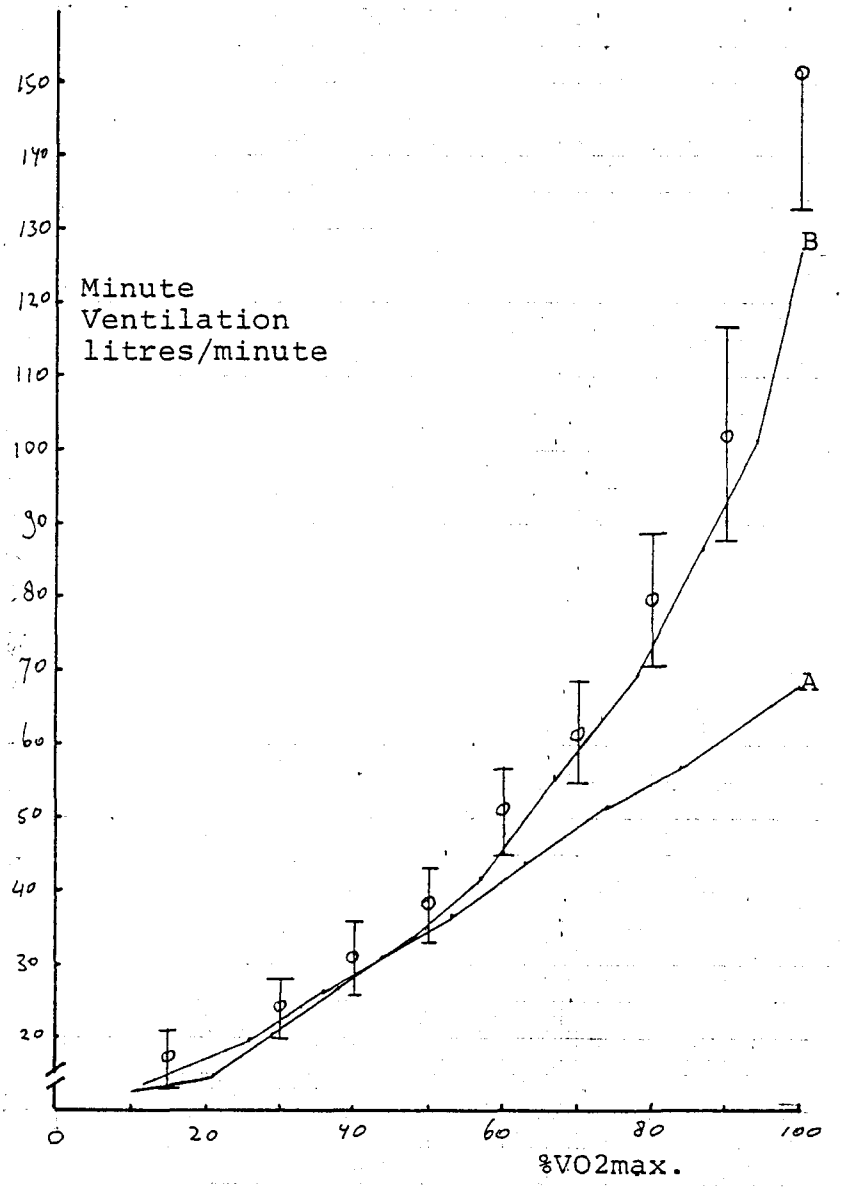
The main reasons for the improvement of carbondioxide output; changes in tissue respiratory quotient, lactate, catabolism and bicarbonate buffers, have already been described in the first paper. Since then, the behaviour of VCO2 has changed very little. As we can see in the graph, VCO2 values are now clearly within the standard deviation of the data.
When the model is adjusted to individual subjects, the results are even closer to the date (performance index=94.9 %).
The point of non linear increase (anaerobic threshold) in CO2 output of the model and the data are also very close (both between 50 and 60 % VO2max).



Graph 9-2; Carbondioxide output in relation to the percentage of maximal oxygen consumption; A:original model; B: recent model. Circles: real test values(+/- SE). (n=6).

Ve: (graph 9-3)

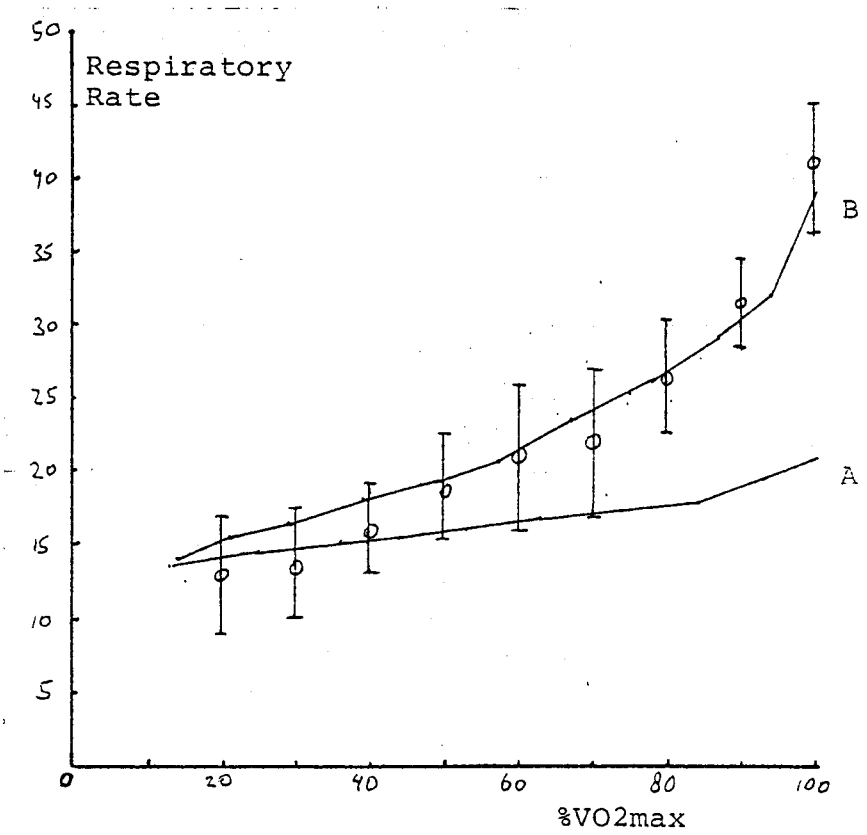
The improvement in minute ventilation (performance index 78.3->88.2 %) is due to two factors:
-the increased drive on ventilation by carbon dioxide output,
+the altered representation of the calculation of mean alveolar pCO2 (chapter II).
Simulated values are within the standard deviation of the data; the point of non linear increase (at approximately 57 % VO2max) is close to the same point in the data (50-60 % VO2max).



Graph 9-3; Minute ventilation in relation to % of maximal oxygen uptake; A: original model; B:recent model. Circles: real test values (+/- SE, n=6).

RESPIRATORY RATE: (Graph 9-4)

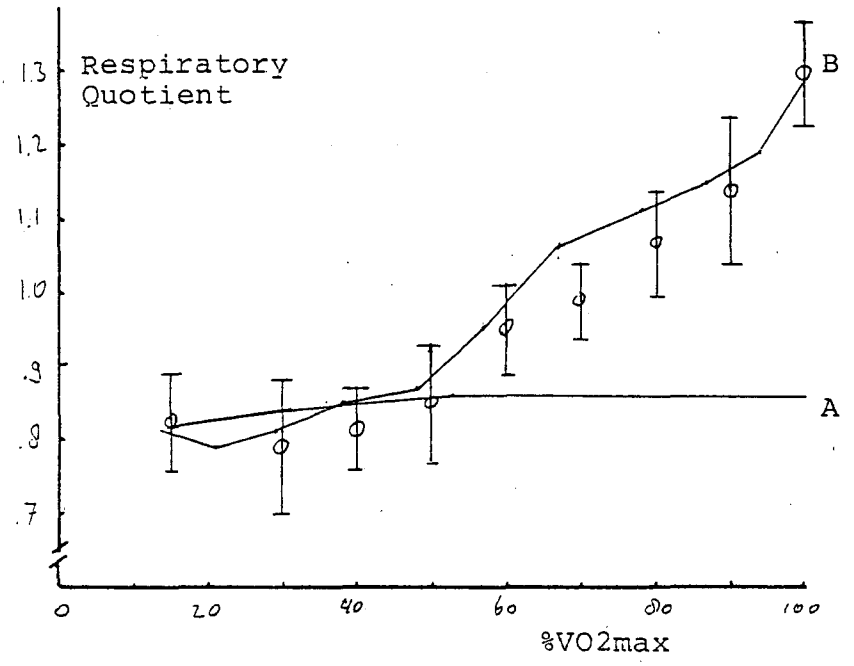
The large improvement in the representation of respiratory rate is clearly visible in the graph, as well as in the improvement of the performance index (69.2->91.9 %). The improvement is primarily due to the altered ventilation-respiration rate relation (chapter III), but through this, of course also to the improvement of minute ventilation itself. Nevertheless, respiratory rate is quite high at low work loads (< 40 % VO2max), which suggests further changes in the regulation of tidal volume and respiration rate.



