TRANSITION FROM AEROBIC TO ANAEROBIC ENERGY PRODUCTION IN HUMAN EXERCISE (ANAEROBIC THRESHOLD)

PARAMETER ESTIMATION ON THE COMPUTER MODEL MACPUF

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APRIL 1981

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PREFACE

As a part of my "doctoraal" study Biology, I am working on a 12 month project at the Theoretical Biology Group of the State University of Utrecht, in co-operation with the Medical department of the Dutch P.T.T.
The investigation is carried out under supervision of Ir. M. Woerlee and Drs. B.D.R. Kluwer.
This paper presents the first 6 month of the project.
I would like to thank the B.G.D./P.T.T. for their support; specially Maarten Woerlee and Ineke Kluwer.
Finally I would like to thank Ria Tervoort and Peter Anderson for their help with typework and ideas for the layout.

I INTRODUCTION

The development of modern machinery and the increased usage of automation in industry have caused a decrease of heavy physical work. In spite of the lightened manual work in many branches of industry there has been an increase in the sick-rate (N.I.P.G.1979) and the number of incapacitated workers (S.V.R.1979). In order to further the search for a possible explanation of this phenomenon, it is necessary to form a concept of the influences of work on man. This influence can be psychological as well as physiological. In order to be able to weigh one influence against the other, a good knowledge of both is necessary. In view of my biological background I chose the investigation of the physiological side of the problem.

What physiological changes are caused by work? This question is studied in exercise physiology. Exercise physiology is studied from two different points of view, each with its own goals: work physiology and sport physiology.

Sport physiology usually searches for methods to increase sport results, to be able to determine the state of training, or to optimalize training programmes. The most interesting factor in sport physiology is the maximal exercise value.

Work physiology has a different goal. It is not so much interested in maximal work capacity, for this can only be used for short periods. For work physiology, the most interesting range of work values are those a person is able to perform for longer periods of time, with short pauses (work day). The maximal work value a person is able to perform for longer periods is called: ENDURANCE CAPACITY.

An important question in work physiology is what the factors are which determine the endurance capacity. Before this question can be investigated, we first need a method to measure endurance capacity. Possible parameters to which endurance capacity can be related are minute oxygen consumption, heart rate, lactate concentration etc. The best method of course would be for test subjects to work at different work rates for long periods (e.g. 2 weeks at 8 hours a day) and then, from the results to calculate endurance capacity. However, it would cost too much time to repeat it for every new subject.

Is it then possible to find a parameter related to endurance capacity which is easier to determine?

Many research workers (LONDEREE 1975, JAGER 1976, KEUL 1978) investigated the maximal oxygen consumption. If a person performs work of increasing load, his oxygen consumption will increase linear to the load up to a certain level. Passing this point, increasing work load will not increase oxygen consumption. This is called: levelling off (see fig. I-1). Work done above this level has to derive its energy completely out of anaerobical processes. VO2-max determination has the disadvantage that tests are very exhaustive, and that tested persons have to be highly motivated to perform work up to the levels needed. Although generally VO2-max increases are combined with endurance capacity increases,(see fig I-2) the authors mentioned did not find significant relations be-

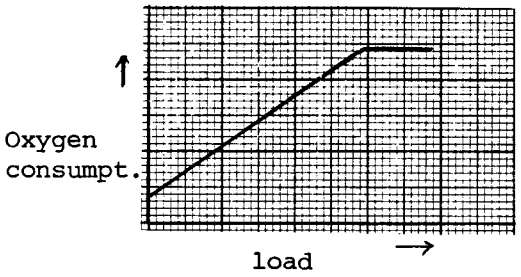


Fig. I-1. Levelling Off.

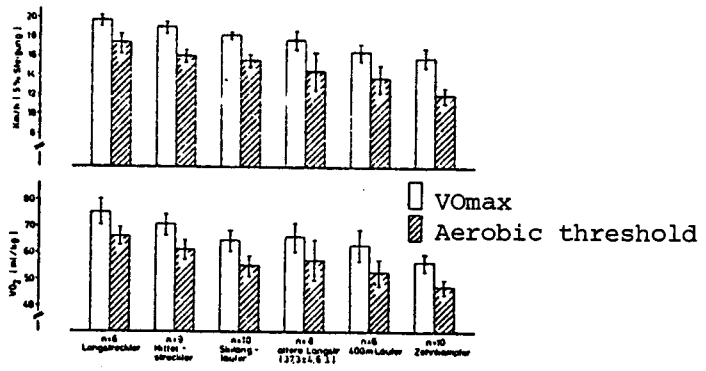


Fig. I-2. Relation between VOmax and Endurance Capacity.(Keul) (1978)

tween VO2-max and endurance capacity.

Other investigations searched for parameters related to the onset of anaerobic metabolism. They found that work, performed over longer periods, had to be done aerobicly, as otherwise it could not be maintained. Endurance capacity will then be the maximal work that can be done without using anaerobic metabolism. WASSERMAN 1973, KEUL 1979, and BUCHBERGER 1979 found that several physiological factors (minute ventilation, expired carbon dioxide (VCO2), respiratory quotient and pH) showed non linear changes, significantly correllated to the onset of anaerobic metabolism. WASSERMAN and WHIPP 1975 then state that: endurance capacity is the level of work just below that at which metabolic acidosis (caused by lactate production in anaerobic metabolism) and associated changes in gas exchange occur. This point is often referred to as the anaerobic threshold. these findings provide us with more parameters for endurance capacity measurements (lactic acid concentration, pH, R.Q., VE, VCO2).

In my study I tried to investigate the relations between these parameters and I tried to investigate the validity of the method of testing. For these purposes I made use of a computer model of human respiration and circulation: MACPUF (Dickinson 1977). First I studied research literature on the subject of work tests, after which I tried to simulate the same tests with the model. Then I compared the results with results from research literature, and in case of deviations I tried to find possible faults in the model, again comparing it with literature. Finally I simulated the tests once more and I compared the results with results from tests done at B.G.D./P.T.T. and with the results of others' research.

II THE ANAEROBIC THRESHOLD.

Each form of exercise is associated with an increase of energy expenditure in the muscle. During short lasting exercise, the energy requirements of the working muscle can be met by the intracellular present energy rich phosphate compounds: ATP and CREATINE PHOSPHATE.

CREATINEPHOSPHATE + ADP -> CREATINE + ATP
ATP -> ADP + PO4 + 33600 JOULE <-> AMP + 2 PO4 + 33600 JOULE PER MOL ATP

The available stores of these compounds wich amount to 20 micromoles/gr. fresh muscle, can cover a work period of up to 20 seconds (see fig. II-1).

If the exercise periods are longer,immediate resynthesis of the energy rich phosphates is necessary, since only ATP can be used directly for muscular contraction.

There are two pathways for the resynthesis of ATP and CREATINEPHOSPHATE:

1 aerobic -oxygen is the ultimate hydrogen acceptor in the degradation of energy delivering substrates.

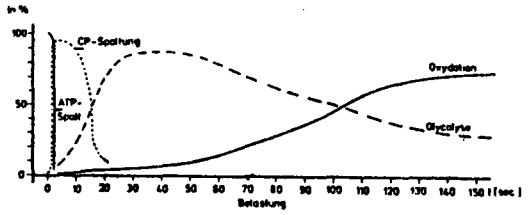
2 anaerobic -degradation of energy delivering substrates without the participation of oxygen. Glucose and glycogen are metabolized, without the use of oxygen, resulting in production of LACTATE (see fig.II-2). This is often assumed to be the only anaerobic pathway. Very little is known about other pathways of quantitatively minor importance with end products ALANINE and GLYCEROL-1-PHOSPHATE and of possible effects of accumulation of these substances on endurance capacity.

In light and moderate exercise, resynthesis of ATP and CR-P will be done aerobically as this has important advantages over the anaerobic pathway; e.g. more ATP/glucose molecule, no lactate production and therefore no pH decrease. For the aerobic resynthesis, extra oxygen has to be delivered to the muscle cells, since only 6 to 8 microlitres of oxygen per gram tissue are stored. This increased delivery is made possible by an increased blood flow and by increased ventilation. As well as for increased oxygen delivery, increased blood flow in prolonged work is also neccesary for:

-increased substrate supply e.g. glucose,lipids, ketone bodies, amino acids, electrolytes.

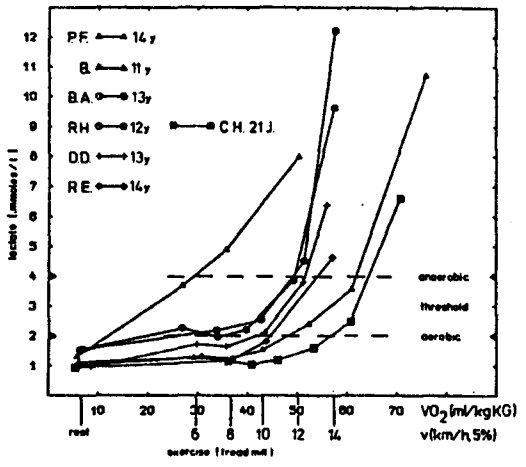
-removal of metabolic waste products as CO2, lactate, pyruvate,ammonia.

-control of local temperature; only a part of metabolic energy production is used for work or chemical reactions; the rest of the energy is lost as heat.



Der Anteil der energieliefernden Substrate an der Energiebereitstellung ist in Abhängigkeit von der Intensität und der Dauer der körperlichen Belastung verschieden. Bei einer starken körperlichen Belastung werden zunächst die energiereichen Phosphate (ATP und CK) ausgeschöpft, die kurzfristig starke muskuläre Belastungen unterhalten können. Mit Beginn der Belastung werden jedoch auch schon Energien über die Glykolyse anaerob bereitgestellt, die ihr Maximum nach 20–40 Sekunden erreichen. Langsam ansteigend kommen die aeroben Vorgänge mehr und mehr zum Tragen und werden schließlich zur fast ausschließlichen Energiequelle für die muskuläre Arbeit

Fig. II-1.
Contribution of energy delivering processes to energy requirement in constant load work (Keul). (1978)



In Abhängigkeit von der Leistungsfähigkeit kommt es im Einzelfall bei einer niedrigen oder hohen Sauerstoffaufnahme/kg Körpergewicht zu einem Anstieg des Laktatspiegels; je früher der Laktatspiegel ansteigt, desto schneller kommt es zum Arbeitsabbruch

Fig. II-3.
Anaerobic threshold determination at 4 mmol/litre concentration value (Keul 1978)

What happens if a person performs work at different constant loads?

At low constant work loads oxygen supply will be sufficiant for body needs. Energy is therefore produced aerobically (see fig. II-2) in the combustion of carbohydrates fats and proteins. Minute ventilation, oxygen consumption, CO2 production and heart rate will increase linear to work load, to meet metabolic needs.

At moderate to heavy constante work loads, the body will not be able to meet oxygen demands immediately. When ATP and CR-P stores are depleted, resynthesis has to be done by anaerobic metabolism (see fig.II-1). This results in the synthesis of lactate. After some time, oxygen supply will become sufficient and anaerobic metabolism will decrease. The increased lactic acid concentration will return to resting values, for the lactate is metabolised to CO2 and H2O in the heart and other muscle cells, or used as a precursor of glycogenesis in the liver. The temporary lactate concentration elevation will result in a temporary increase of the respiratory quotient (VCO2/VO2), as lactate, being a stronger acid, will force bicarbonate stores to split into H2O and CO2, resulting in an extra CO2 removal in the lungs (VCO2). A second factor accounting for some temporary increase in respiratory quotient is the temporary shift to a relatively higher percentage of carbohydrate combustion (see chapter III-4 R.Q.).

At very heavy work loads, the oxygen supply will not be able to meet metabolic oxygen needs. Therefore anaerobic metabolism will stay active, resulting in a definite increase in lactic acid concentration. This causes a decrease in HCO3- concentration, a decrease of blood pH, an increase in VO2 and in R.Q.. There will be a shift to 100 percent carbohydrate combustion (R.Q.->1.) as this provides more energy per oxygen molecule than fat or protein combustion. After some time, glucose stores will become depleted and slowly relatively more fat will be combusted.

The highest work rate at which after some time oxygen supply is still able to meet metabolic oxygen demands is called the ANAEROBIC THRESHOLD. This is equivalent to maximal endurance capacity, as it has showed in experiments to be the maximal work rate a person is able to perform for longer periods.

Anaerobic threshold can also be determined in ramp load tests. In these tests, with continually increasing work load, we also find a first part in which oxygen supply is sufficient. Then at a certain point anaerobic metabolism starts to compensate energy shortness as oxygen supply is not sufficient anymore. This results in an increase of lactate level and coincides with non-linear increase of respiratory minute volume (VE) respiratory quotient and carbon dioxide production. This has been defined by WASSERMAN et. al.1973, 1975 as the anaerobic threshold.

Comparing these results (A.T. determined at the point of first increase in lactate level) with results from constant load tests, values for anaerobic threshold in ramp tests are rather low. The explanation may be that these first signs of anaerobic metabolism in ramp tests would disappear when work is continued at the present work load, as they would in a constant load test. There-

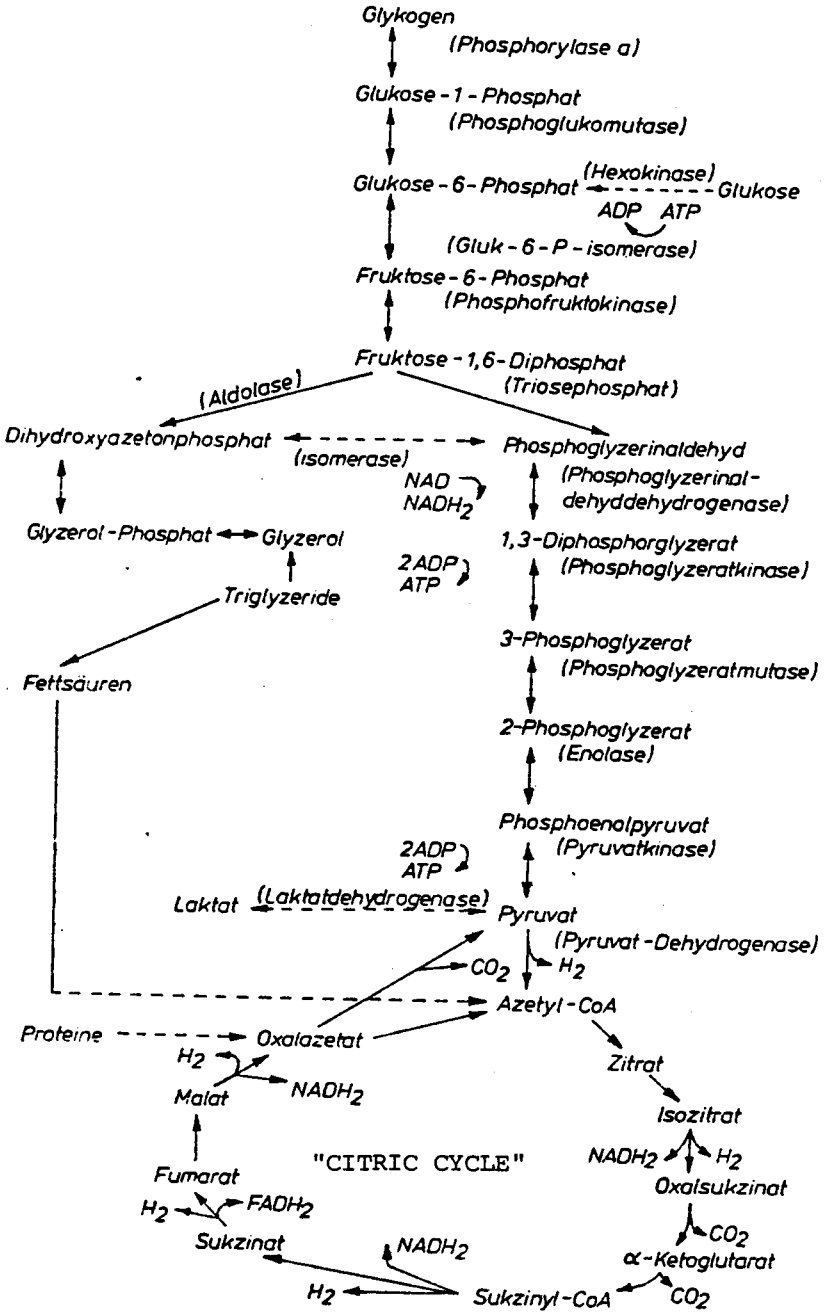


Fig. II-2. Simplified presentation of muscle metabolism, aerobic, entering the Citric Cycle, or anaerobic, resulting in the formation of Lactate (Senger 1977)

fore, according to anaerobic threshold definition, the anaerobic threshold would not yet be reached.