Graph 9-4; Respiratory rate in relation to % of maximal oxygen uptake; A:original model; B:recent model; Circles: real test values (+/- SE, n=6).

RESPIRATORY QUOTIENT: (Graph 9-5)

For the respiratory quotient, the important changes were already made and described in the first paper. The behaviour (see graph) has become much more realistic (P.I. 85.3 -> 94.9 %) through the regulation of tissue respiratory quotient. However, I think that this change in the representation of tissue respiratory quotient should be validated with more information from research literature.

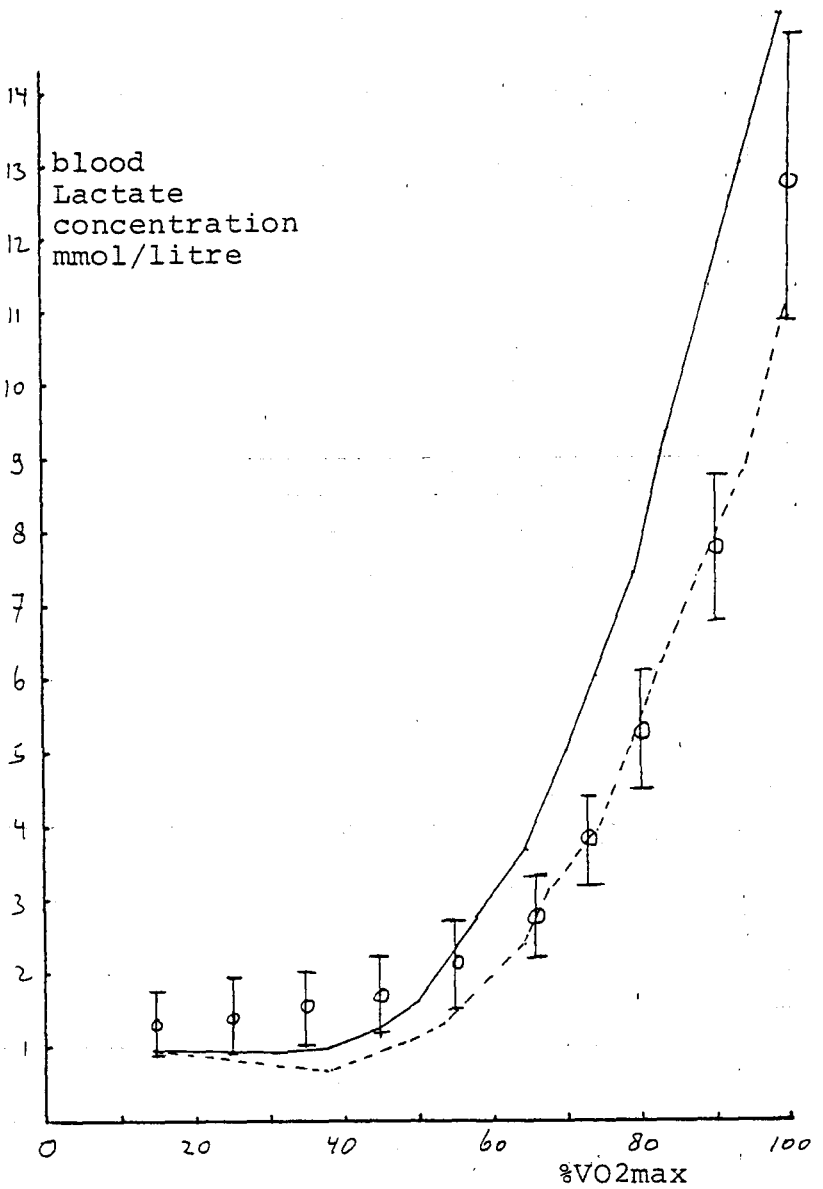


Graph 9-5;Respiratory quotient in relation to % of maximal oxygen uptake; A:original model; B:recent model. Circles:real test values (+/-SE, n=6).

LACTATE: (Graph 9-6)

Although the shape of the lactate curve has become more realistic, it's quantitative results still need to be improved. At low level of work, the difference between the simulation results and the data are mainly due to the difference in resting lactate levels. This could be adjusted rather easy; but the necessity of such a change is questionable as most literature results (Kelman 1975, Wasserman 1975, Keul 1979) suggest a range of resting lactate levels between .5 and 1.8 mmols/litre.
At higher work levels (above 60 % VO2max) lactate concentration is too high (see graph). In the graph I also presented results for a fitness value of 31, which appears to produce more realistic resulta at these high work levels. Therefore it is advisable to reduce the fitness value in the model, for the simulation of average fit subject. (This might also ask for a reconsideration of the influence of fitness on the regulation of strokevolume)

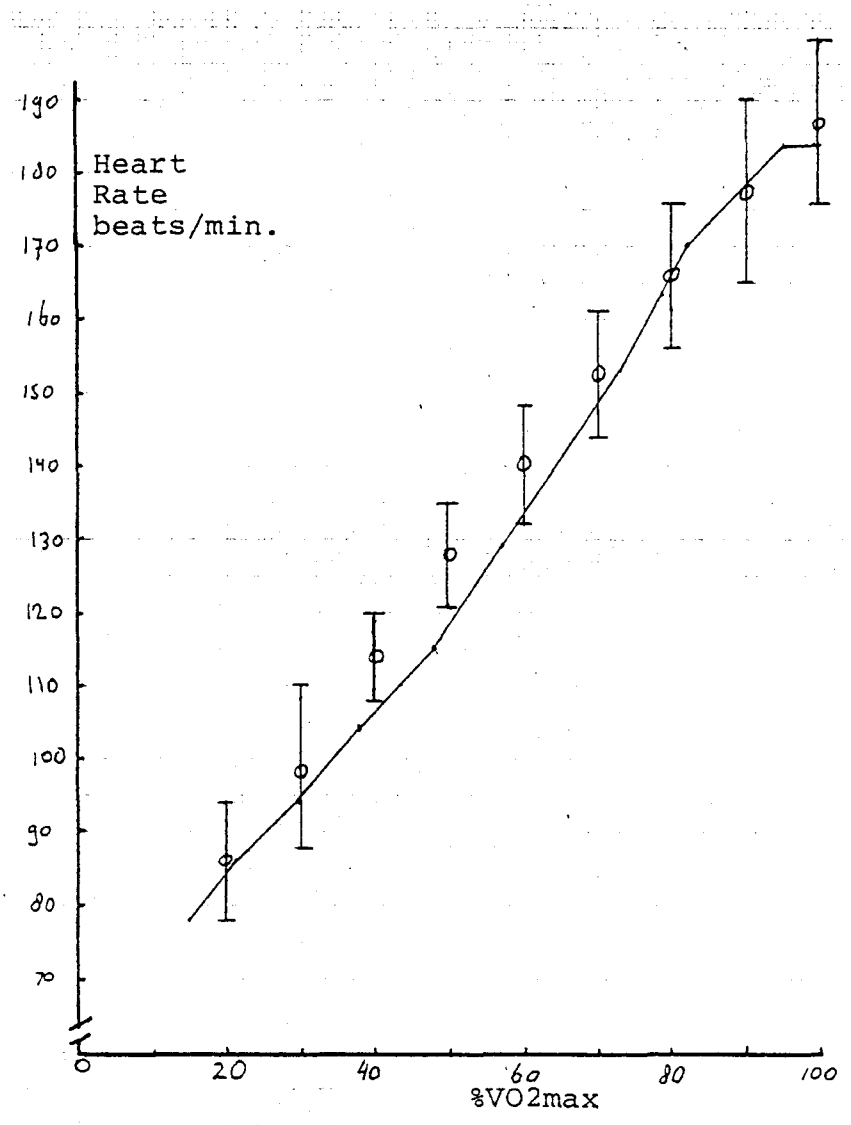
The deduction of the anaerobic threshold from lactate concentration is, as mentioned in my first paper, very dependant on the criterion which is used.
The 4 mmol/litre value is reached at 65 and 75 % VO2max (fitness 33 and 31); the 2 mmol/litre value at 53 and 60 % VO2max, and the point of increase above resting levels at 40 and 48 % VO2max. When we compare these values to the anaerobic threshold values deducted from minute ventilation and minute carbondioxide output, we find that the 2 mmol/litre value reflects those best. This is the case for both the model and the data.



Graph 9-6 Blood lactate concentration in relation to % of maximal oxygen uptake; continuous line:fitness33; dotted line: fitness 31. Circles:real test values (+/-SE,n=4).

HEART RATE: (Graph 9-7)

As the original model did not calculate the heart rate, we cannot compare it's performance index with the value of the recent model. In the graph, we see a reasonable resemblance between model values and data. The part where the model values are not within the standard deviation of the data (40 and 50 % VO2max) suggests that the strokevolume rises too fast at these loads, which might be reduced in the future.

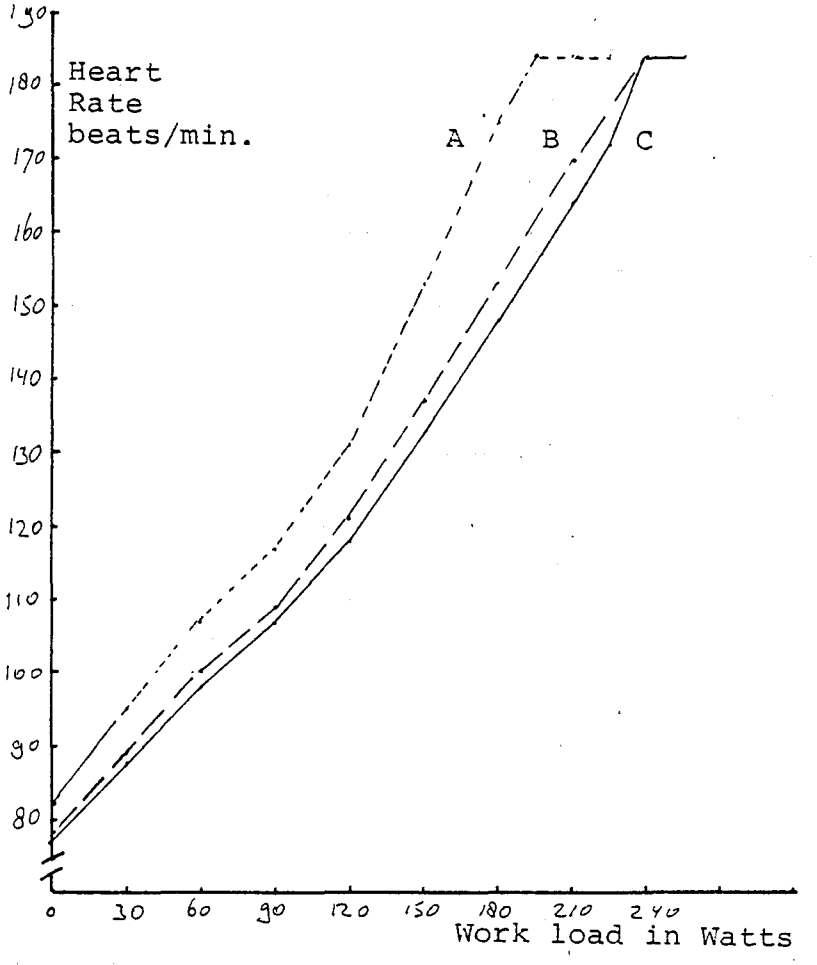


Graph 9-7;Heart rate in relation to % of maximal oxygen consumption. Circles:real testtvalues (+/-SE,n=6).

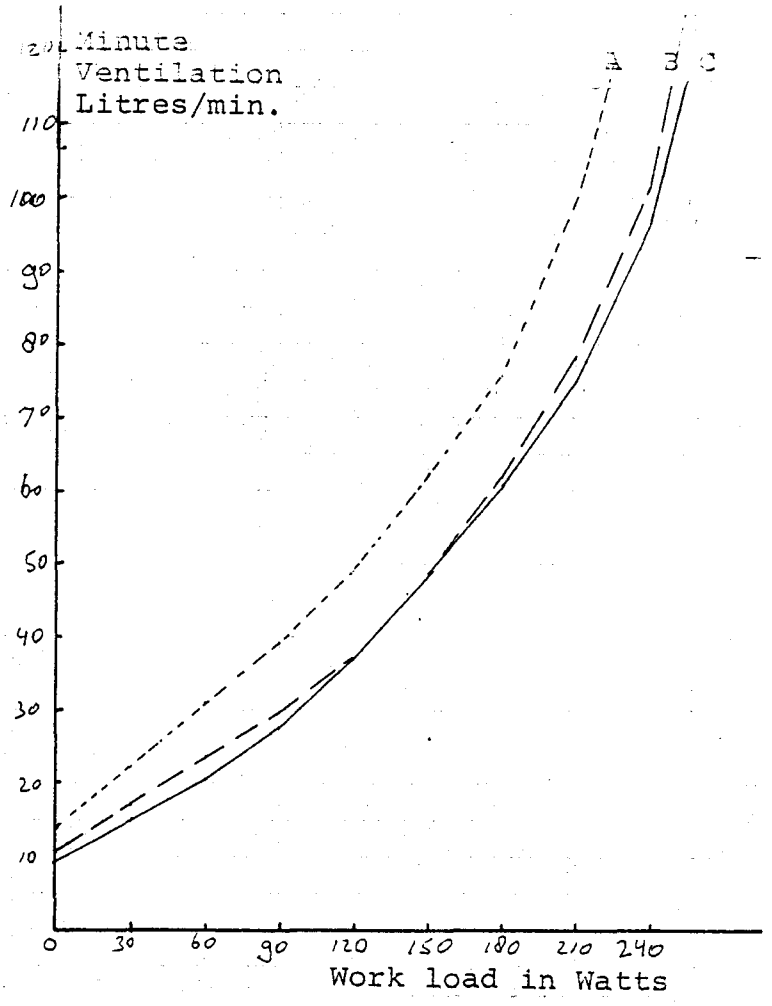
For a further validation of the model, I simulated influences of changed fractions of inspired oxygen and of influences of reduced strokevolume.

B

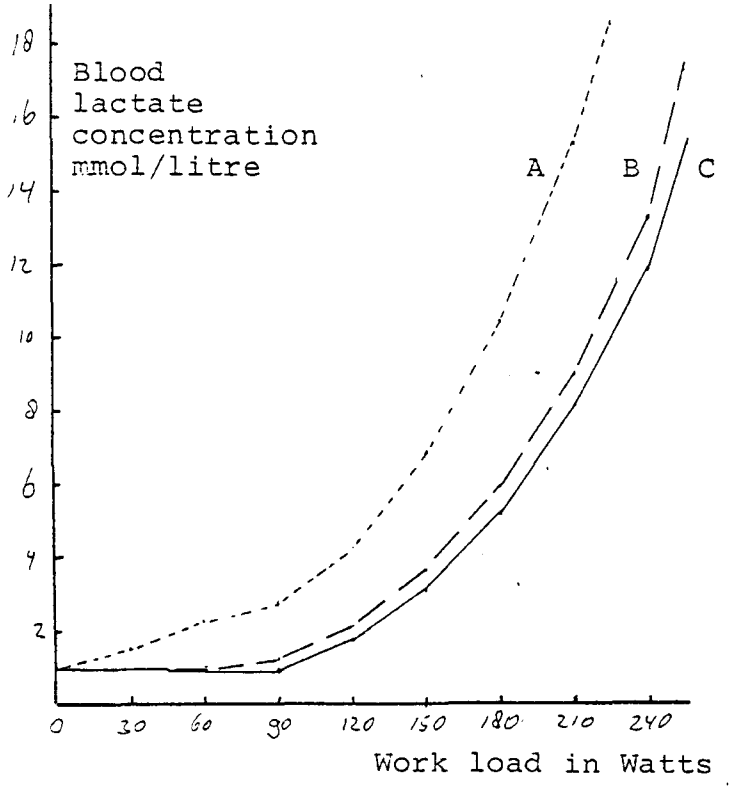
The results for changed oxygen fractions in inspired air seem to be quite realistic (graph 9-8, 9-9, 9-10). The lower (higher) oxygen content of the inspired air results in a lower (higher) oxygen content of the blood (dissociation curves). In order to maintain the same oxygen delivery to the tissues, cardiac output and therefore heart rate (as well as ventilation) have to rise (fall). However, oxygen delivery to the tissues will remain a little too low (high), and therefore a greater (smaller) amount of lactate will be produced.
This behaviour is indeed present in the model simulations.