This problem finds its main cause in the time constants of the involved body systems (VO2, VE, lactate metabolism). In all tests there is a delay between the load change and the body reaction to this change. The presence of such a delay will result in an oxygen shortness and thus in lactate formation even below the A.T.. It depends on the way of testing if this delay remains present (ramp test with large increments) or disappears (constant load test).

For this reason other authors (KINDERMANN 1979, KEUL 1978) stated that in ramp test the anaerobic threshold would be reached when lactate concentration reaches the steep part of its increase, empirically determined at a lactate concentration of 4 mmol per litre blood (see fig. II-3). This definition is more in accordance with the A.T. definition in constant load tests.

III MACPUF, THE MODEL.

Macpuf is a computer model of human respiration, written in FORTRAN, incorporating lungs, airways and blood circulation. It was designed to acquire a simulation facility for medical students instruction, for clinical problem solving, individual study and research.

Pulmonary gas exchange is based on a RILEY-three-compartment model (RILEY 1949). In one compartment, blood flow and ventilation are ideally matched. Of the other two, one is ventilated but not perfused (dead space) and one is perfused but not ventilated (venous admixture). The three-compartment model gives a representation of oxygen transport from the alveoli into the venous blood and of carbondioxide in return, thus determining arterial gas tensions and composition. The arterial blood passes round to the tissues, where, according to metabolic needs, oxygen is extracted and carbondioxide is produced. Then, the now venous blood returns to the lungs (see fig. III-1).

The carriage of gases in the blood is governed by the mathematical expressions of KELMAN, describing oxygen and carbondioxide dissociation curves. Natural ventilation is controlled by known influences: partial arterial oxygen pressure (PaO2), partial arterial carbondioxide pressure (PaCO2) and by an additional central neurogenic drive, which has been arbitrarely made proportional to oxygen consumption . In case the tissues acquire an oxygen debt, proportional anaerobic respiration results in the generation of lactic acid and carbondioxide, with appropriate changes in pH and with appropriate effects on other mechanisms.

The basic model uses values representative for a 70 kg. young adult,who at rest, consumes 250 cc. oxygen per minute (STPD). Standard the model computes at each 10 sec. (changable) interval the tensions, contents, and total amounts of oxygen and carbondioxide in the alveoli, in idealized pulmonary capillary blood, in arterial blood, in the tissues generally, in the brain, and in mixed venous blood returning to the lungs (see fig. III-2). Arterial bicarbonate, alveolar ventilation, expired Respiratory quotient, tidal volume, effective dead space, effective venous admixture, predicted cardiac output and cerebral blood flow are also computed. A test is made for lethal changes in pH and blood gases at each iteration step, and if these limits are transgressed, "death" results. At the end of each run, appropriate symptoms and nursing reports are issued. Any changes in the model can be made in an interactive dialogue between user and programme before each run. There is also the possibility of storage of the present state of the simulated subject, so that several tests starting with the same values can be done.

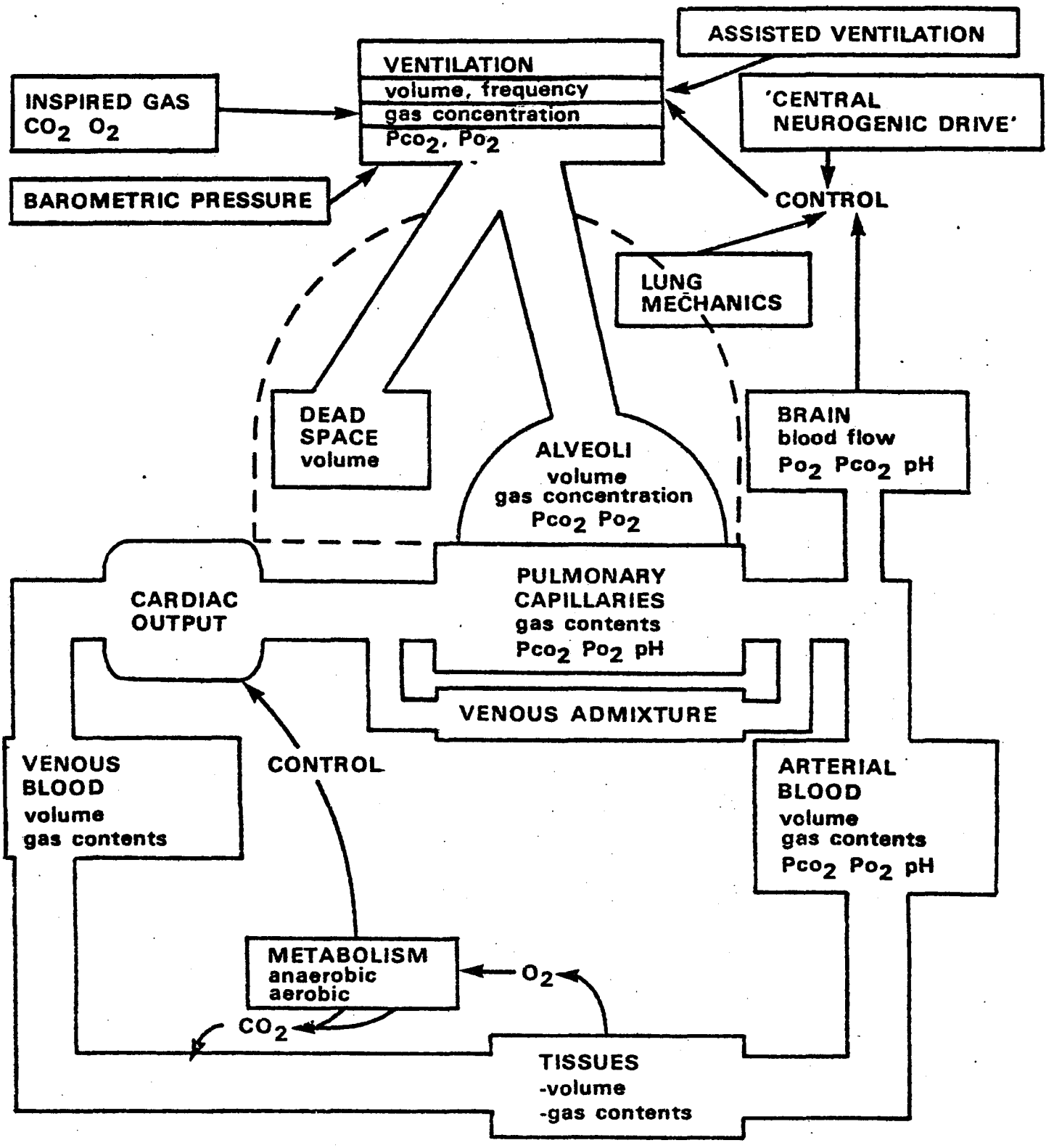


Fig. III-1. Principal components of MACPUF:

III-1 INPUT PARAMETERS

To exchange information between user and model, Macpuf provides the possibility of an interactive dialogue. With this it is possible to manipulate the simulated person and his environment. Further, run parameters can be changed to alter integration interval, run time and type of output. For Anaerobic Threshold simulation the most important input factors are:

A intergration interval.
B sample frequency.
C work rate.
D work pattern.

A INTEGRATION INTERVAL.

For accurate simulation results it was necessary to test the model for various intervals of time. Normally a 10 sec. interval is used; but it soon appeared that in excercise simulations with its high Ventilation and cardiac output values, the 10 sec. interval is far too long to get truly realistic results. The model responds at high exercise values simulated with 10 sec. integration intervals with error messages due to a too long integration interval. This was prevented by reducing the time interval to one sec.

To get more background information on this problem a study was made of the behaviour of a simple first order process with several combinations of integration methods and intervals. (this was done in C.S.M.P. on a Dec. 10 Computer.). From the information I obtained from these simulations, in combination with Macpuf using the Euler integration Method, I concluded that a 1 sec. integration interval would be accurate enough for my simulation purposes.

B SAMPLE FREQUENCY.

The second important input factor is the frequency of output values, the sample frequency. Macpuf, in its original state, gives an output of the most important variables at every itteration interval, and a list of an even greater group after each run. For our purposes two things are important in relation to the output frequency for a good representation of the physiological processes.

- which sample frequency is needed for comparing results with literature?
- is this frequency allowed in macpuf, taking account of model construction, integration interval and integration Method?

In the literature we find two main methods of collecting measurements:

- breath by breath registration.
- sampling at a certain time interval (e.g. 1-4min.).

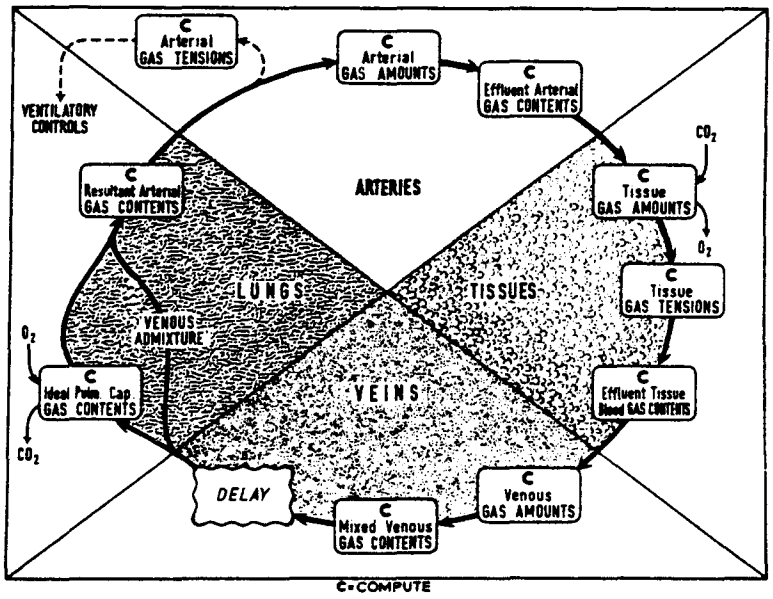


Fig.III-2. Summary of main computational processes completing the circulation. (Note that the computation in each compartment involves a new estimate of gas amounts and finally of gas concentrations which are passed on to the next compartment in sequence) (Dickinson 1977)

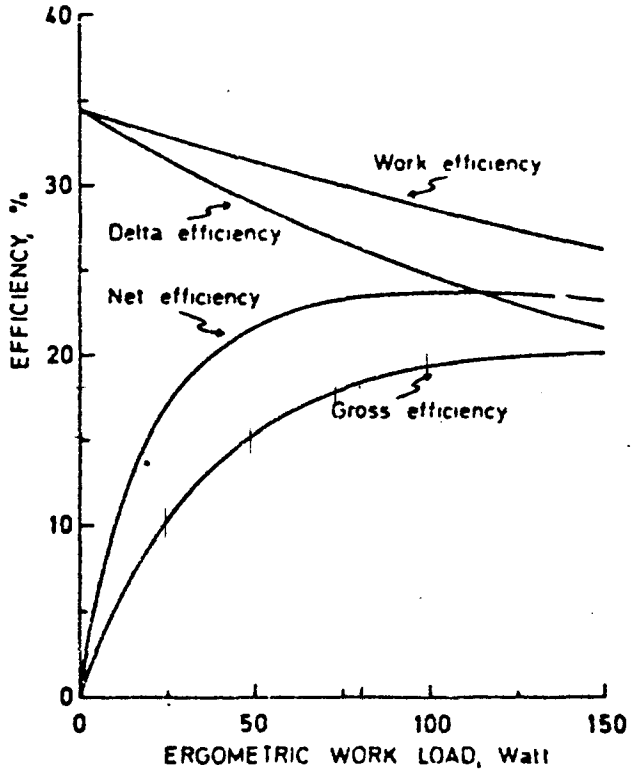


Fig. III-3. Effects of work load on efficiency calculations in steady-rate cycle ergometer exercise (Hesser 1977)

The representation of ventilation in Macpuf primarily assumes that the interval between successive computations is as long as the duration of one complete breath. Thus, whenever respiration rate or integration interval is changed, the assumed equality disappears. In spite of the fact that this potential inaccuracy is reduced by incorporation of a function of fractional time (=integration interval) and respiratory rate, most accurate results can only be expected when the itteration interval is the same as the the time of one breath. In my simulations, respiration rate shows changes of more than 300 per cent when work rate is increased from rest to 300 watt at a constant integration interval. For this reason I doubt the validity of Macpuf for breath by breath simulations. One more factor concerning the validity of breath by breath measurements is of course the integration interval and method that is used. At a respiration rate of 30 and fractional time of 1 sec., breath by breath registration would result in sampling every second computation. It is questionable if this is acceptable for factors closely related to breathing, e.g. PaO2, PaCO2.

Sampling at certain time intervals as suggested in literature does not create any problems regarding model construction, integration interval and methods; given sample intervals of 1 min. or more and work increments up to 25 Watt/min. As described in the paragraph on the integration interval, I also did some simulations on a first order process for a better understanding of the problems mentioned above.

C WORK RATE.

In literature, work rate is usually given in WATTS or KPM/MIN. These values cannot be used as input for MACPUF. The model expresses work rate as percentage of resting metabolism energy use. This demands a knowledge of the relation of external work and metabolic energy expenditure. External work is usually measured in ergometer tests (bicycle,treadmill) ,which is a rather direct method. Metabolic energy use (internal work) has to be calculated indirectly from oxygen consumption. The relationship between external and internal work is called EFFICIENCY .

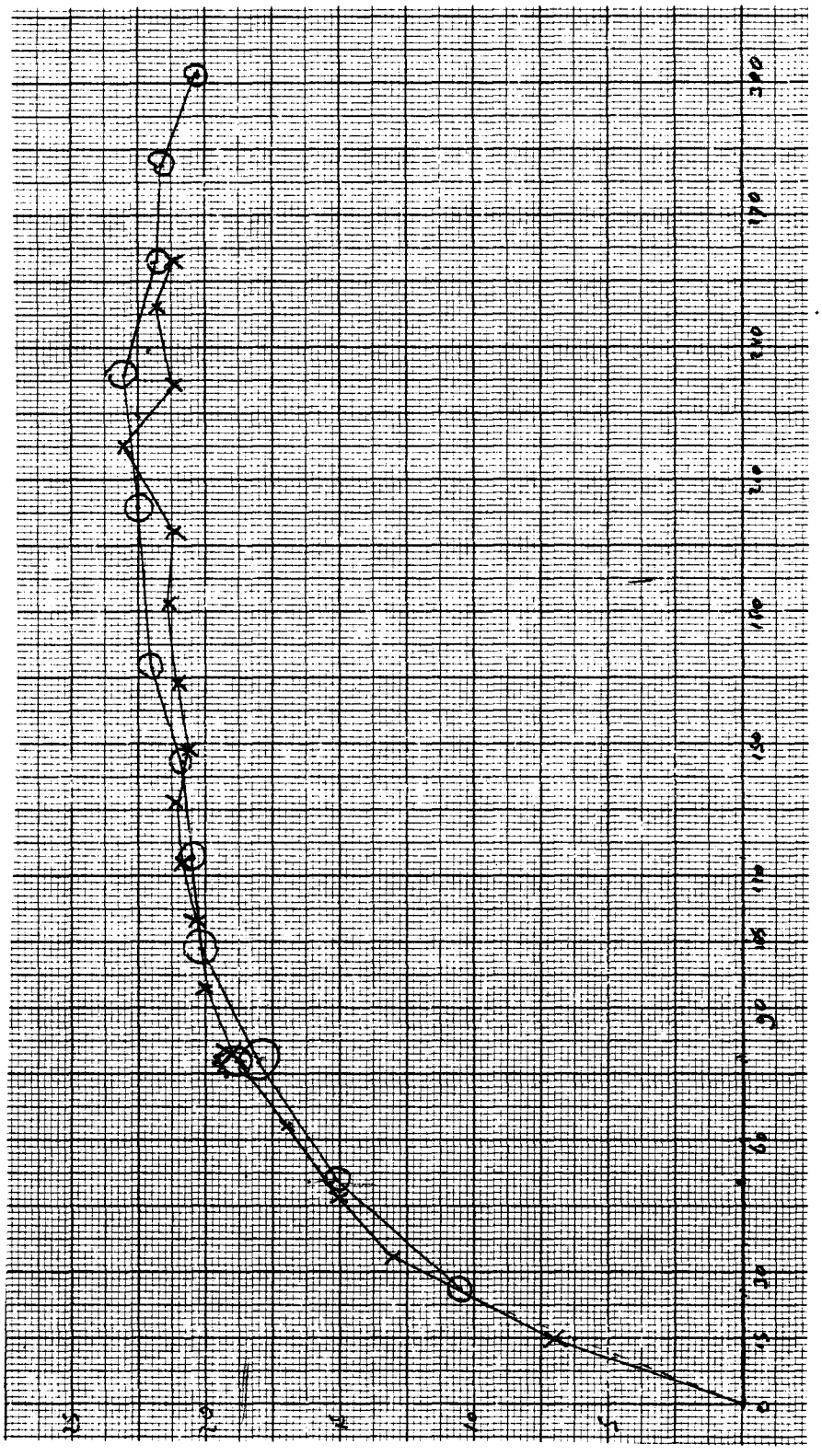
EFFICIENCY

According to HESSER 1977 there are four ways of determining efficiency, which will vary depending on the factor used for correction of baseline VO2 (resting oxygen consumption). These four ways are :

-GROSS EFFICIENCY (no base line correction),
EFFICIENCY=EXTERNAL LOAD/INTERNAL ENERGY EXPENDITURE

-NET or MECHANICAL EFFICIENCY (resting metabolism as base line correction),
EFF.=EXTERNAL LOAD/(INTERN. EN. EXP.-RESTING ENERGY EXP.)