Graph 9-8;Heart rate in relation to work load in three different inspired oxygen fractions: A:12%,B:21% and C:32%.



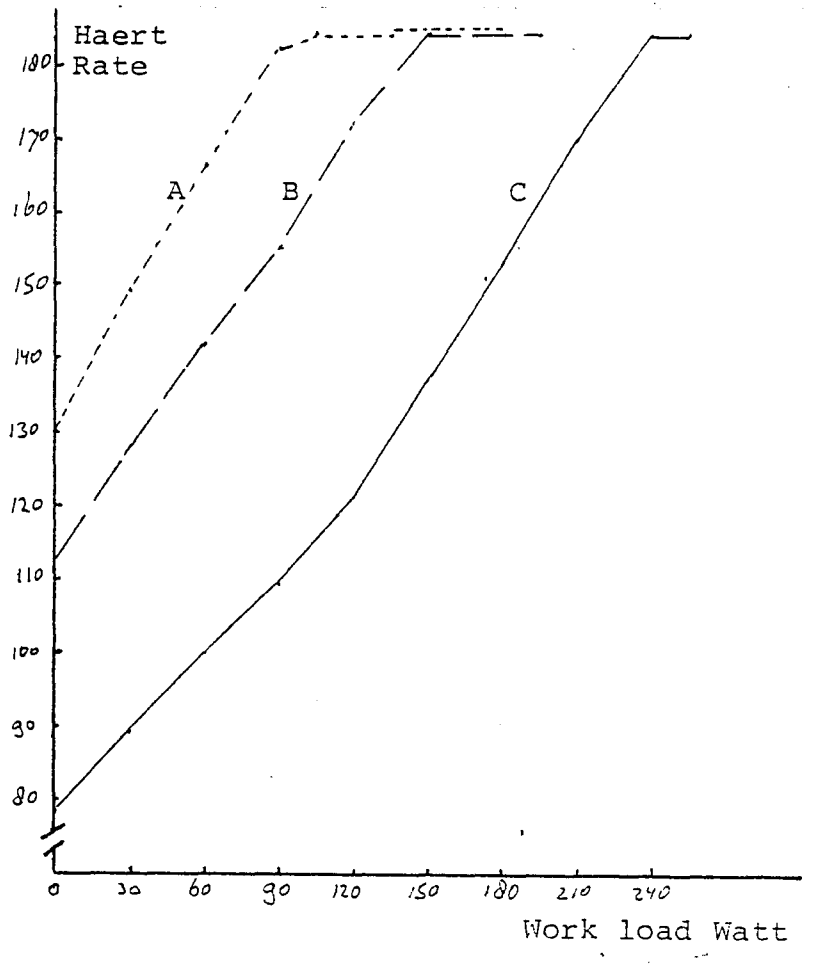
Graph 9-9 Minute ventilation in relation to work load for oxygen fractions in inspired air of A:12,B:21 and C:32 %.



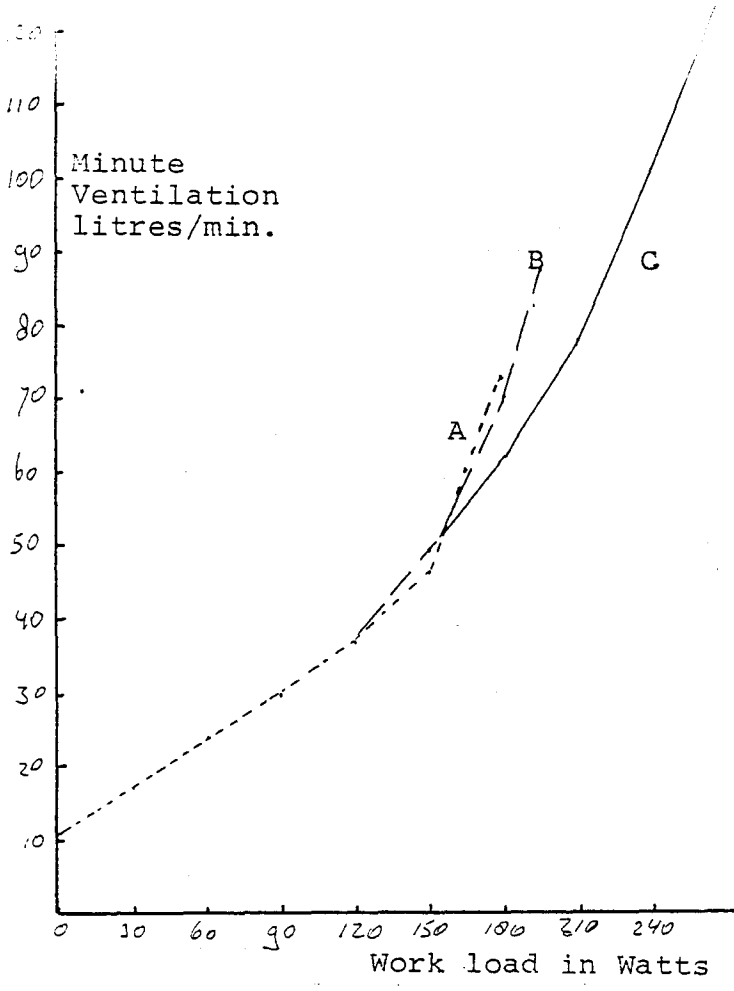
Graph 9-10 Blood lactate concentrations in relation to work load for three different inspired oxygen fractions: A:12,B:21,C:32 %.

C

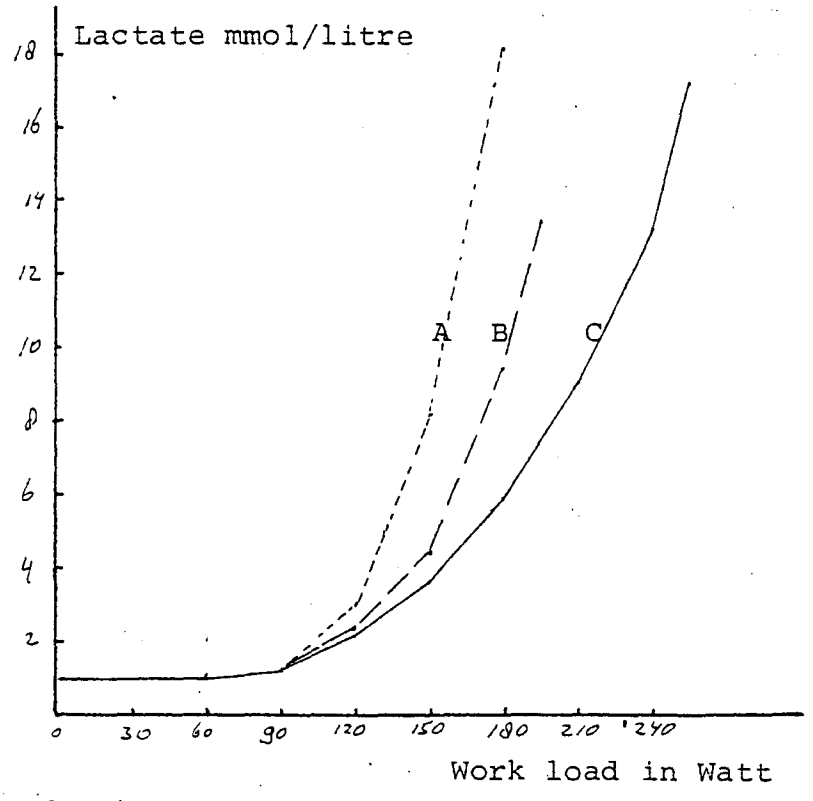
A reduced strokevolume can be compensated by a raised heart rate. When heart rate becomes limited, compensation stops, which results in a too small blood flow for the given work load; too low oxygen delivery, and therefore: increased ventilation and lactate production.
This is also shown by the model (graph 9-11,12 and 13).
In capter VII I discussed the unrealistic long continuation of the exercise test, once the maximal heart rate was reached.
This continuation is visible in graph 9-11. As described in chapter VII, this behaviour can be improved by splitting up the blood flow into a constant flow for the organs and a flow, related to work load for the muscles. The fact that this improvement was not sufficient, and the results of the model, without the influence of the oxygen saving effect of lactate production (graph 7-5) show the necessity of a reconsideration of the value of this oxygen saving effect, and the related value of lactate production. In the model, all the produced lactate " saves " oxygen, as it does not enter the citric cycle. The model does not take account of the amount of lactate which is later (at other sites) burnt with oxygen in the citric cycle to H2O and CO2 (see first paper: lactate removal). Calculations showed that at an oxygen uptake of ca. 3 litres, the amount of oxygen which is used for lactate catabolism amounts up to two litres (65 %) (values from 15 Watt/min. test). This indicates that the idea of lactate being a "waste" product after it has saved oxygen is questionable.



Graph 9-11 Heart rate in relation to work load for simulations of reduced stroke volume. Stroke volume= A:60%,B:70%, C:100% of normal.



Graph 9-13 Blood lactate concentration in relation to work load for the simulation of reduced stroke volume to A:60, B:70,c:100 % of the normal value.



Graph 9-12 Minute ventilation in relation to work load for simulation of reduced stroke volume to A:60,b:70,C:100 % of the normal value.

It seems more realistic to approach lactate as a preferrable substrate in exercise, after it is produced at other sites in the body, with insufficient oxygen supply and/or with a mainly glycolitic metabolism (e.g. fast twitch fibers).
This would mean that in cases where oxygen is available for lactate catabolism , the oxygen saving effect for the body as a total has to be reduced. In cases where oxygen is not available, as in cardiac arrest, the oxygen saving effect would then still be able to perform its original behaviour.

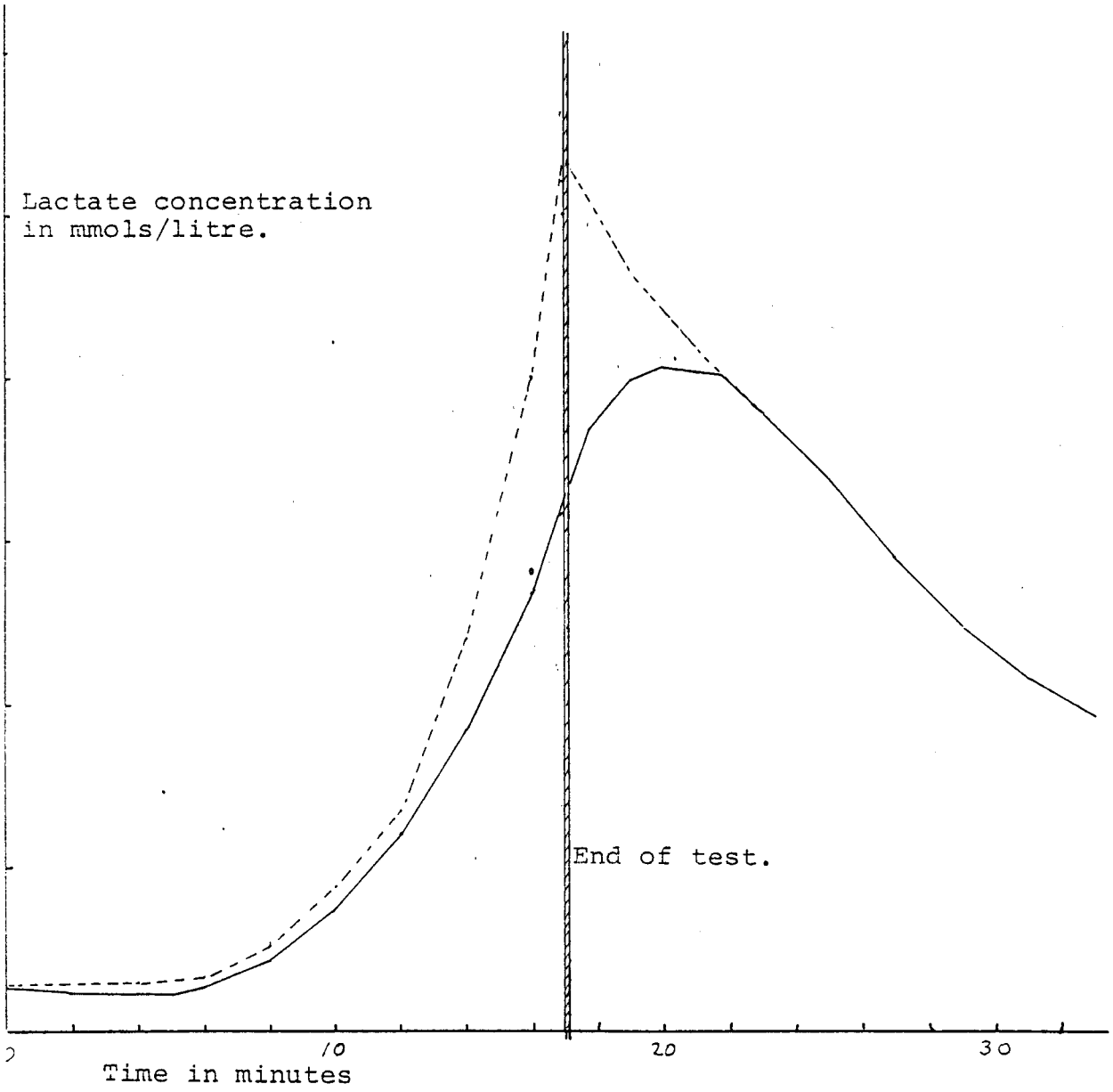
D

In graph 9-14, I presented the behaviour of working muscle and blood lactate concentration, during and after a 15 Watt/min. Incremental test, in the model with a separated lactate production compartment. During the test, blood lactate concentration is very similar to blood lactate concentration in the model without the separate lactate production compartment (see graph 9-13 and 9-6). Working muscle lactate concentration remains close to blood lactate concentration until the tissue pH drops below 7.2. From this point (13-14 min. in the graph) muscle lactate concentration increases very fast compared to blood lactate concentration due to the reduced transport of lactate from muscle to blood (see chapter VI).
The exercise is stopped at a working muscle pH of 6.5 and at a tissue pH of 7.1. At this point, muscle lactate is 27 and blood lactate 16 mmols/litre.

After the end of the test, muscle lactate concentration decreases, whereas blood lactate continues to increase until both values are equilibrated. Then both values decrease.
The maximal blood lactate value occurs about 4 minutes after the end of the exercise, which is in accordance with findings of Freund and Zouloumian (1981, first article).
For the decrease of muscle lactate concentration, we find a half time of ca. 11 minutes; for blood lactate concentration, the half time is ca. 12 minutes, starting at maximal lactate levels, and ca. 17 minutes starting from the end of the test.
These results were reached, by manipulation of the constant in the lactate transport equation for lactate transport from muscle to blood. Changing the constant, changes the relation between maximal muscle and blood lactate concentrations, as well as the time constants of equilibration between muscle and blood lactate concentration after the test.

In the simulation of the period immediately after the exercise, it appears that oxygen consumption drops very fast to resting levels. This is caused by the strong correlation between work load and oxygen consumption in the model. The model does not take account of the extra oxygen which is needed to catabolize the high lactate amounts, present at the end of the exercise period. If the model would take account of the higher oxygen need, we would find a delay in the return of VO2 to

resting levels.
This once more (as also discussed in C) suggests the need of the incorporation of the influence of lactate catabolism on oxygen consumption.