-WORK EFFICIENCY (zero load pedalling as base line correc-



Work load (WATTS)

Efficiency

Fig.III-4. Work rate-efficiency relation; data from B.G.D./P.T.T.

tion),
EFF.=EXT. LOAD/(INT. EN. EXP.-0 LOAD PEDALLING ENERGY EXP.)

-DELTA EFFICIENCY (ratio of delta work, accomplished to delta energy expended).
EFF.=DELTA EXTERNAL LOAD/DELTA INTERNAL ENERGY EXPENDITURE

from fig. III-3 we can see that efficiency values are dependant on efficiency definition. As i used, besides literature, results from exercise tests at B.G.D./P.T.T., I preferred to calculate efficiency in their way: GROSS EFFICIENCY. In these B.G.D. tests, metabolic energy use was calculated from oxygen consumption with the formula:

Metabolic energy use= (0.23*R.Q.+0.77)*5.873*V02*60
(V02 in0litres/min.)

The only value in MACPUF with which I could use this formula, was the resting oxygen consumption of 250 cc. which was equal to a metabolic rate of 100 percent (compared with resting metabolism). Calculation with the formula, mentioned above resulted in: 100 percent of resting metabolism=84.04 Watts internal energy use,(R.Q.=0.8) or: 1 watt internal energy use=1.19 percent of the resting metabolism. With this information, metabolic energy use and external work rate can be represented as a percentage of resting energy use; and this can be used as input for macpuf.

To create the possibillity of giving input values in watts external energy production, the following programme part was inserted in subroutine DEADY:

input:
xxx=work rate in watts
WRATE=XXX
call functn (WRATE,EFFIC,FUN3,10)
a function generator for the relation of workrate and efficiency values (see fig. III-4); data stored in array fun3 (10 points)
XXX=(WRATE*1.19*100)/EFFIC
calculation of XXX=metabolic energy use in percentage of resting metabolism
IF (WRATE.LT.3.0) XXX=100.
Preventing calculation errors for very low external loads and for rest (WRATE=0)

As there was just one reference point in MACPUF,it should be noted that these calculations were made without taking account of respiratory quotient changes caused by changes in food utilisation at higher work rates. As we can see in the formula mentioned above, these changes will influence the relation between internal and external energy use. As we are going to discuss in chapter TISSUE RESPIRATORY QUOTIENT, several authors (ASTRAND 1970, BOCK 1928) found that in exercise, tissue respiratory quotient will change from about 0.7 to 1.0, as a result of the switchover to 100 percent glucose utilisation. This food utilisation change might result in oxygen-energy relation changes up to 6 a 10 percent. Energy

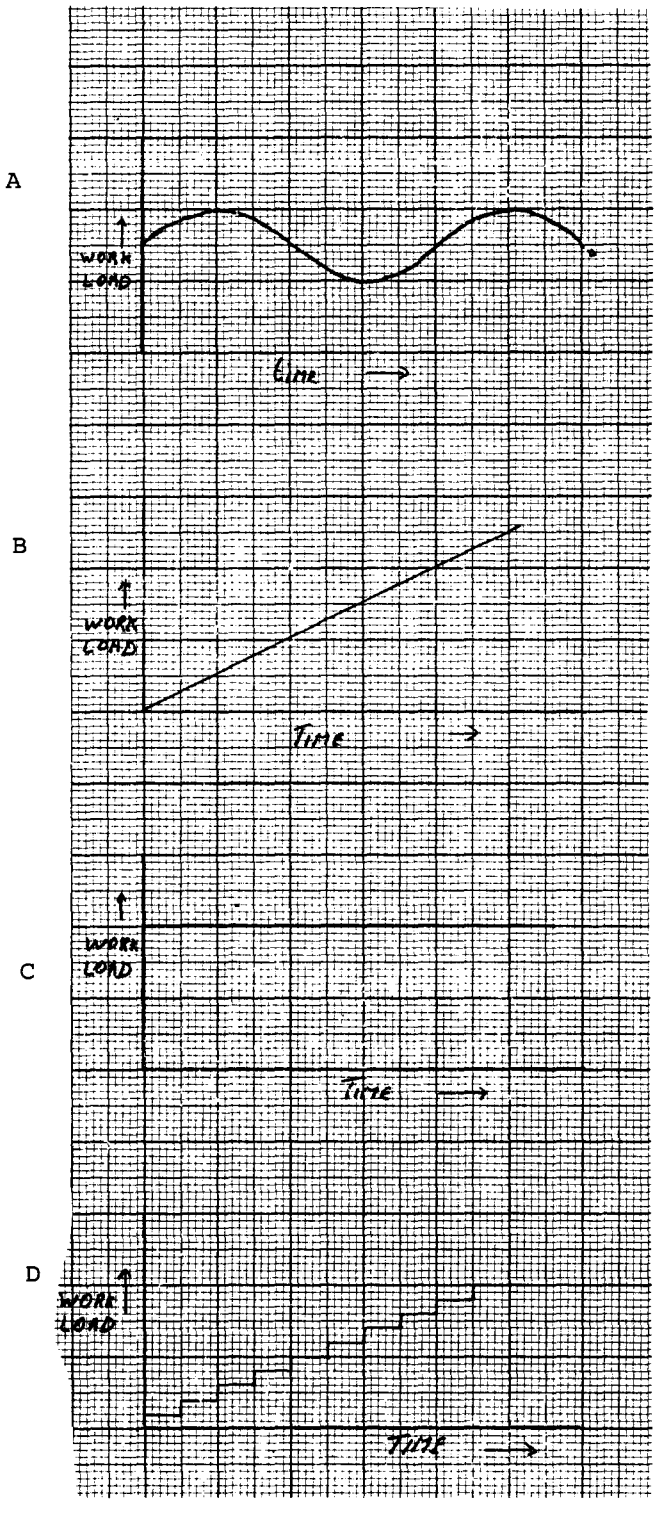


Fig.III-5 A sinusoidal, B ramp, C constant, D incremental-work pattern.

derived from food:

-100 percent proteins 18.76 joule/litre oxygen.
-100 percent fat 19.47 joule/ litre oxygen.
-100 percent glucose 20.98 joule/litre oxygen.

D WORK PATTERN.

The last important input parameter is the work pattern. In literature we find three often used work patterns (see fig. III-5 A-C):

-a- sinusoidal work
-b- ramp function work
-c- constant load work.

From sinusoidal work load tests, dynamic characteristics of physiological responses to work can be analyzed. However, the procedure of this analysis is a rather complex and time consuming operation. For this reason I preferred the use of constant load and ramp function work. In literature it is suggested that, from these two, the ramp function test has, for my purposes, an advantage above the constant load work test: more information can be obtained from one ramp test than from one constant load test. One important factor is the visibility of linearity. For visualising of linearity we would need many constant load tests, but just one ramp test. However, constant load tests were used for some simulations of literature, and also to give an extra criterion for checking the model if it has already been confirmed by ramp tests. For practical reasons the ramp function test was presented as an incremental test (see fig. III-5 D).

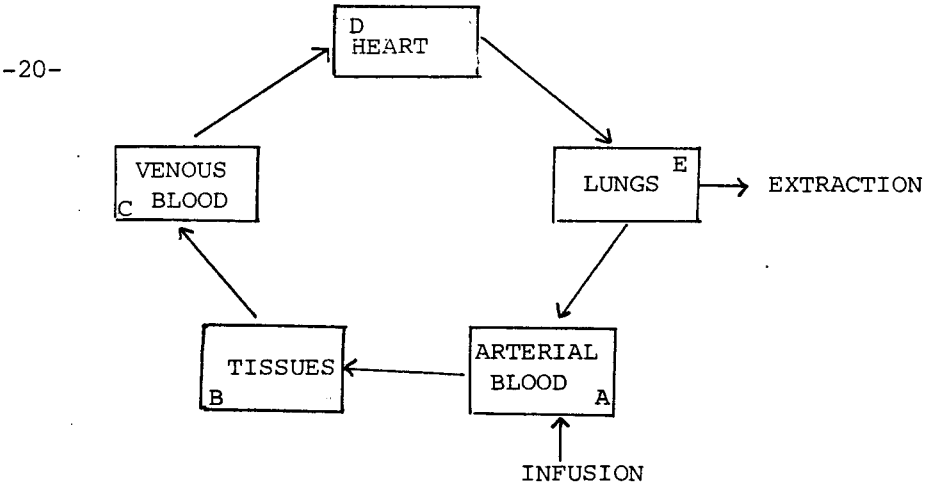


Fig. III-2-1. Presentation of circulation.

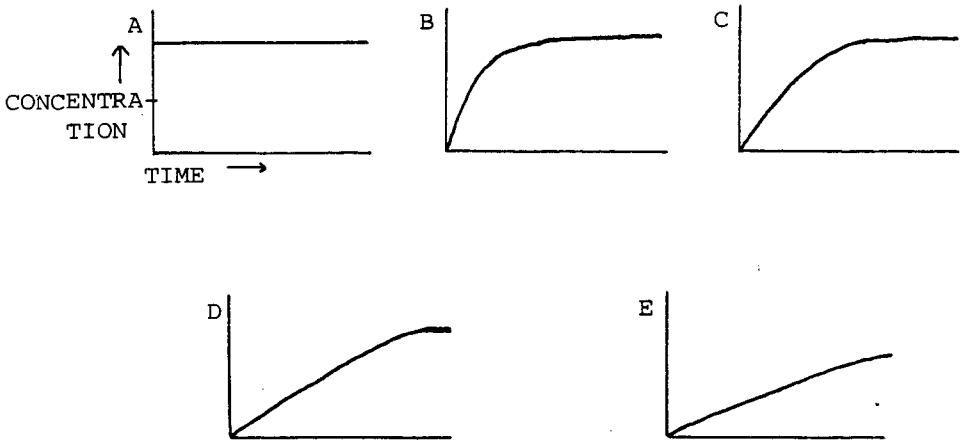


Fig. III-2-2. concentration transient in circulation without Delay.

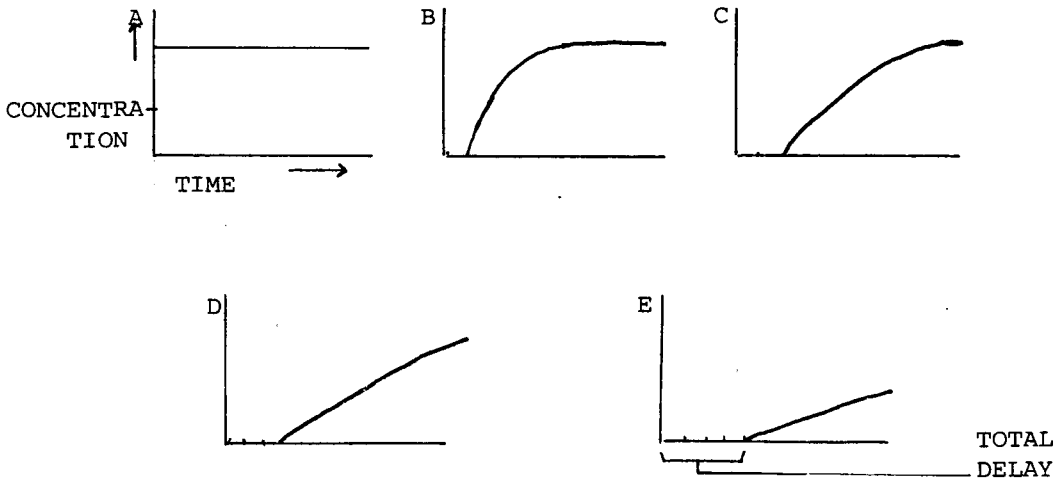


Fig. III-2-3. concentration transient in circulation with Delay.

III-2 TIME DELAY IN BLOOD CIRCULATION.

A model of blood circulation could be presented as in fig. III-2-1 which is principally equal to the circulation representation in macpuf. Any change (e.g. an infusion of a substance in the arterial blood which is removed from the blood in the lungs) will be transferred through the circulation. The substance concentration will change in the compartments as presented in fig. III-2-2 if we would compute concentrations in all compartments, any change in compartment one (arterial blood) will be transferred to compartment five (lungs) in the first integration interval (although the change in five will be much smaller than the change in one). The amount and time of substance arrival wil be influenced by the duration of the integration interval. The result is that any substance could pass the whole circulation network and arrive (in a much smaller concentration) in the same compartment in the second integration interval, which can be 10 seconds as well as 1 second. This is not realistic.

A realistic circulation time (arm vein to same arm vein) would be an average of 25 seconds (DICKINSON 1977). Not 60 seconds as one would conclude of 5 litres blood content and a cardiac output of 5 litres/minute; there are distant body regions, contributing little to whole body oxygen consumption, with very slow blood flow. So there also must be parts of the circulation which are more important for oxygen consumption and in which circulation is faster. Realistic presentation of our circulation model with a circulation time of 25 seconds is presented in fig. III-2-3. Dr. Dickinson has chosen in MACPUF for a total circulation time at rest of 20 seconds. The original presentation of the time delay in MACPUF is:

```
      SUBROUTINE DELAY
        COMMON KT,KL,INI,NW1,NW2,JKL,NPRT,LDISP,KA,ITRIG(73),NEOF,NW
        COMMON NFLAG,J3,ISPAR,NA,NB,NC,ND,NE(8)
        COMMON NARTI,MT,K2,K4,INDEX
        COMMON T1(30),VO2CT,T2(29),VC2CT,T3(19),FT,T4(4),VC3MT,T5(6),
     X COADJ,T6(3),TC2PR,T7(23),TDLAY(40)
C DELAY LINE FOR CIRCULATION OF GASES ETC
      NFT=IFIX(13.2*SQRT(COADJ*FT))
      IF (NFT-10) 110,110,100
  100 NFT=10
  110 M=INDEX+NFT-1
      DO 140 I=INDEX,M
      N=I
      IF (N-10) 130,130,120
  120 N=N-10
  130 TDLAY(N)=VO2CT
      TDLAY(N+10)=VC2CT
      TDLAY(N+20)=VC3MT
  140 TDLAY(N+30)=TC2PR
      N=INDEX+NFT
      IF (N-10) 160,160,150
  150 N=N-10
```

```
  160 VO2CT=TDLAY(N)
      VC2CT=TDLAY(N+10)
      VC3MT=TDLAY(N+20)
      TC2PR=TDLAY(N+30)
      INDEX=N
      RETURN
      END
```

its mechanism, based on the formula:

```
NFT=IFIX(13.2* SQRT (COADJ*FT))
COADJ=CARDIAC OUTPUT      FT=INTEGRATION INTERVAL
```

shortens or raises the delay time when cardiac output is raised, respectivly shortened, and it keeps delay time constant when the integration interval is altered.

This representation of circulation time is rather different from the presentation in fig. III-2-3. The delay is not present in all parts of the circulation but just at one point (see fig. III-2). Dr. Dickinson chose for a delay at the venous compartment. Although this is a strong simplification, it produces good results and saves very much computer time compared to a delay in all compartments.

The subroutine delay was designed for integration intervals between 2 and 10 seconds. As I was going to use 1 second integration intervals I had to alter subroutine delay, preventing an unwanted shortening of the delay time. In order to keep the structure of subroutine delay the same, I first changed array TDLAY from 40 to 80 compartments, also adapting the rest of the subroutine to this amount. When I was inspecting the results, I noticed a difference between values calculated in the original model and values given as example in the book. In consultation with Dr. Dickinson (see appendix) I decided to alter subroutine delay, changing the formula for NFT, and creating the possibillity of the usage of 1 second integration intervals. The description of the new programme part is:

```
      SUBROUTINE DELAY
        COMMON KT,KL,INI,NW1,NW2,JKL,NPRT,LDISP,KA,ITRIG(73),NEOF,NW
        COMMON NFLAG,J3,ISPAR,NA,NB,NC,ND,NE(8)
        COMMON NARTI,MT,K2,K4,INDEX
        COMMON T1(30),VO2CT,T2(29),VC2CT,T3(19),FT,T4(4),VC3MT,T5(6),
     X COADJ,T6(3),TC2PR,T7(23),TDLAY(80)
C DELAY LINE FOR CIRCULATION OF GASES ETC
      NFT=IFIX(32.2*FT*SQRT(COADJ))
      IF (NFT-20) 110,110,100
  100 NFT=20
  110 M=INDEX+NFT-1
      DO 140 I=INDEX,M
      N=I
      IF (N-20) 130,130,120
  120 N=N-20
  130 TDLAY(N)=VO2CT
      TDLAY(N+20)=VC2CT
```

```
      TDLAY(N+40)=VC3MT
  140 TDLAY(N+60)=TC2PR
      N=INDEX+NFT
      IF (N-20) 160,160,150
  150 N=N-20
  160 VO2CT=TDLAY(N)
      VC2CT=TDLAY(N+20)
      VC3MT=TDLAY(N+40)
      TC2PR=TDLAY(N+60)
      INDEX=N
      RETURN
      END
```

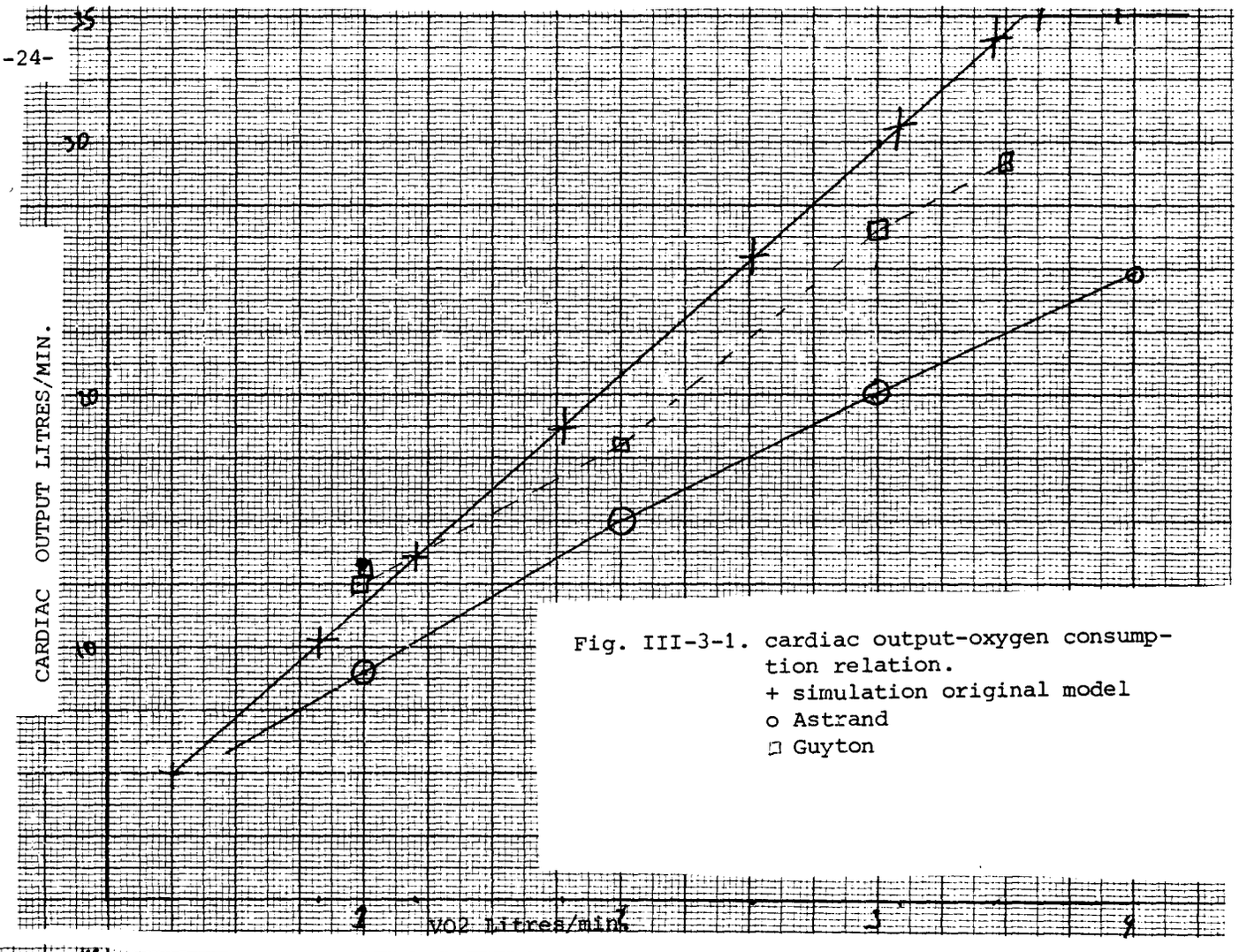


Fig. III-3-1. cardiac output-oxygen consumption relation.
+ simulation original model
o Astrand
□ Guyton

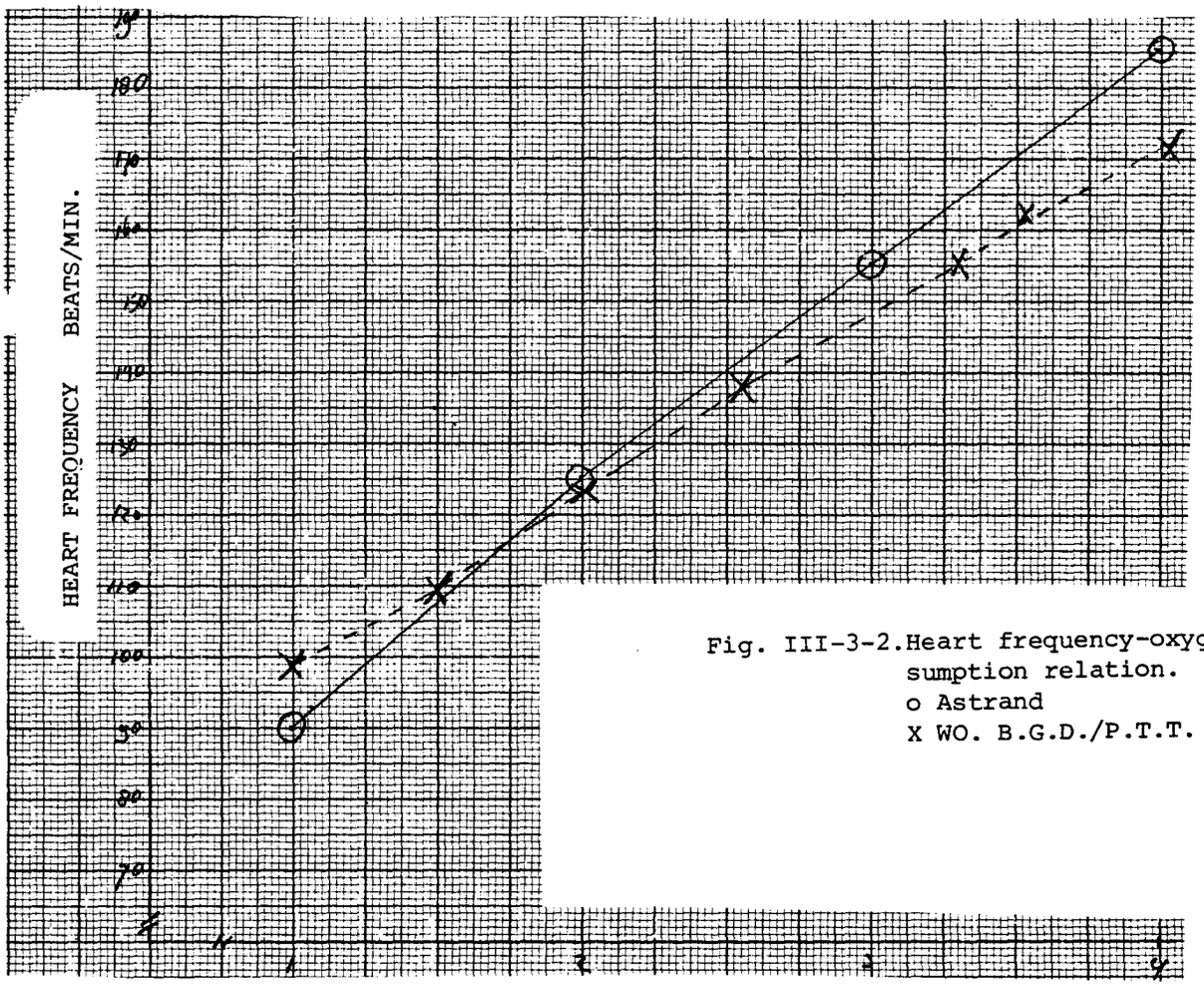


Fig. III-3-2.Heart frequency-oxygen consumption relation.
o Astrand
X WO. B.G.D./P.T.T.

III-3 THE CARDIAC OUTPUT.

Comparing some ramp function work load simulation results with values from literature, it struck me that, in work, cardiac output was clearly higher in Macpuf simulations. E.g. at a certain VO2, Astrand (1970), Guyton (1971) and also Dickinson (1977) give much lower cardiac output values than Macpuf. (fig.III-3-1). The first question was as to whether this difference is a result of differences between ramp load measurements in Macpuf, and possibly a sum of constant load measurements by Astrand, Guyton and Dickinson. As the authors do not give any information about their way of measuring, I tried to investigate if their values differ from other known cardiac output values, obtained from ramp load exercises.
On account of a shortage of cardiac output values, I had to use heart frequency to compare Astrand and Guyton values with others. For this I used values of BGD/PTT tests and values from BUCHBERGER (1979). If the difference between ASTRAND and GUYTON on the one hand and MACPUF on the other would have been caused by a difference in work pattern, one would expect that, when comparing ASTRAND and BGD/PTT ramp test values, the values of ASTRAND for heart rate would also be lower, than the BGD/PTT values. This is certainly not the case. (fig. III-3-2). From this I conclude that the MACPUF values for cardiac output really are too high.
The next question is of course, what possible causes there might be for this deflection. Two possibilities are deviations in:

-1- the oxygen content of the blood
-2- the cardiac output-oxygen consumption relation

-1- this might be caused by the influence of dissociation curves of oxygen and carbondioxide in the lungs and the tissues. But the lungs dissociation curves are very well known (KELMAN), and although tissue dissociation curves are more critical, they would be very difficult to work on, as there is very little research literature available on this item. Another cause could be the Haemoglobine concentration in the blood. MACPUF uses a value of 14.8 gr/100 ml. for men and 13.5 gr/100 ml. for women. GUYTON gives an average value of 15 gr/100 ml. with maximal values (after acclimatisation at great heights) of 22 gr/100 ml. The MAC GRAW-HILL encyclopaedia of science and technology gives a value of 16 gr/100 ml. for men and 14 gr/100 ml. for women. So, one might say that haemoglobine concentration in MACPUF is a little too low. Simulations with a haemoglobine concentrations of 15 to 16 gr/100 ml. result indeed in a lower cardiac output, but the effect is too small to cover the difference between MACPUF and literature values.

-2- as the physiological changes do not solve the problem, we should take a look at the models oxygen consumption-cardiac output relation. The description of cardiac output is given as:

```
C(7)= CONSO*PD*.00081*(TEMP-26)**1.05
C(9)=(C(7)-CONSO)*.01
C(8)=(30.-PEEP*5/ELHST)*.0016*CONOM*(TEMP-12.2)
C(16)=CO*.01          Y=RO2CT*.056
```

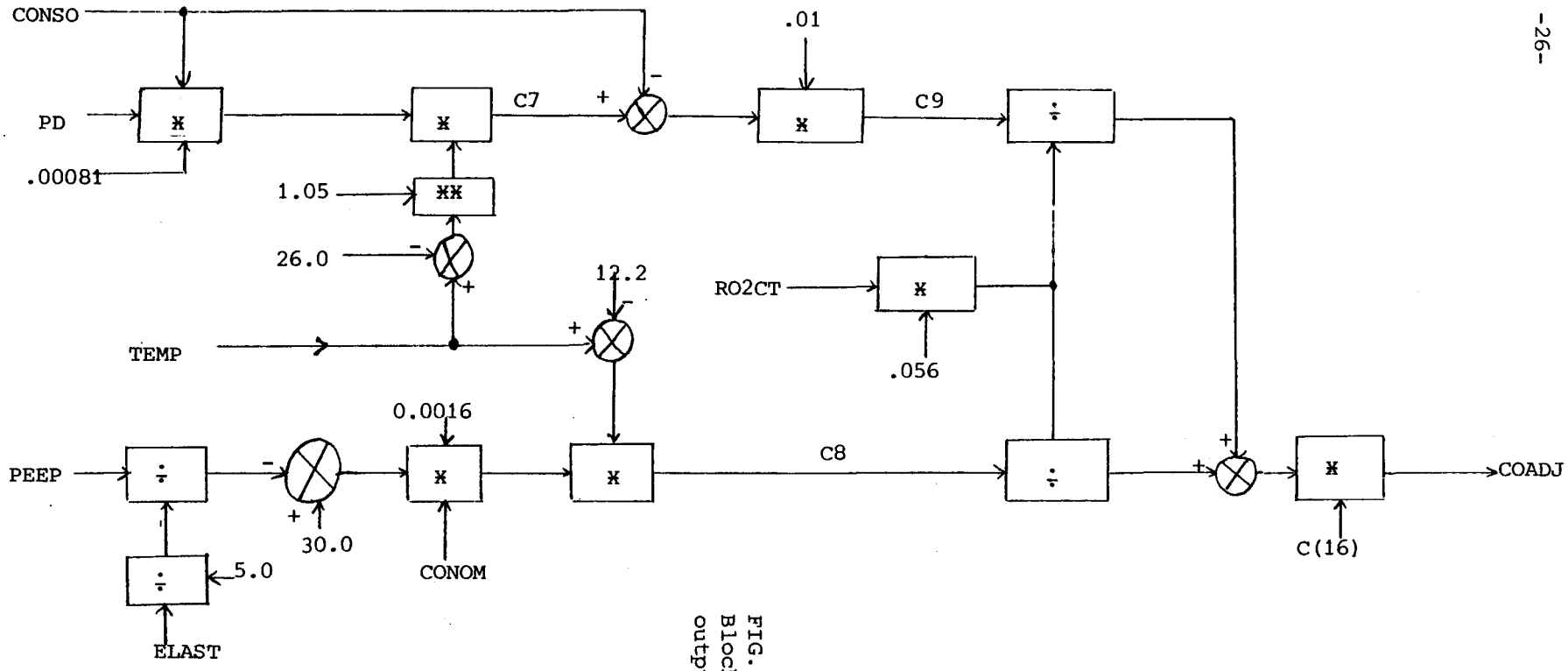


FIG. III-3-3
Block scheme of cardiac output representation.