Graph 9-14; Lactate concentration in blood (continuous line) and in the muscles (dotted line), during and after a 15 Watt per min. incremental test (model with seperated lactate production compartment).

CONCLUSION AND PROPOSAL FOR FURTHER RESEARCH

Reaching the end of this project, I think that the behaviour of MACPUF in exercise has improved significantly. The variables which are usually measured in exercise tests: Ve, VCO2, VO2, respiratory rate, heart rate and lactate, show at this stage in the model a realistic behaviour. The same is true for less measured variables as PaCO2, $HCO3^-$, and pH.

In the simulation of exercise in cardiac disease, some unrealistic behaviour is still present. Nevertheless, I think that with the incorporation of a split blood flow, and especially of a reduced oxygen saving effect, (by the incorporation of lacate catabolism influence on VO2 and of the influence of oxygen availability on lactate catabolism) this unrealistic behaviour will disappear. However, these points need further study.
Another item which needs further study, but which seems very promising is the incorporation of the separated working muscle compartment. An interesting feature of this change is the influence on the time constants of lactate transport from muscle to blood and of lactate removal after the exercise.

APP. I PIIPERS BUFFERING MODEL

In order to get some additional information on the effect of lactic acid formation on muscle and blood pH, Dr.Jones and I decided to build a simple three compartment model with information from an article by Johannes Piiper: " Buffering of lactic acid produced in exercising muscle " .
The three compartments are: intracellular fluid, extracellular fluid and blood.
Intracellular fluid and blood contain bicarbonate as well as non bicarbonate buffers; extra cellular fluid contains only bicarbonate buffers.
Data for the model are presented in graph app-1. Piiper assumes that pH in intra and extracellular fluid are equal and that pH changes in extracellular fluid and blood relate to each other as 1 to 2.
In the program I incorporated two possibilities:
1. the direct calculation of the influence of any addition of H+ ions on pH and buffer quantities, and:
2. the time course of this buffering process, governed by the diffusion constant between these compartments.
An example of the results of an addition of 20 meq H+ per kilogram muscle is given in graph app-1, middle and lower panel.

Some definitions and used formula's:
Buffer value B= the amount of H+ ions bound per unit volume of buffer solution and per change of pH.

B= DELTA [H+]/-DELTA pH

Buffer capacity K: total amount of H+ bound by buffering per change of pH.

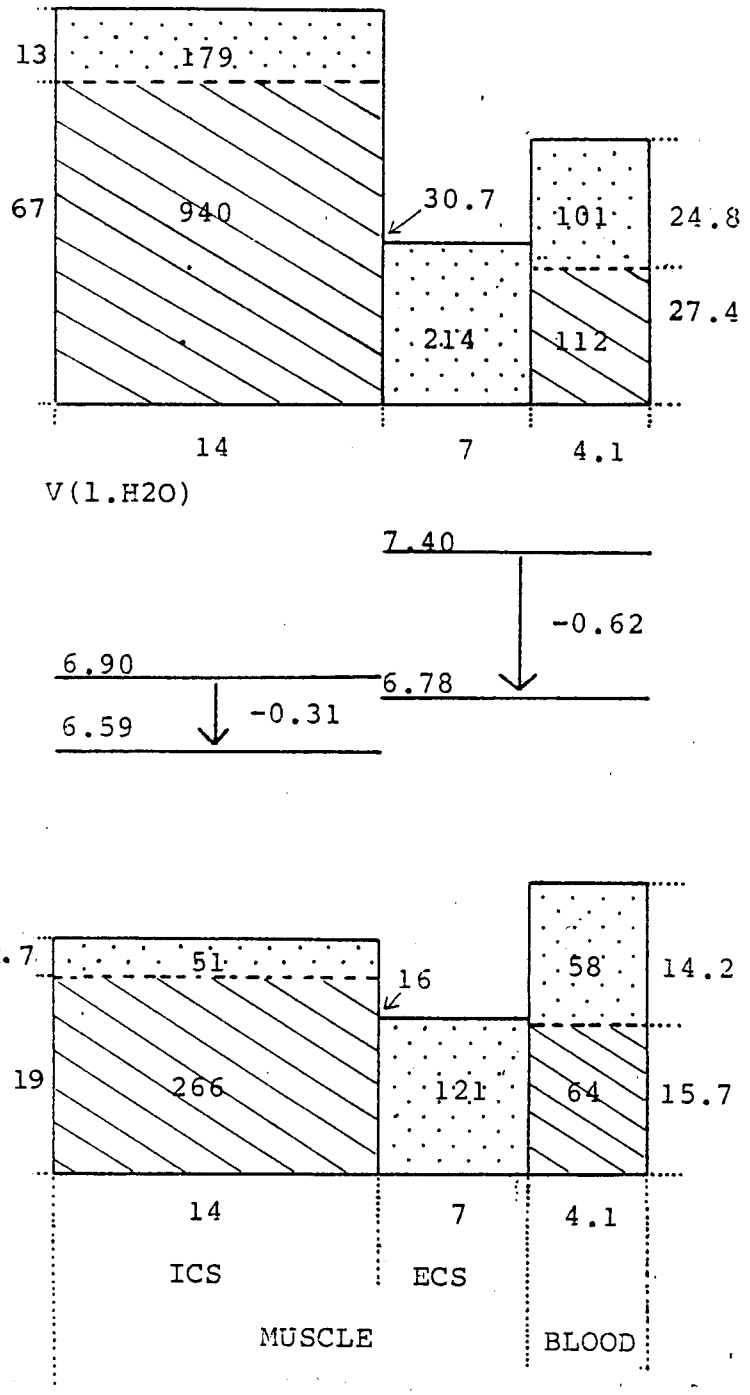
K=B*VOLUME

Total amount of H+ bound: H+b= B*VOLUME*(-DELTA pH)

PROGRAM LISTING

```
$CONTROL SEGMENT=MAIN                                                    10
      PROGRAM BUFFER                                                     20
C                                                                        30
C                                                                        40
C+++++++++++++++++++++++++++++++++++++++++++++++++                       50
C                                                                        60
C           GEORGE HAVENITH                                              70
C           NOVEMBER 18 1981                                             80
C  PROGRAM TO SIMULATE THE EFFECT OF H+ FORMATION                        90
C COINCIDING WITH LACTATE FORMATION, ON PH                              100
C AND BUFFER AMOUNTS IN A THREE COMPARTMENT MODEL                       110
C COMPARTMENTS: INTRACELLULAR MUSCLE FLUID                              120
C               EXTRACELLULAR MUSCLE FLUID                              130
C               BLOOD                                                   140
C LITERATURE: BUFFERING OF LACTIC ACID, PRODUCED                        150
C IN EXERCISING MUSCLE; JOHANNES PIIPER                                 160
C                                                                       170
C+++++++++++++++++++++++++++++++++++++++++++++++++                      180
      DATA BA,BB,BC,OBA,OBB,OBC,VOLA,VOLB,VOLC                          190
     X/13.,30.7,24.8,67.0,0.0,27.4,14.0,7.0,4.1/                        200
C RALATION BETWEEN PH CHANGE PER COMP DHA:DHB:DHC                       210
      DATA DPHA,DPHB,DPHC/1.,2.,2./                                     220
      DISPLAY "GIVE ADDITION OF H+ (MEQ/KG MUSCLE)"                     230
      READ (5,*) XXX                                                    240
      ADDH=2.*VOLA*XXX                                                  250
      DISPLAY " THIS EQUALS TOTAL ADDITION OF",ADDH,"MEQ"               260
      N=1                                                               270
      BICA=BA*VOLA                                                      280
      OBICA=OBA*VOLA                                                    290
      BICB=BB*VOLB                                                      300
      OBICB=OBB*VOLB                                                    310
      BICC=BC*VOLC                                                      320
      OBICC=OBC*VOLC                                                    330
```

```
C TOTAL BUFFER CAPACITY FOR EACH COMPARTMENT                                    340
      BUFA=BICA+OBICA                                                          350
      BUFB=BICB+OBICB                                                          360
      BUFC=BICC+OBICC                                                          370
C CHANGE IN H+ RELATED TO PH CHANGE IN DIFFERENT                               380
C COMPARTMENTS                                                                 390
      DHA=BUFA*DPHA                                                            400
      DHB=BUFB*DPHB                                                            410
      DHC=BUFC*DPHC                                                            420
C RELATE TO TOTAL H+ CHANGE                                                    430
      TDHA=DHA/(DHA+DHB+DHC)                                                   440
      TDHB=DHB/(DHA+DHB+DHC)                                                   450
      TDHC=DHC/(DHA+DHB+DHC)                                                   460
C CALCULATE END (STEADY STATE) DIVISION OF                                     470
C PRODUCED H+                                                                  480
      ASS=TDHA*ADDH                                                            490
      BSS=TDHB*ADDH                                                            500
      CSS=TDHC*ADDH                                                            510
C CALCULATE END (STEADY STATE) PH CHANGE                                       520
      DPHASS=ASS/BUFA                                                          530
      DPHBSS=BSS/BUFB                                                          540
      DPHCSS=CSS/BUFC                                                          550
C START AT END ADDITION OF H+ TO COMP A                                        560
      AT=ADDH                                                                  570
      BT=0.                                                                    580
      CT=0.                                                                    590
C PRINT VALUES                                                                 600
       DISPLAY "BUFFER CAP. INTRACELL. COMP.=",BUFA                            610
      DISPLAY "BUFFER CAP. EXTRACELL. COMP.=",BUFB                             620
      DISPLAY "BUFFER CAP. BLOOD           =",BUFC                             630
      DISPLAY "ADDED H+ =",ADDH                                                640
      DISPLAY "AMOUNT OF H+ BUFFERED PER COMPARTMENT:"                         650
      DISPLAY "INTRACELL=",ASS,"EXTRAC.=",BSS,"BLOOD=",CSS                     660
      DISPLAY "PH CHANGE FOR COMPARTMENTS:"                                    670
      DISPLAY "INTRA=",DPHASS,"EXTRA=",DPHBSS,"BLOOD=",DPHCSS                  680
C EFFECT OF ADDH IN COMP A                                                     690
      DDPHA=ADDH/BUFA                                                          700
      DDPHB=0.                                                                 710
      DDPHC=0.                                                                 720
C EFFECT OF ADDH ON COMP A                                                     730
      DBICA=BICA/BUFA*ADDH                                                     740
      DOBICA=OBICA/BUFA*ADDH                                                   750
C INITIALIZE DBICB/C AND DOBICB/C                                              760
      DBICB=0.                                                                 770
      DBICC=0.                                                                 780
      DOBICB=0.                                                                790
      DOBICC=0.                                                                800
C RUN TIME AND DIFFUSION SPEED                                                 810
      DISPLAY " DO YOU WANT TO SIMULATE TIME COURSE OF H+ TRANSPORT?"          820
      DISPLAY " YES=1; NO=0"                                                   830
      READ (5,*) K                                                             840
      IF (K.EQ.0) GOTO 200                                                     850
      DISPLAY "GIVE DIFFUSION CONSTANT FOR EXTRA-INTRA MUSCULAR FLUID"         860
      DISPLAY "BETWEEN 0. AND 1."                                              870
      READ (5,*) DIFAB                                                         880
      DISPLAY "NOW FOR EXTRA MUSC.-BLOOD"                                      890
      READ (5,*) DIFBC                                                         900
      DISPLAY " TYPE NUMBER OF ITERATIONS"                                     910
      READ (5,*) NN                                                            920
      DISPLAY " FOR EACH ITERATION DISPLAYED:"                                 930
      DISPLAY "PH CHANGE IN INTRA/EXTRA/BLOOD COMPART."                        940
      DISPLAY "CHANGE IN H+ BUFF. BY BICARB. AND NON-BICARB. BUFFERS"          950
       DISPLAY " FOR AECH COMPARTMENT"                                         960
C ALLOW DIFFUSION                                                              970
 100  AT2=AT-(BSS/ASS*AT-BT)*DIFAB                                             980
      BT2=BT+(BSS/ASS*AT-BT)*DIFAB+(BSS/CSS*CT-BT)*DIFBC                       990
      CT2=CT-(BSS/CSS*CT-BT)*DIFBC                                            1000
C CALCULATE PH CHANGE                                                         1010
      DDPHA=DDPHA+(AT2-AT)/BUFA                                               1020
      DDPHB=DDPHB+(BT2-BT)/BUFB                                               1030
      DDPHC=DDPHC+(CT2-CT)/BUFC                                               1040
C CALCULATE CHANGE IN BUFFERS                                                 1050
      DBICA=DBICA+(AT2-AT)*BICA/BUFA                                          1060
      DOBICA=DOBICA+(AT2-AT)*OBICA/BUFA                                       1070
      DBICB=DBICB+(BT2-BT)*BICB/BUFB                                          1080
      DOBICB=DOBICB+(BT2-BT)*OBICB/BUFB                                       1090
      DBICC=DBICC+(CT2-CT)*BICC/BUFC                                          1100
      DOBICC=DOBICC+(CT2-CT)*OBICC/BUFC                                       1110
C PRINT PH CHANGE AND BUFFER CHANGE                                           1120
      DISPLAY N,DDPHA,DDPHB,DDPHC                                             1130
      DISPLAY DBICA,DOBICA,DBICB,DOBICB,DBICC,DOBICC                          1140
C T2=T                                                                        1150
      AT=AT2                                                                  1160
      BT=BT2                                                                  1170
      CT=CT2                                                                  1180
      N=N+1                                                                   1190
      IF (N.GE.NN) GOTO 200                                                   1200
       GOTO 100                                                               1210
 200  CONTINUE                                                                1220
      DISPLAY " END PROGRAM "                                                 1230
      STOP                                                                    1240
      END                                                                     1250
```



Graph app-1 Buffering of H+ ions formed in muscle.
Upper panel: abcissa, volume V, ordinate:buffer value B (in meq./litre H2O); area buffer capacity in meq./pH unit.
Middle panel: pH changes.
Lower panel: abcissa: volume V; ordinate: amount of H+ bound per unit volume; area: amount of H+ buffered (PIIPER).

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Appendix

LIST OF FORTRAN SYMBOLIC NAMES

Floating point variables

The standard method of construction of most of the Fortran symbolic names for variables in the programme was described in Chapter 4. Summarising, the first letter specifies a compartment:

A—Alveolar; B—Brain; E—Effluent arterial blood flowing to tissues; P—Pulmonary capillary (idealised); R—Arterial; S—Slow tissue store (for nitrogen); T—Tissue; U—Bubbles in tissues (if present); V—Venous

The second two letters specify the nature of the material or measurement, e.g.:

O2—Oxygen; C2—Carbon dioxide; C3—Bicarbonate; N2—Nitrogen

The final two letters specify the type of measurement, e.g.:

MT—Amount of something in cc STPD (gas) or mmol (bicarbonate); CT—Content of something, in cc STPD/100 ml (gas) or mmol/litre (bicarbonate); PR—Partial pressure, in mmHg (torr); PH—pH (second 2 letters omitted—e.g. brain pH is represented by 'BPH')

Thus arterial blood carbon dioxide content is represented by RC2CT, and AN2MT represents the amount of nitrogen in the alveolar compartment.