COADJ=(C8/Y+C9/Y)*C16
CONSO= RESTING OXYGEN CONSUMPTION (250 CC.)
PD=METABOLIC RATE
TEMP= TEMPERATURE PEEP=POSITIVE END EXPIRATORY PRESSURE
ELAST=ELASTANCE , CONOM=RESTING CARDIAC OUTPUT (5 L/MIN.)
RO2CT=ARTERIAL OXYGEN CONTENT, CO=CARDIAC FUNCTION AS
PERCENTAGE OF NORMAL (100)
COADJ=EFFECTIVE CARDIAC OUTPUT (5 L/MIN.)

For better visibility of its mechanism, i presented the programme part as a block scheme. See fig. III-3-3..

If we take a look at fig. III-3-2, we can see that the difference between the curves of the cardiac output is mainly a difference in angle. So we might say that delta cardiac output divided by delta oxygen consumption is too high in MACPUF. In fig. III-3-3 we can see that delta oxygen consumption is represented as:

C(7)-CONSO.

the formula of cardiac output could, (in our case) be reduced as follows:

COADJ=DAMP(1/Y*(C8+C9)*C16)
DAMP presents a function for damping of fast changes (see programme).

As Y=RO2CT.056, and RO2CT=19 (RO2CT is not changed very much in exercise as it is arterial) y is approximately one. C16 has also a value of one and c8 remains constant at constant temperature. This results in:

COADJ=DAMP(CONSTANT+0.01 DELTA OXYGEN CONSUMPTION).

Literature values for delta cardiac output/delta oxygen consumption differ from 5 to 6 (ASTRAND) to 6 to 7 (GUYTON). The present model value is about 9 . Reducing the model value to 6 means reducing delta cardiac output/delta oxygen consumption ratio by 2/3. In the formula this would be accomplished by:

COADJ=DAMP(CONSTANT+0.067 DELTA OXYGEN CONSUMPTION).

this has the same effect as changing the expression for c(9):

C(9)=(C(7)-CONSO)*.0067.

Simulations with the new formula produce results, similar to literature: the DELTA CA-OUT/DELTA OXYGEN CONS. ratio is now about 6. One more cardiac output factor that should be kept in mind, when discussing simulation results, is the presence of a maximal cardiac output. When the maximal cardiac output is reached it shows great influence on other physiological factors, as blood lactate concentration and minute ventilation. In the original model it is reached, simulating high exercise values. It is determined in the formula:

CAMAX.=(210-0.65*AGE)*.0008*HT.

so it is only dependant on the age and the height of the tested subject (and on the sex as is defined else where). In reality there certainly are more factors that would be of influence on maximal heart output, e.g. the state of training can have a great influence ("sport heart"). From this it is evident that the ca-max. should be handled carefully as it might blur the effects of other physiological processes if it is set too low, and, if it is set too high, its influence could be underestimated.

III-4 THE RESPIRATORY QUOTIENT.

The importance of respiratory quotient measurements for anaerobic threshold determination is not yet clear. Although many authors (WASSERMAN WHIP 75, WASSERMAN WHIP and KOYAL 73, REITERER 1977, DAVIS-FRANK, DAVIS-VODAK 1976) have found non-linear increases of respiratory quotient (in relation to work rate) above the anaerobic threshold, there are others (BOUHUYS 1966) who claim that it remains constant. A clear relationship between anaerobic threshold and respiratory quotient has not yet been proved. The main problem is that respiratory quotient is not a directly measured parameter, but that it is a calculated value from carbondioxide production (VCO2) and oxygen consumption (VO2):

$$RQ=VCO2/VO2.$$

As oxygen consumption is mostly considered to be rather linear, non-linearity in respiratory quotient would be a reflection of non-linearity in VCO2. So, investigation of respiratory quotient is closely related to investigation of VCO2. Two causes for non-linearity in VCO2 and respiratory quotient can be:

-1-acidosis of the blood
-2-changes in food utilisation.

III-4-1 ACIDOSIS OF THE BLOOD.

As already described in the chapter on A.T., blood pH will decrease in exercise above a certain level. This is the result of an oxygen shortage in the energy delivering body cells: the citric cycle can not be finished, pyruvate and NADH2 accumulate and the first is anaerobicly converted to lactate, producing 2 ATP per molecule pyruvate (see fig. II-2). Being a stronger acid, lactate will force bicarbonate to convert into carbonic acid or dissolved CO2. In this way, partial CO2 pressure is elevated, resulting in an extra elevation of VCO2 and respiratory quotient so it should be possible to measure respiratory quotient or VCO2 increase as an indication of lactic acid accumulation, and therefore of anaerobic metabolism. The advantage of this method, would be that anaerobic threshold determination would become easier: lactic acid has to be measured from blood samples, VCO2 can be measured externally (non invasive).

III-4-2 FOOD UTILISATION.

Influences of food on respiratory quotient are well known. Normal resting respiratory quotient is 0.75 to 0.80, caused by the combustion of a mixture of food components. If the resting body would use a 100 percent of carbohydrates, fats or proteins, the effect on respiratory quotient would be as presented in fig. III-4-1.
From this it is easy to see that diet can be of great importance

	Respiratory Quotient:
$C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$ Glucose	$\frac{6}{6} = 1.00$
$C_{57}H_{104}O_6 + 80\ O_2 \rightarrow 57\ CO_2 + 52\ H_2O$ Triolein	$\frac{57}{80} = 0.71$
$2\ C_3H_7O_2N + 6\ O_2 \rightarrow (NH_2)_2CO + 5\ CO_2 + 5\ H_2O$ Alanine	$\frac{5}{6} = 0.83$

Fig. III-4-1. Utilisation of oxygen and release of carbondioxide during the oxidation of carbohydrate, fat, and protein. The R.Q. for each of these reactions is calculated. (Guyton 1971)

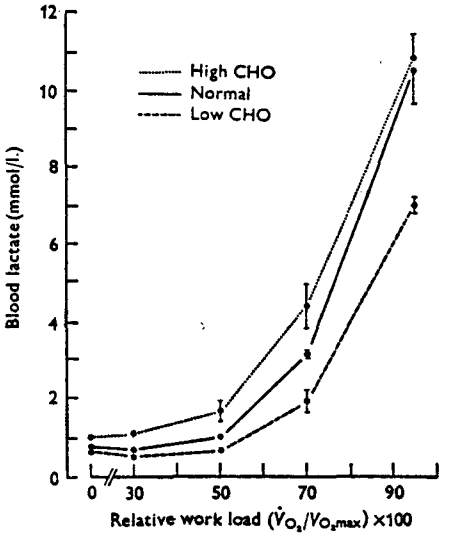


Fig. III-4-2. Blood Lactate concentrations after graded exercise on normal, low and high carbohydrate (CHO) diets (Kelman 1975)

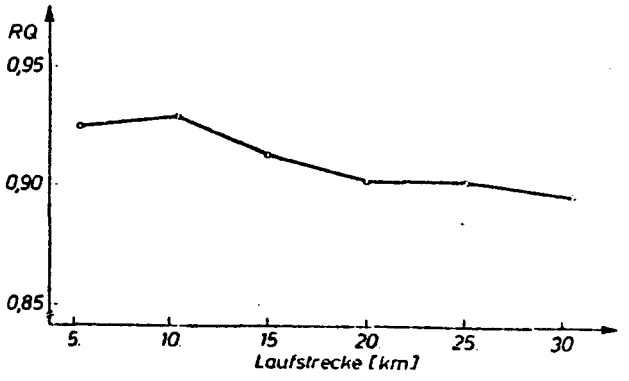


Fig. III-4-3. Constant load test. Decrease of R.Q. with increasing test duration, caused by increased Fat metabolism (Senger 1977)

when respiratory quotient is used as an indicator for metabolic acidosis; primarily because diet can raise respiratory quotient independent of metabolic acidosis (BOCK 1928) and secondly because diet influences the rate of lactic acid accumulation (fig. III-4-2), resulting in an influence on the rate of respiratory quotient raise. Both these influences are possibly due to an influence of diet on the muscle's resting glucose concentration. Kelmans findings seem to be in contradiction with glucose having a high calorific value. Producing more energy per oxygen molecule than fat or proteins, one would expect a lower lactic acid production at high CHO diet. An explanation could be found in the pathway of the different food components (see fig. II-2). Combustion of glucose results in production of pyruvate, combustion of fat does this much less. In anaerobic conditions, higher accumulation of pyruvate in glucose combustion will result in a higher turnover from pyruvate to lactate, in agreement with KELLMAN''S (1975) findings.

Comparing old research values with new ones it would be important to know, if and how diet composition has changed. (such as more fats in modern foods). Also time duration between meal and test can influence respiratory quotient (GUYTON 1971). In the first hour after a meal, respiratory quotient is almost 1.0 and after 6 hours it will have decreased to 0.7. This points out that in test series, unity of time between meal and test is important, as well as that duration of tests, involving respiratory quotient, should not exceed certain limits.

Besides external influences on food utilisation (diet) there is also an internal factor, determining the choice of food components: metabolic energy need. Regarding energy contents of food, in relation to oxygen consumption we find:

100 percent carbohydrates 20.98 joule/litre O2
100 percent fat 19.47 joule/litre O2
100 percent proteins 18.76 joule/litre O2.

This means that by utilising carbohydrates, more energy can be produced out of a certain amount of oxygen. Whenever oxygen delivery to tissues is a limiting factor, carbohydrates combustion would be an advantage over fat and proteine combustion. In work, comparatively more glucose is used in relation to fat and proteins then in rest, some times even up to 100 percent glucose (ASTRAND). As seen in fig III-4-1, this will have its reflection on respiratory quotient (carbohydrates produce more CO2 per joule than fat and proteins). During moderate work, glycogen utilisation speed is not much higher then its synthesis speed from fat and the velocity of other energy producing processes. Respiratory quotient will be approximately 0.8.

At more severe work rates, muscles use stored glycogen, a process considered to occur with the velocity of the first order. Respiratory quotient approaches unity. Fat conversion, at a considered velocity of the second order, will not be of great influence until glycogen stores are considerably lowered. (BOCK 1928). At this point, once more the duration of an experiment gets important. Experiments (for A.T.determination) longer than ca 30 minutes, can become difficult to elaborate, combining possible increase of respiratory quotient caused by metabolic acidosis and decrease

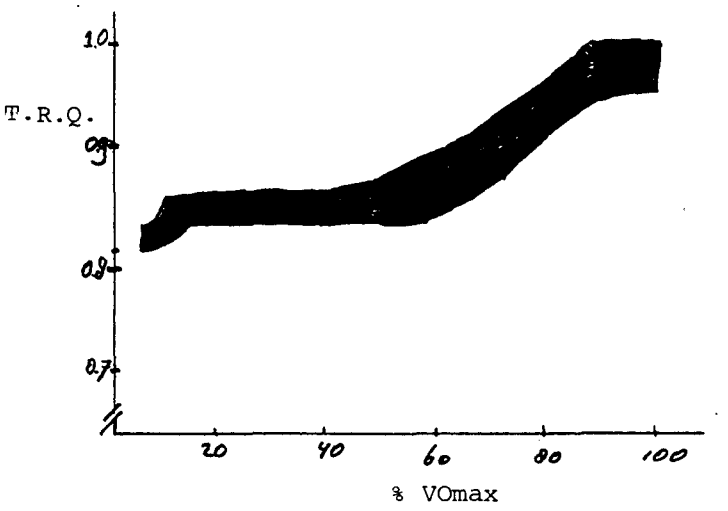


Fig. III-4-4. Relation between tissue respiratory quotient and relative VOmax (Astrand1970).

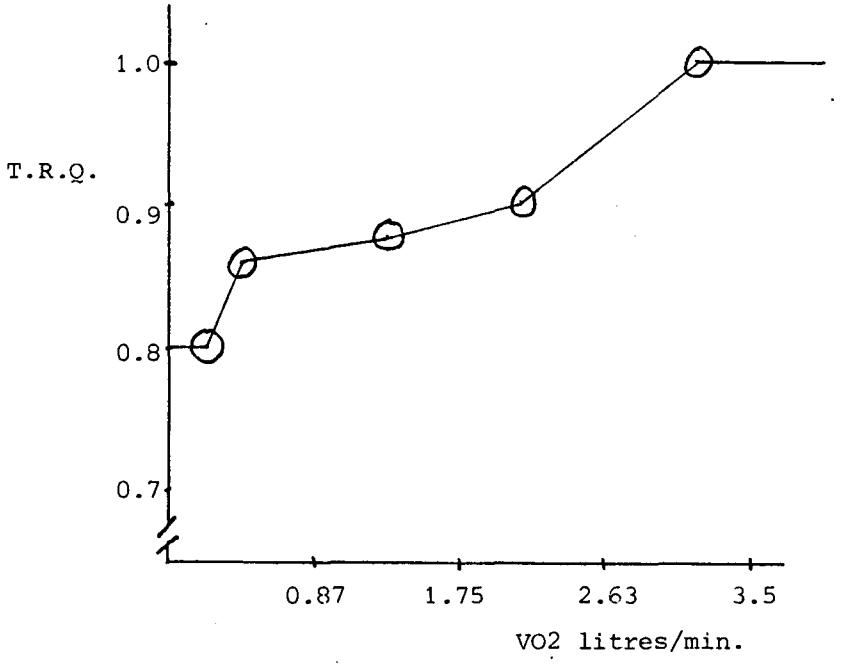


Fig. III-4-5. Relation between tissue respiratory quotient and absolute VO2 values as incorporated in MACPUF.

caused by change from carbohydrate to fat combustions. (see fig. III-4-3)

Recently, LEMON (1980) suggests that protein catabolism contributes more significantly to exercise than is generally assumed. (GUYTON 71,ASTRAND 70,SENGER 77). This might be a results of the inhibiting effect of lactate on fat conversion (SENGER). Nevertheless this contribution will be very small in short duration tests (<30 min).

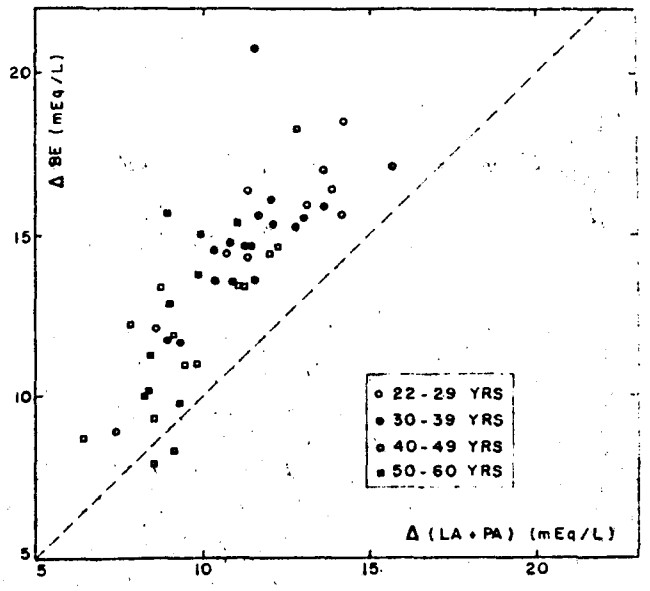
The work rate-food utilisation effect described above is also dependent on the state of training (BOCK). Training influences the cellular metabolism. The switch from fat to 100 percent glucose utilisation is shifted to higher work levels, caused by a relatively higher fat conversion.

III-4-3 RESPIRATORY QUOTIENT REPRESENTATION IN MACPUF.

As most research tests have used normal mixed diets, I chose not to adapt the model for external influences on respiratory quotient. These changes would have been rather complex, as diet does not only influence respiratory quotient directly, but also indirectly via lactic acid production (KELLMAN 1975). But as MACPUF has no adaptation for respiratory quotient to internal influences (food-energy relation), and as this could be of influence on anaerobic threshold determination, i chose for the creation of a food utilisation-energy need relation. ASTRAND gives a relationship between VO2-max. and the food components combusted (fig. III-4-4). As seen above, these values are generally in agreement with information obtained from BOCK in the cases that exercise duration does not exceed 30 minutes.