Non-standard floating point variables in main programme

Other floating point, i.e. non-integer, variables are mostly chosen to have some mnemonic value. A complete list of these non-standard, non-integer symbols appears below, in alphabetical order:

ADDC3	Manually changeable variable specifying number of mmol bicarbonate to be added to the body: initialised at 0, and returned to zero after use
AGE	Age in years
AVENT	Alveolar ventilation, in cc/iteration interval (BTPS)
AZ	Percentage normal response of ventilation to altered H^+ and PCO_2 stimuli
BAG	Volume of a bag, if used, in cc BTPS
BAGC	Volume of CO_2 in the bag, in cc STPD
BAGO	Volume of O_2 in the bag, in cc STPD
BARPR	Barometric pressure, mmHg or KPa
BO2AD	Index of brain oxygenation adequacy (normally = 1.0)
BULLA	Symbolic name for added dead space—normal value = 0 cc (BTPS)
BZ	Percentage normal response of ventilation to hypoxia
C	Array storing precalculated run parameters (see subroutine CONST)
CBF	Cerebral blood flow, in ml/100g/min
CO	Cardiac function, as percentage normal average for the subject
COADJ	Effective cardiac output, from nominal cardiac output and adjustments, l/min

COMAX	Maximum cardiac output, in l/min
CONOM	Nominal resting cardiac output, l/min
CONSO	Tissue oxygen consumption, nominal resting value, cc/min STPD
CZ	Percentage normal response of ventilation to increased metabolic requirements and to intrinsic neurogenic drive
DSPAC	Dead space, in cc BTPS
DVENT	Total ventilation, l/min (BTPS)
ELAST	Elastance, cm H_2O/l
FADM	Fixed venous admixture, i.e. complete right-to-left shunt, as percentage of cardiac output
FEV	Forced expired volume in 1 second
FIC2	Inspired carbon dioxide percentage
FIO2	Inspired oxygen percentage
FT	Fractional time interval, in min (normal 0.16667, = 10 s)
FTCO	Local variable incorporating effective cardiac output and fractional time
FTCOC	Same but including an allowance for wasted tissue perfusion, related to fitness
FVENT	Alveolar ventilation, in l/min
FY	Local variable describing (1) tissue buffering with changing PCO_2, and (2) extra dead space under certain conditions (Chapter 11)
HB	Haemoglobin, in g/100 ml
HT	Height, in cm
PC	Respiratory exchange ratio during last iteration interval (also used as a local variable)
PC2	Local variable, arterial or end inspiratory PCO_2, mmHg
PCV	Packed cell volume, percentage
PD	Metabolic rate as percentage normal resting value
PEEP	Positive end-expiratory pressure (cm H_2O)
PG	Index affected by severity and time of brain oxygen inadequacy, to determine death and syptoms
PJ	Arterial oxygen saturation, percentage
PL	Index determining operative mode during bag collection, rebreathing and tracheal obstruction experiments (see subroutine BAGER)
PO2	Local variable, arterial or end-inspiratory alveolar PO_2, mmHg
PR	Percentage normal coupling of ventilatory drives to resultant ventilation
PW	Effective operative venous admixture effect (percentage cardiac output), taking all factors into account
QA	Net oxygen uptake per unit time interval, cc STPD
QB	Net carbon dioxide output per unit time interval, cc STPD
REFER	120-element DATA array for initialisation of new subjects (see subroutine MINIT)
REFLV	Reference volume of the lungs, used to return lung volume after prolonged tracheal obstruction
RRATE	Respiratory rate, in breaths/min
RVADM	Extra shunt effect brought in for emphysematous patients when specified (normally = 0)
SAT	Local saturation returned to main programme from subroutine GASES
SHUNT	Right-to-left shunt, as a ratio of the unshunted flow
SIMLT	Multiplier for S.I. unit/mmHg conversion
SPACE	Inspiratory/expiratory duration ratio (normally 0.4)
SVENT	Total effective drive to ventilation, taking most variables into account, l/min
T	120-member array containing COMMON variables and parameters

TC2RF	Reference value for detecting changes in tissue PCO_2
TDLAY	40-member array storing tissue CO_2 content and pressure, pH and bicarbonate for the venous delay line
TDUMP	160-member array storing similar sets of values for use in backtracking
TEMP	Body temperature, in °C
TIDVL	Tidal volume, cc BTPS
TJJ	Eight-member array storing a string of variables to be output in columns
TND	Counter in seconds
TRQ	Tissue respiratory quotient
TVENT	Total stimulus to ventilation, in l/min
TVOL	Effective tissue fluid volume, as litres of extracellular fluid
U	Local variable—used in several places
V	Local variable—used in several places
VADM	Nominal value for dynamic venous admixture, varying with lung oxygenation, etc. (percentage)
VBLVL	Venous blood volume, in ml
VC	Vital capacity, in litres
VLUNG	Volume of the lung, in cc BTPS
W	Local variable—used in several places
WT	Weight, in kg
X	Local variable—used in several places
X109–X110	Spare variables not in present use
XDSPA	Extra dead space specified by altered function tests for specified subjects (cc BTPS)
XMALE	Index specifying male (1) or female (0)
XVENT	Local variable describing volume ventilated out in one iteration interval (cc BTPS)
Y	Local variable—used in several places
Z	Local variable—used in several places

Integer factors and variables

The list that follows is in alphabetical order:

I	Local integer variable
INDEX	Keeps a log of the position of the 'pointer' in the venous delay line in subroutine DELAY
INI	Logical number of the input unit. In interactive use this will always be the console Teletype or equivalent; otherwise could be a card-reader
ISPAR	Index specifying suppression of 5 out of 6 lines of output (2), 29 out of 30 lines (3) or no suppression (1)
ITRIG	72-element array representing 72 spaces across a line of the keyboard typewriter, each element being a single alphanumeric character. Reading of instructions is transferred into this array as blanks, numbers or separators
ITRIG(73)	The 73rd element of this (same) array is used to control printing of current values of the first 6 parameters after each run. If less than 2, the table is printed; otherwise printing is suppressed
J	Local integer variable
J3	Time in minutes since creation of a new subject
JKL	Index governing input of sequences of numbers separated by blanks. Normal value = 1; zero ends sequence of numbers (see subroutines DEADY and NXTWD)
K2	Index specifying previous occurrence of severe symptoms (= 1); or absence of same (= 0) (for comparison with K1)
K4	Index specifying previous occurrence of minor symptoms (= 1); or absence of same (= 0) (for comparison with K3)

KL	Logical number of unit displaying output most suitable for a lineprinter if available (cf. KT). If output is all to be directed to a Teletype or equivalent, KT and KL should be the same
KT	Logical number of output most suitable for operator interaction. If all output is to be directed to a Teletype or equivalent, KT should have the same logical number as KL
LL1	1st entry to MINIT inserts normal values into DUMP store (LL1 = 10). After new subject set up, LL1 = 1. LL1 = 2 calls for a new subject after 'DEATH'; LL1 = 3 calls for the same, after arithmetic errors.
LL2	Spare index not in present use.
LL3	Index controlling output from subroutine QUERY displaying text when setting up the model: normal = 2; abbreviated introduction = 1; research application without introduction or graphs (= 0). Subsequently codes explanations from subroutine QUERY in response to typing 'Q'
LL4	Counter (1 to 6) for suppression of 5 out of 6 lines of output, when specified by index ISPAR
LL5	Normal acceptable values (= 0). Impossible values make this index = − 1 and lead to same situation as simulated 'DEATH'
MORAN	Local integer variable controlling main programme loop
MT	Prints final computed values after each run (= 1); or not (= 0)
N	Local integer variable
NA	Specifies number of iterations of main programme loop until next halt (default = 18)
NARTI	Specifies natural ventilation (1), or artificial ventilation (0)
NB	Specifies suppression of main programme output display during creation of preset or specially created patients, using CLIN1 or CLIN2 subroutine (= 2); or no such suppression, as in normal use (= 1). If NB = 0 graph scales are printed
NC	Type of output: standard (1); graphs only (2); selected values (3); all values (4)
ND	Time in seconds
NDUMP	20-element array holding COMMON integer values from NFLAG to INDEX, used during 'BACKTRACK' by means of subroutine DUMP
NE	Eight-element array holding the factor numbers of 8 variables whose values can be displayed by the 'SELECTED VALUES' option. Default values for NE(8) are: 69 33 51 35 60 41 72 and 74. These numbers correspond to expired R.Q.; arterial pH; total ventilation; alveolar ventilation; arterial bicarbonate; alveolar PO_2; arterial PO_2; and arterial PCO_2. Changeable by user interaction from subroutine DEADY
NEOF	Specifies maximum number of integer or floating point numbers that the next call to subroutine NXTWD can accommodate. Normal (= 1): set to zero after call completed
NFLAG	Normal use (1). If 'BACKTRACK' after 'DEATH' is requested, NFLAG = 0, which prevents the creation of a new subject by subroutine MINIT
NO	20-element array held for reference in a DATA statement, and used for initialising COMMON integer values from NFLAG to INDEX
NREPT	Specifies number of repetitions of main programme loop. During setting up of a new subject, NW = 1; thereafter is set equal to index NA at end of each run
NTAB	20-element array equivalent to COMMON integer values from NFLAG to INDEX
NW	Index specifying that a new subject has been created and not so far changed (1); or that changes have already been made (0)