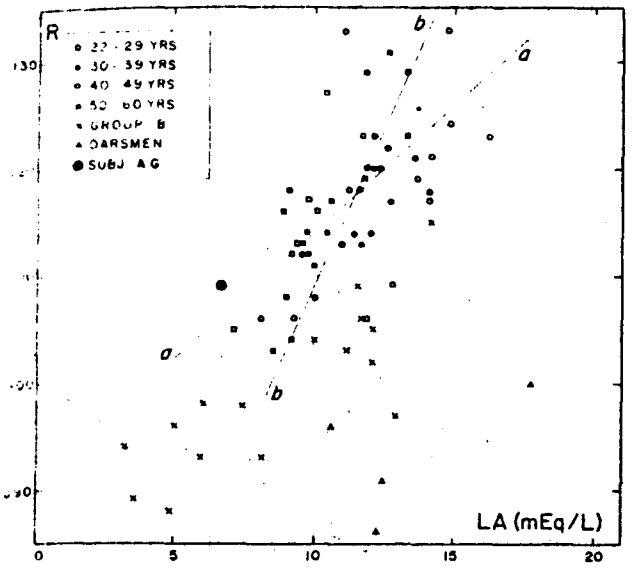
In the model it is not possible to relate tissue respiratory quotient (respiratory quotient at the place where the food is combusted) to percentage of VO2max, so VO2max had to be converted to absolute values. I arbitrarily choose for tissue respiratory quotient reaching unity at VO2 of 3.5 litres. This is rather high for normal subjects, but most research tests make use of athletes. Incorporation in MACPUF was done in subroutine function with data as presented in fig. III-4-5

As the influence of lactic acid production on VCO2 and respiratory quotient was already present in MACPUF, it is now possible to investigate the importance of metabolic acidosis for VCO2 and respiratory quotient on one hand and of food utilisation on the other.



Ordinate: changes of base excess after maximum work in all subjects of group A. *Abscissa:* changes of lactate plus estimated pyruvate in the same experiments; see text for the method of estimating pyruvate. Each point indicates a single work experiment. Line of equality (broken line) at 45°.

Fig. III-5-1. (Bouhuys 1966).



Ordinate: respiratory quotient after maximum work (group A) and after maximum or submaximal work (group B). *Abscissa:* blood LA content for the same experiments. Regression lines drawn for the data in group A only: R = 0.902 + 0.024 LA (line aa), and LA = −7.97 + 16.51R (line bb). Correlation coefficient r = +0.622.

Fig. III-5-2. (Bouhuys 1966).

III-5 LACTIC ACID.

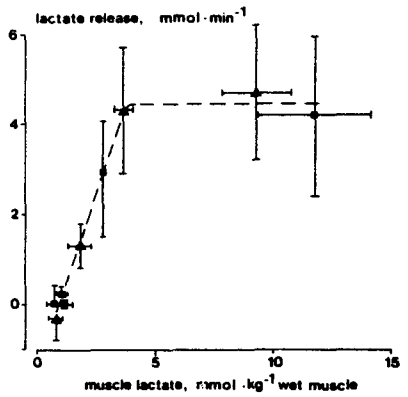
As mentioned before, lactate (lactic acid) concentration in the blood is often used to measure the rate of anaerobic metabolism. Lactic acid is the closest related factor to anaerobic energy delivery, being a product of this metabolism. All other measurable parameters,ventilation, VCO2, respiratory quotient, base excess, are influenced indirectly by anaerobic metabolism, through pH, buffers etc. This results e.g. in an overestimation of anaerobic metabolism by the base excess value of the blood and in an underestimation by the standard bicarbonate value (see fig. III-5-1 and III-5-2).

Lactic acid, being anaerobically produced out of pyruvic acid in working muscles, enters the blood stream and is then distributed over the body. It is removed from the blood by the liver, the kidneys, the heart, the resting and the non-hypoxic working muscles. In the kidney, lactic acid is excreted into urine at the other removal sites, lactic acid is reconverted into pyruvic acid, from where it can enter glucogenesis (specially in the liver), the citric cycle, or is burnt to CO2 and H2O (especially in the heart muscle). (see fig. II-2)

In this production-removal balance, lactic acid concentration in the blood is not always representative for lactic acid concentration in the working tissues, where anaerobic metabolism takes place. A possible cause for this can be found in a maximum level for lactic acid release from muscles into the blood. This is a result of translocation hindrances for lactic acid within exercising muscles (JOHRFELDT 1978)(see fig. III-5-3). The location of these hindrances is not yet clear, possibilities are location:

-a-in the cell membrane, influencing active transport , or
-b-extra cellulair e.g. shortage of blood capillaries in working muscles, resulting in a passive limitation of diffusion processes (diffusion surface).

So, for a realistic presentation of lactic acid distribution it would be necessary to create an extra compartment for lactic acid release from muscle to blood. In MACPUF and most research literature (WASSERMAN 1973,KEUL 1978, KINDERMAN 1979) lactic acid concentration is measured in the blood. This will result in an underestimation of lactic acid production in working muscles and therefore of anaerobic metabolism at heavy work loads (above 80 percent VO2-max). For lower work loads, blood and muscle lactic acid concentration will be approximately the same. Because there is very little literature on muscle lactic acid concentrationin relation to blood lactic acid concentration, and as anaerobic threshold work loads are usually lower than work loads with limited lactic acid transport, I decided not to introduce the required muscle lactic acid storage compartment. Although lactic acid concentration in the blood appears to be an indirect factor for anaerobic metabolism too, it is accepted as an indicator for anaerobic metabolism by many authors (BOUHUYS 1966,KEUL 1978,1979,HOLLMAN 1973, KOYAL 1976,WASSERMAN 1973).



(Johrfeldt 1978).

Fig.III-5-3 Release of lactate from leg in relation to muscle lactate concentration. Mean ± SE of values obtained at rest (●), and after 4 min (▲) and 12 min (■) of exercise.

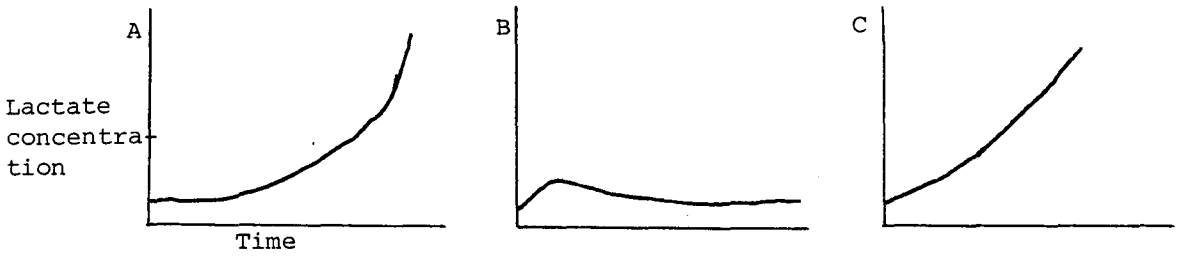
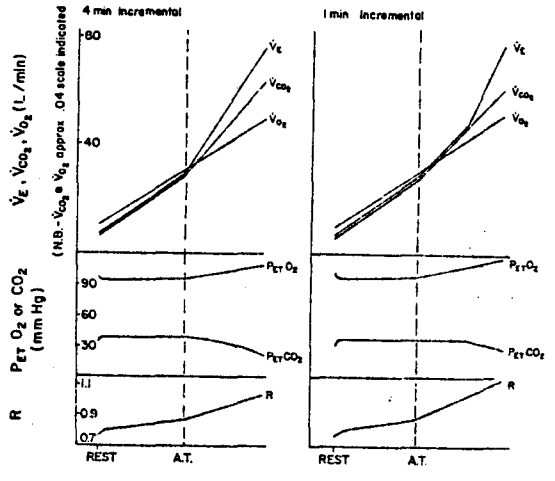


Fig. II-5-4. Behaviour of lactic acid concentration in A ramp, B moderate constant, and C heavy constant load tests.

Fig.III-5-5 (Wasserman) (1975).



Changes in minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}o_2$), CO_2 production ($\dot{V}co_2$), end-tidal CO_2 ($P_{ET}CO_2$), end-tidal O_2 ($P_{ET}O_2$), and the gas exchange ratio (R) for exercise tests in which work rate is 4-min or 1-min incremented each. The vertical dashed lines indicate the anaerobic threshold (AT). The differences between the 1-min and 4-min incremental work tests are described in the text. (Schematized from the data reported in reference 19.)

Lactic acid concentration in blood shows different behaviour in ramp tests and in constant load tests (see fig, III-5-4). In ramp tests, lactic acid concentration shows no increase at low work rates, a slow increase at moderate work rates and a heavy increase, at high work rates. In constant load tests lactic acid concentration shows no increase at low work rates, an increase at first, followed by a decrease to the original or to a slightly increased level at moderate work loads, and a definitive increase at high work loads. The low and high work loads mentioned above could be translated into work loads below and above the anaerobic threshold, the moderate work into work between aerobic and anaerobic threshold. Below the aerobic threshold, lactate formation and utilisation are equal. Passing the aerobic threshold, lactate production increases as well as lactate catabolism, although catabolism will start to rise with some delay. This results in the decrease of raised lactic acid concentration in the constant load test but not in the ramp test as production keeps increasing before catabolism is able to match it. Above the anaerobic threshold lactic acid concentration continually increases as catabolism reaches a maximum value, lower than production. The absolute work rate values for aerobic and anaerobic threshold for different individuals show great variations. Research literature, using lactate as an indicator for the reaching of the anaerobic threshold points out several possible causes for these difference :

-definition of lactic acid in relation to anaerobic threshold.
-difference between cycle and treadmill work.
-fitness.
-genetic differences between individuals.
-age.

These causes will not only influence the lactic acid- anaerobic threshold relationship alone. It is evident that they will influence many other physiological factors (ventilation, VCO2, pH etc.). The reason for dealing with them in this chapter is that the physiological factors are not only closely related to lactic acid but often changes in these factors (VCO2, pH, respiratory quotient) are even caused by lactic acid concentration changes.

III-5-1 ANAEROBIC THRESHOLD DEFINITION.

A INCREMENTAL WORK

Anaerobic threshold determination is strongly influenced by anaerobic threshold definitions.

-1-WASSERMAN and WHIPP 1973 state that the anaerobic threshold is the level of work or oxygen consumption, just below that at which metabolic acidosis and associated changes in gas exchanges occur (at about 2 mmol lactate/l)(see fig. III-5-5)

-2-KINDERMANN 1979 suggests that the threshold should be divided in three phases:

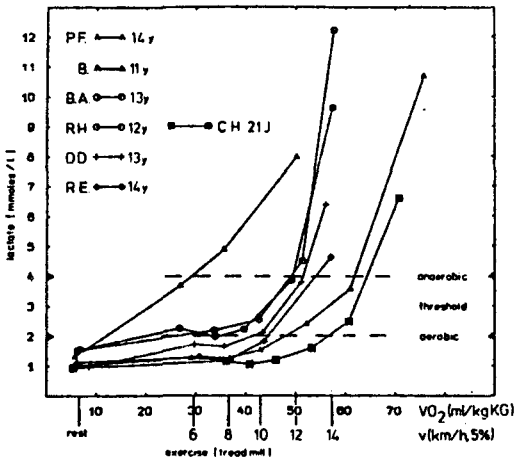


Fig. III-5-6. Aerobic and anaerobic threshold determination at the 2 and 4 mmol/litre value (keul1978).

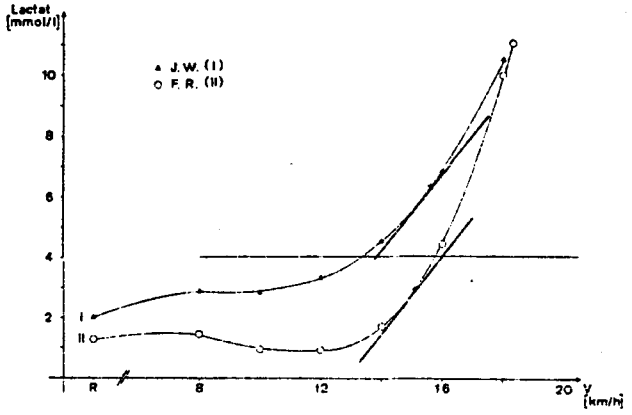


Fig. III-5-7. Anaerobic threshold determination with angle of increase of 51 degrees 34" (keul1979).

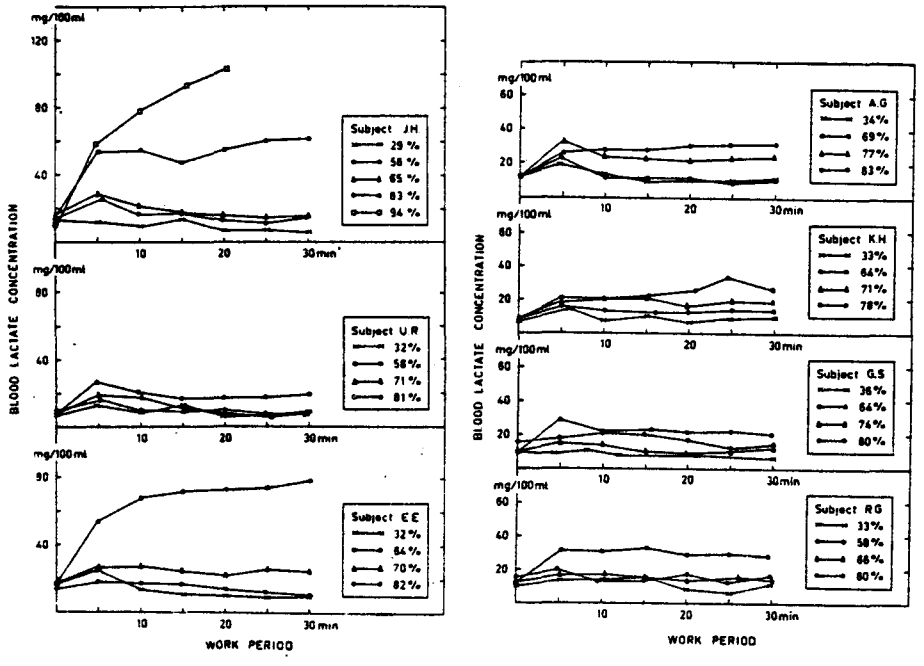


Fig. III-5-8. (Hermansen) (1972).

. Individual values for the blood lactate concentration during continuous treadmill running at different speeds for 30 min.

-a-aerobic threshold (equal to WASSERMAN´´S anaerobic threshold), approximately 2 mmol/l lactate. First significant elevation of lactic acid level, non-linear increase of ventilation and respiratory quotient.
-b-aerobic-anaerobic transition: approximately 2 to 4 mmol/l lactate.
-c-anaerobic threshold: approximately 4 mmol lactate;steep part of exponential increase in lactate concentration (see fig. III-5-6). The values of 2 and 4 mmol in these definitions were determined emperically .

-3-KEUL 1979 doubts the validity of these definitions using absolute lactic acid concentration for individual anaerobic threshold search. The reasons he gives are the presence of many interindividual differences based on genetic composition and differences in the state of training, resulting in changes of lactic acid formation or utilisation. To characterise maximal endurance capacity (which is the same as the anaerobic threshold in KINDERMANN´S definition) he determined the average angle of lactic acid concentration increase in relation to treadmill speed at the 4 mmol/l lactate value in a large group. (KEUL states that in a large tested population, max. endurance capacity can be characterized by an average of 4 mmol/l lactate). This results in a calculated angle of 51 degrees 34" (see fig. III-5-7). As KEUL already suggested, 4 mmol/l. as absolute value can be regarded as representing average values for a large population. On the opposite KEUL´s method is more valuable for individual anaerobic threshold determination.

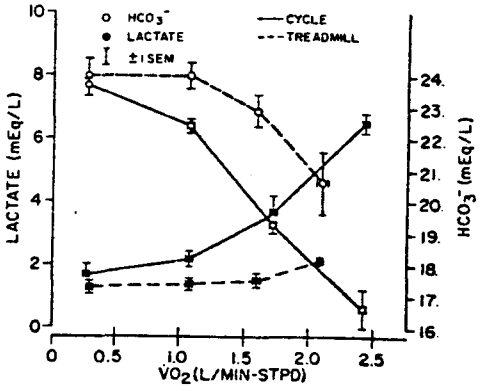
Aiming at the simulation of an average subject in bicycle ergometry, I used for MACPUF the 4 mmol/l. defenition from KINDERMANN , as KEUL results from treadmill tests are not yet confirmed in bicycle ergometry, and as there exists an important difference in the shape of the lactic acid curve between incremental bicycle and incremental treadmill exercise.

B CONSTANT LOAD WORK

For constant load work, another definition is used. Most common is defining anaerobic threshold as the work level just below the point at which lactic acid concentration does not reach a steady state (see fig. III-5-8). From various tests, this maximal steady state was determined at an average of about 4 mmol/litre lactate concentration, which indicates the relation of the constant load test definition with the incremental test definition from KINDERMANN.

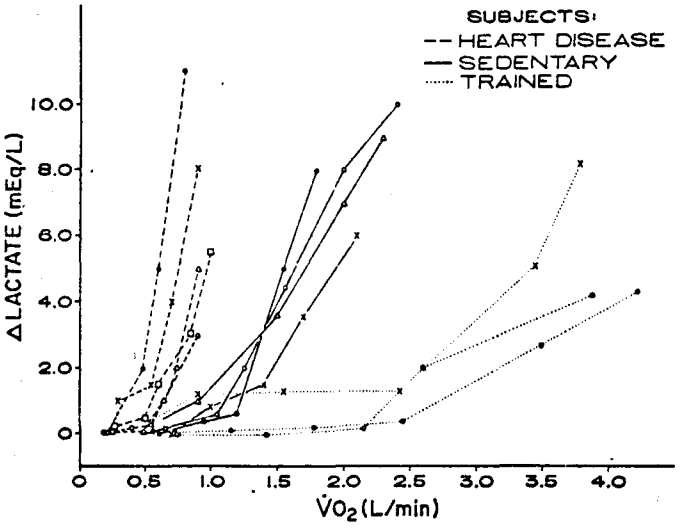
III-5-2 DIFFERENCE BETWEEN BICYCLE AND TREADMILL WORK.

In order to be able to compare bicycle with treadmill work rates, NERAUX (1977) designed a method to transfer work rates from bicycle (resistance) to treadmill (speed and angle) and reverse, using oxygen consumption and heart rate as references. KOYAL (1976) found for other physiological parameters significant diffe-



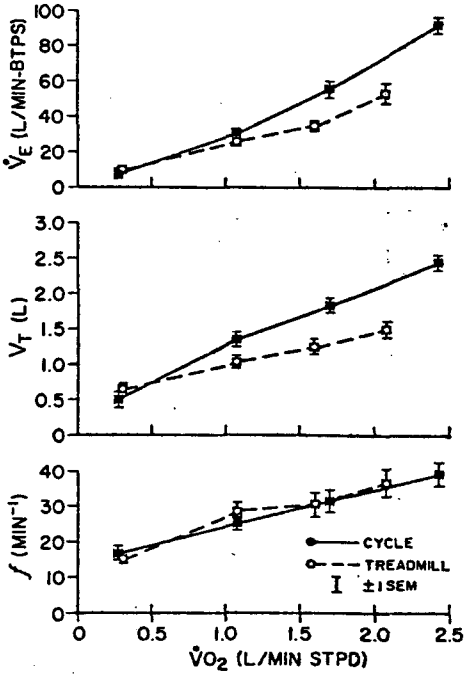
. Arterial lactate and bicarbonate (HCO_3^-) during cycle ergometer and treadmill work at several levels of O_2 uptake ($\dot{V}O_2$).

Fig. III-5-9. (Koyal1976).



Change in lactate concentration during graded exercise testing in patients with cardiac disease (primarily mitral valve disease), sedentary subjects, and well-trained normal subjects.

Fig. III-5-11. (Wasserman).. (1975).



Comparison of minute ventilation ($\dot{V}_E$), tidal volume (V_T) and breathing frequency (f) between cycle ergometer and treadmill exercise at various levels of O_2 uptake ($\dot{V}O_2$).

Fig. III-5-10. (Koyal). (1976).

rences between bicycle and treadmill work. Ventilation, tidal volume and lactate concentrations were higher in cycle ergometer work and PaO2, PaCO2, {HCO3-} and pH were higher in treadmill work, at various levels of O2 consumption. (see fig. III-5-9 and III-5-10).

He suggests that the smaller muscle mass used in cycling to generate the same power output as for equivalent treadmill work, causes the mean metabolic rate per unit of contracting muscle mass to be greater during cycling work. This would result in an earlier start of anaerobic metabolism in the used muscles and therefore produce a greater metabolic acidosis in cycling work. CERRETELLI (1979) on the contrary, finds that less lactate (and therefore lower metabolic acidosis) would be accumulated in the blood if the involved muscle mass is smaller. It should be noticed that CERRETELLI investigated arm-leg differences and that his "smaller" muscle mass was the arm, with the leg, being the "larger" muscle mass. This is a principal difference with KOYAL's investigations, in which he compares "legs" with "legs and other muscles". DAVIS , when comparing arm with leg exercise, found results in agreement with KOYAL's findings. He suggests that his results can be attributed to specific training adaptations. His test subjects were trained in leg work but not in arm work. This partially explains CERRETTELLI's findings as part of his tested persons were trained in both arm and leg exercise resulting in a relatively lower lactic acid concentration in arm exercise.

III-5-3 FITNESS.

Lactic acid concentration in exercise tests is highly dependable on the subjects state of training. Differences were found, comparing subjects before, during and after a training period (DAVIS 1979, HAGBERG 1978), as well as comparing groups of subjects with different states of fitness (CERRETELLI 1979, WASSERMANN 71). It is suggested that training increases oxydative capacity by increasing the number of mitochondria (KIESSLING, IVY 1980), the cellulair enzymes (HOLLESZY,IVY 1980) and possibly the ratio slow twitch/fast twitch fibres (IVY), resulting in increased lactic acid catabolism. Training also increases maximal heart output and blood perfusion, resulting in higher oxygen delivery, and thus in lower lactic acid production. (see fig. III-5-11 and III-5-12) besides lactic acid production, training also influences tissue, respiratory quotient (BOCK 1928,IVY 1980), showing an increase in the rate of lipid oxidation, slowing of the rate of glycolysis and inhibiting lactic acid formation. In addition, the trained muscle may increase its capacity for resisting lactic acid production by shunting of a larger portion of pyruvate to alanine instead of lactate (MOLE).

III-5-4 GENETIC DIFFERENCES.

The cellular factors mentioned above (mitochondria, enzymes etc.) are also dependant on the genetical composition of a subject. Besides these, also muscle composition has a genetical base. (see fig. III-5-13)

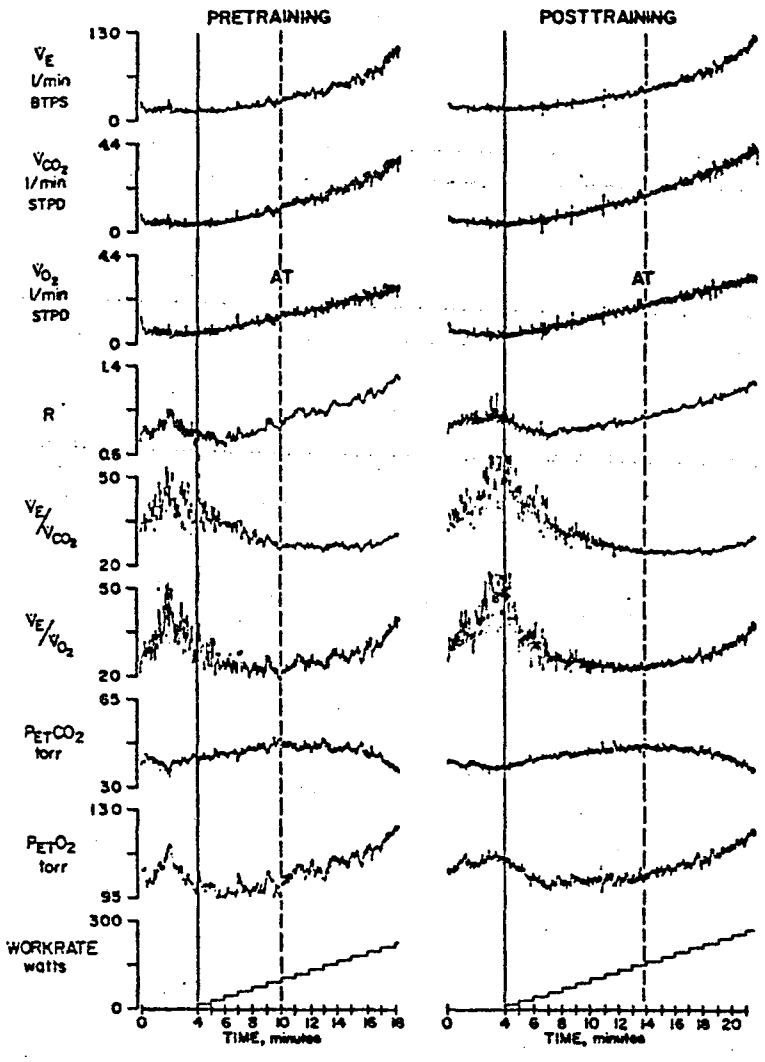


Fig. III-5-12. (Davis1979).

Example of AT detection from ventilatory and gas exchange responses to a 1-min incremental (15-W) test, pre- and posttraining, for experimental subject (*HS*). *Solid vertical line* denotes onset of positive work rate, i.e., transition from unloaded cycling to 15 W. *Dashed vertical line* denotes AT.

The ratio of Slow Twitch/Fast Twitch fibres is an important factor for the determination of work capacity, primarily due to the high oxidative capacity of the Slow Twitch fibre type. This means that a relatively high percentage of Slow Twitch fibres is correlated with a high work capacity and a high anaerobic threshold. (see fig. III-5-14)

It is suggested, that the Slow Twitch/Fast Twitch ratio is generally determined by genetical influence and that only a small fraction is contributed by the influence of training.

III-5-5 AGE.

Another factor influencing anaerobic threshold and therefore lactic acid concentration is the age of the tested subjects. (see fig. III-5-15)

With increasing age, it is found that Maximal Cardiac output (in l/min.), resting lung volume as well as vital capacity decreases (GUYTON fig. III-5-16), thus lowering maximal work capacity and possibly anaerobic threshold. This should be kept in mind when comparing research values, concerning different age groups.

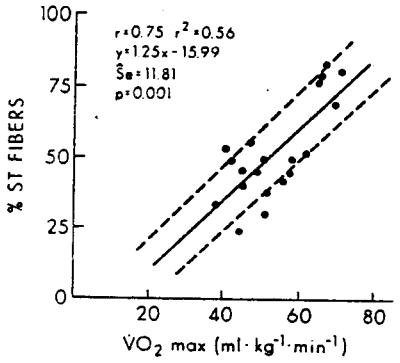
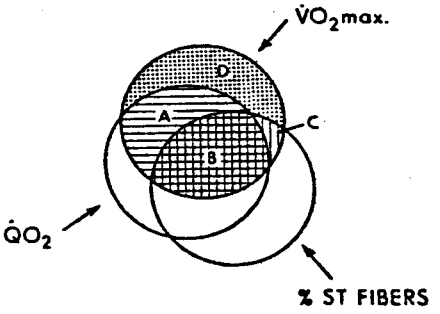


Fig. III-5-13. (Ivy 1980).

Relationship between maximum oxygen consumption ($\dot{V}O_{2\,max}$) and % ST fibers of the vastus lateralis muscle. Broken lines represent standard error of estimate (Se)

Fig. III-5-14. (Ivy 1980).

A diagrammatic representation of the common variance between $\dot{V}O_{2\,max}$ and $\dot{Q}O_2$, $\dot{V}O_{2\,max}$ and ST fibers, and the combined effect of $\dot{Q}O_2$ and fiber type on $\dot{V}O_{2\,max}$. Variance was determined by the coefficient of determination (r^2). A and B Common variance between $\dot{V}O_{2\,max}$ and $\dot{Q}O_2$. 66%. B and C Common variance between $\dot{V}O_{2\,max}$ and % ST fibers. 56%. C Common variance between $\dot{V}O_{2\,max}$ and % ST fibers minus $\dot{Q}O_2$. 14%. D Variance unaccounted for by $\dot{Q}O_2$ and % ST fibers 28%



(QO2 is muscle respiratory capacity)

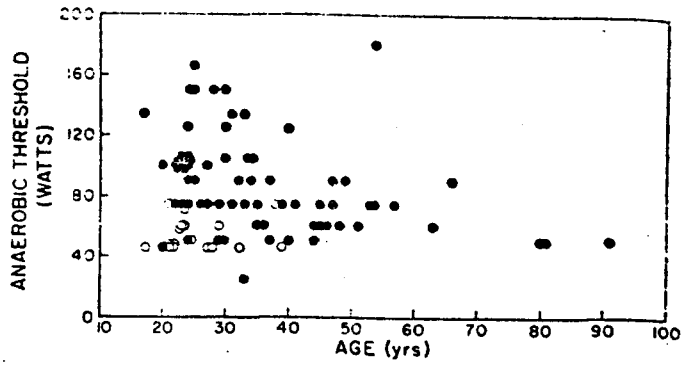
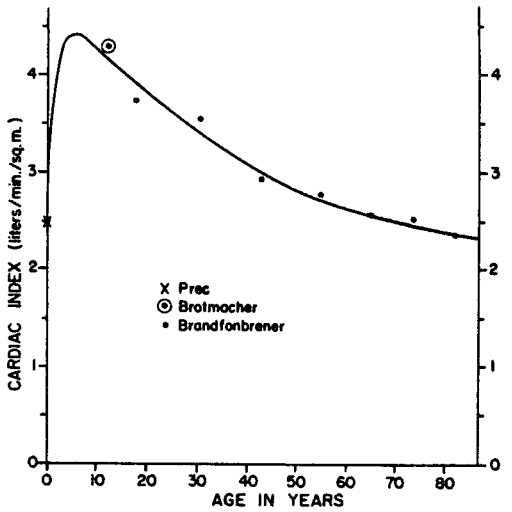


Fig. III-5-15. Anaerobic threshold values for 85 normal subjects. Solid point are males and circles are females. (wasserman 1973).

Fig. III-5-16. (guyton1971).



Cardiac index at different ages. (From Guyton: Cardiac Output and Its Regulation.)

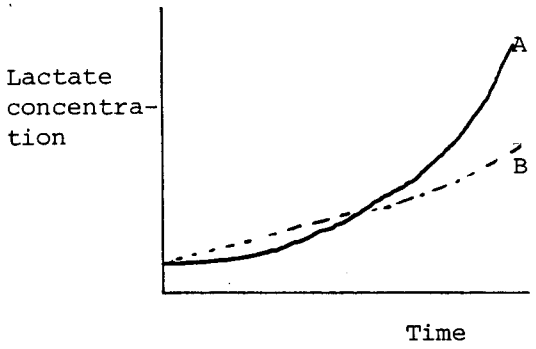


Fig. III-6-1.
A literature values
B Macpuf values

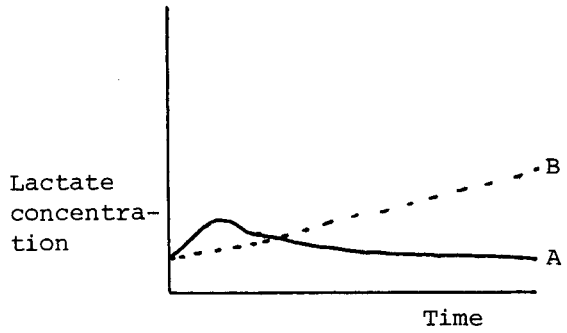


Fig. III-6-2.
A literature values
B Macpuf values.

III-6 LACTIC ACID IN MACPUF.

When comparing lactic acid concentrations from simulations with research values there was an important difference between ramp test simulations and constant load test simulations. In ramp test simulation lactic acid accumulation starts at very low work rates , increases very slowly, resulting in relatively, high anaerobic threshold values (for average tested persons) and low lactic acid concentration at the highest work levels(see fig. III-6-1)

Using the definition that anaerobic threshold in constant load tests is determined at the work rate where lactic acid keeps increasing, anaerobic threshold in constant load simulation is very low. In the constant load test simulation, even at very low work rates (e.g.30 watts), lactate starts to accumulate(see fig. III-6-2)

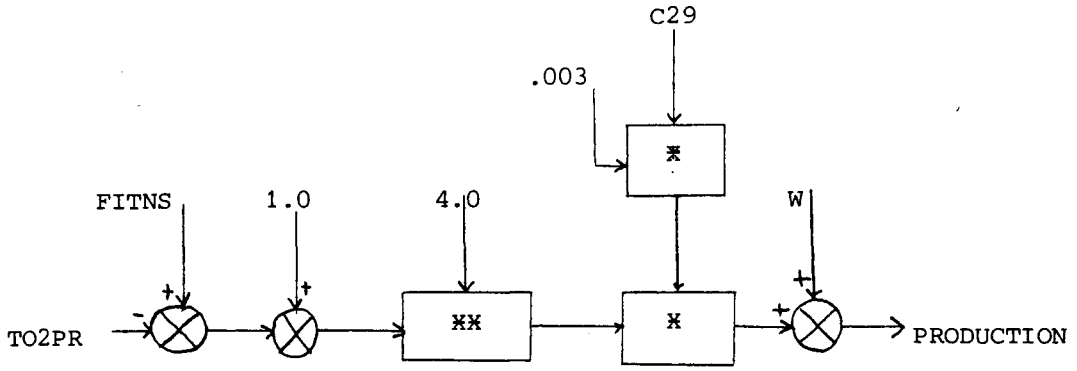
This means for the model that in ramp tests, total lactic acid production is too low, and in constant load tests, total lactic acid production at low work rates is too high. This assumed contradiction may have its roots in the lactic acid synthesis-catabolism relation. For treadmill exercise, the contradiction is still present, but the ramp test results are more like research values then in bicycle exercise.

III-6-1 REPRESENTATION OF LACTIC ACID SYNTHESIS.

This is represented by the block schema of fig. III-6-3. The question is what adaptations will be needed to reach results, in agreement with research values. Regarding ramp tests I studied the influence of fitness and of changes in lactic acid synthesis. Fitness, used as reference to TO2PR (mm Hg) for determination of lactic acid production start, is preset at 33 and can be changed within the range 30-37. Fitness values above 33 simulate unfitness; values below 33 simulate increased fitness.

Lowering fitness produces an earlier start and higher final values of lactic acid production. Raising fitness (<33) produces a delay of the start and lower final values of lactic acid production. These influences are generally in agreement with research results concerning fitness (usually the state of training). However, it is impossible to adapt the shape of lactic acid concentration increase, only by the use of changed fitness. The starting point of lactic acid increase can be delayed by raising fitness, but this results also in an unwanted decrease of lactic acid concentration at higher work values. When I used changes of lactic acid production, I found a reverse rela tionship. Lactic acid concentration at high work rates can be raised by increasing lactic acid production, but this does not influence starting point of lactic acid accumulation (see fig. III-6-5)

Finally I used combination of various setpoints (fitness<33) and raised production to adapt the shape of the lactic acid curve.



TO2PR= tissue oxygen pressure
FITNS= fitness
C29= constant related to body size
W= basel spillage rate of lactate

Fig. III-6-3. Block scheme for lactate synthesis.

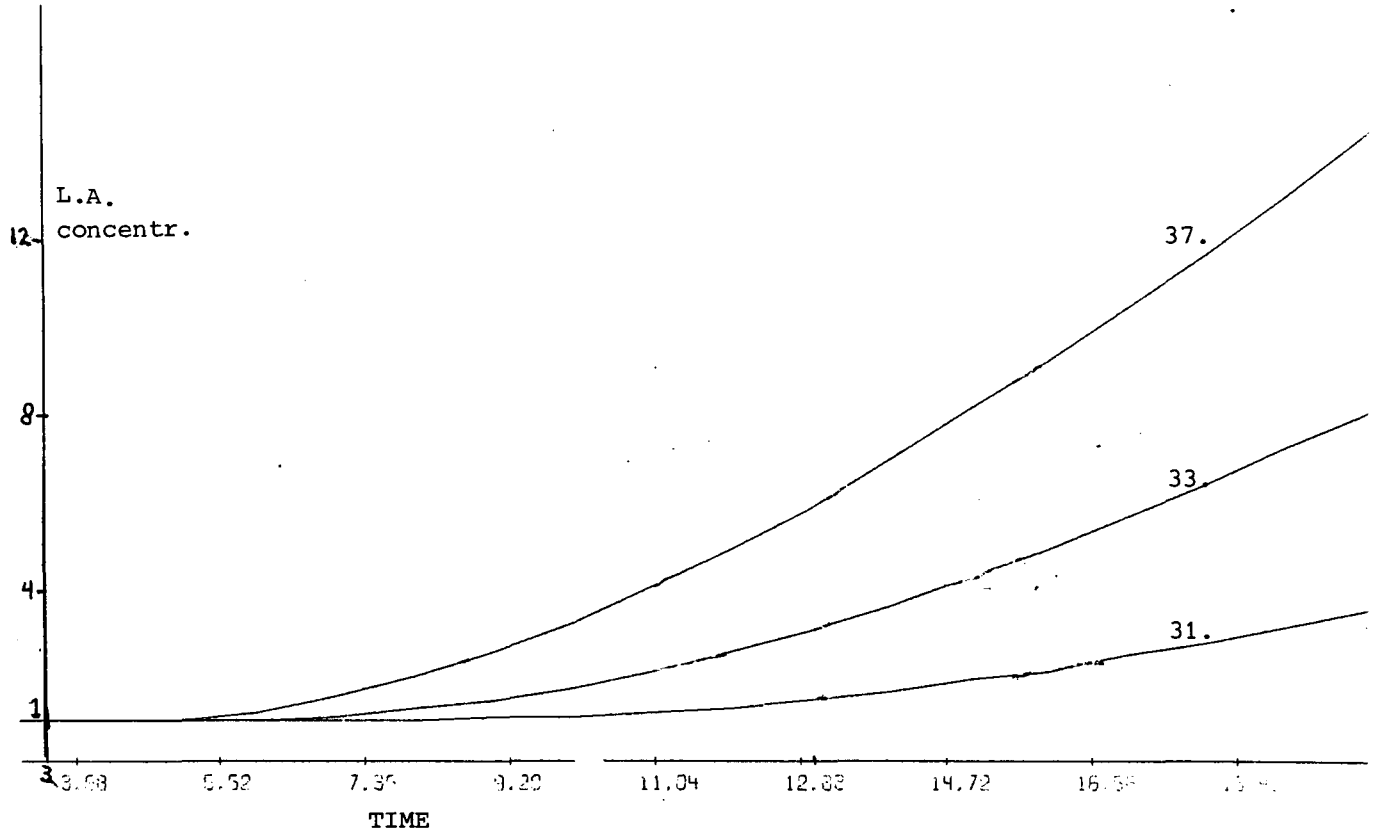


Fig. III-6-4. incremental test, 15 watt/min. fitness factor 31,33,37. test starts at TIME=3.0

Although this produced fairly good results, i did not make any further calculations in this direction, because results were not realistic when I tried to simulate constant load tests. These indicated that deviations of MACPUF could not only be due to lactic acid synthesis, but that lactic acid catabolism also had to play a part.

III-6-2 LACTIC ACID CATABOLISM

Lactic acid catabolism in MACPUF incorporates lactic acid catabolism in the liver and the kidneys and in the muscles. The representation in the programme is:

```
      X=TPH*10.-69.
      Y=RLACT*C29
      Z=Y*(X*.8612+.0232*2.**((8.-TPH)*3.33)+COADJ*.01)
      Z=Z*TO2PR*.04
      X=C24-COADJ
      IF (X) 630,630,620
620   Z=Z*COADJ/C24
630   V=W-Z
      TLAMT=TLAMT+V
```

TPH=TISSUE PH
RLACT=LACTIC ACID CONCENTRATION OF BLOOD (1 MMOL/LITRE)
C29=FACTOR PROPORTIONAL TO BODY SIZE
COADJ=CARDIAC OUTPUT (5 LITRES/MINUTE)
TO2PR=TISSUE OXYGEN PRESSURE (40 MM HG.)
Z=LACTIC ACID CATABOLISM/INTEGRATION INTERVAL
W=LACTIC ACID PRODUCTION /INTEGRATION INTERVAL
TLAMT=TOTAL LACTIC ACID AMOUNT IN BODY (35 MMOL.)

or for a block scheme see fig. III-6-6.

Catabolism in kidneys and liver is made proportional to blood lactic acid concentration and dependant on tissue pH (DICKINSON). Low tissue pH increases kidney catabolism but decreases liver catabolism (COHEN). Muscle catabolism is dependant on cardiac output and therefore indirectly on oxygen consumption and on the closely to oxygen cons. related metabolic rate. Catabolism is decreased when tissue oxygen pressure falls.

In the original model, simulating constant load tests, the ratio of lactic acid production / lactic acid catabolism is too high at low work levels. This results in lactate accumulation at these levels, which is not in accordance with literature (DAVIS). Altering this ratio (i.e. lowering) by changing model parameters, is possible by lowering production and/or raising catabolism.

Lowering production in general would not be preferrable as it would result in further decrease of lactic acid concentration in ramp tests at all work levels and so create a larger difference with values from research literature (see lactate production).

This leaves alterations in lactate catabolism. Liver catabolism is not likely to be increased as it reaches values in accordance with values from ROWELL (1966) of about 150 mg/min. There is

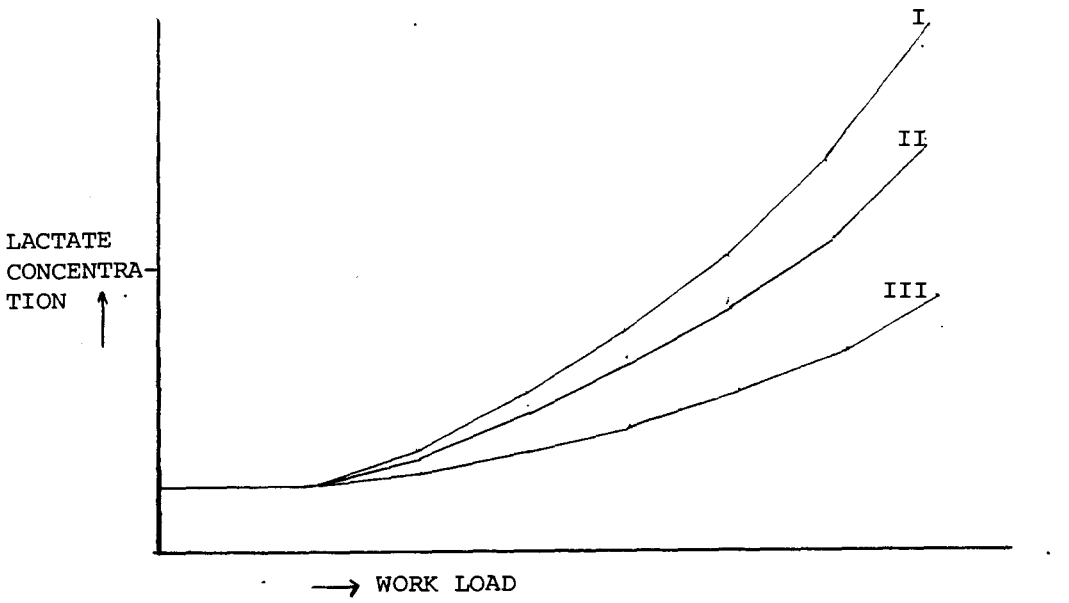
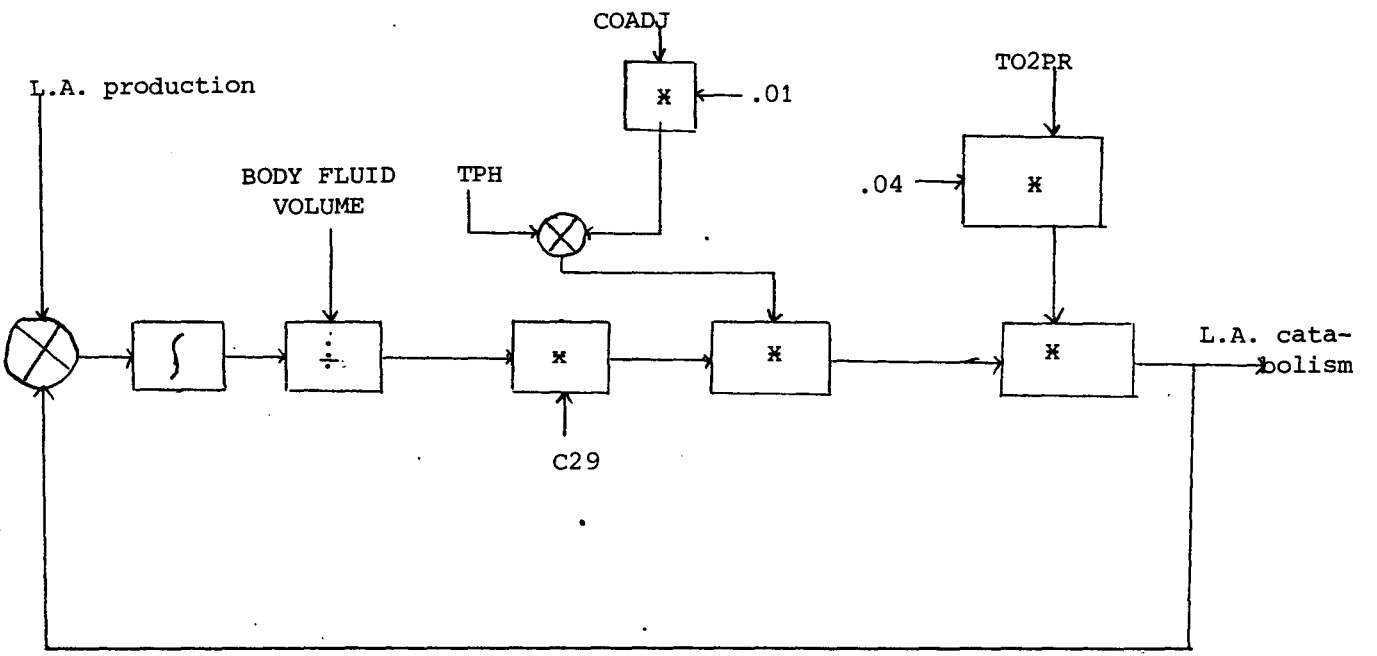


Fig. III-6-5. Influence of various power functions for lactate production on blood lactate concentration.
I fifth, II fourth, III third power function.

Fig. III-6-6. Block scheme, lactate catabolism.



just one factor in the lactic acid catabolism representation which is dependant on work rate: the lactate catabolism in non hypoxic muscles and other non hypoxic tissues. This is presented by the term:

Y*(COADJ*.01)

The physiological meaning of this term is that increased circulation creates an increase of available capillairy endothelium surface through which catabolising power of muscles can be increased (DICKINSON). Other studies (HERMANSEN AND STENSVOLD 1972) suggest that not only non hypoxic muscles contribution to catabolism increases with increasing metabolism, but that also working, hypoxic muscles play an important part.

Lactic acid production has a fourth power relation to tissue oxygen pressure and therefore indirectly to oxygen consumption. This causes lactate production to increase much faster whenever anaerobic metabolism is present than it does to catabolism, resulting in the netto over production at low work rates.

Also, lactic acid catabolism keeps increasing up to the highest work levels, which is in contradiction with studies of TASKIN, GOLDSTEIN AND SIMMONS (1972) and with studies of HERMANSEN and STENSVOLD in 1972 (see fig. III-6-7).

As the studies of HERMANSEN and STENSVOLD were the only available with data, I tried to interprete these data for my purposes. The main difficulty in this interpretation was the difference in methods between the tests of HERMANSEN and STENSVOLD and the tests I tried to simulate. They have gathered results from constant load tests in treadmill exercise, and start their tests with maximal lactate concentration values (22 mmol/litre). Our tests on the contrary are mainly ramp tests in bicycle exercise and start with resting lactate concentration values (1 mmol/litre).

Although one has to be very careful when comparing treadmill and bicycle exercise and comparing constant load results with ramp test results, I think that in this case the difference in starting values for lactate concentration is the main problem.

It is often suggested (ROWELL ´66, ELRIDGE ´75) that lactic acid catabolism in the liver is linearly related to lactate concentration in the blood. Dr. Dickinson suggests that this is also the case for other adequately oxygenated tissues. This would mean that a great part of lactate catabolism is lineaally dependant on lactic acid concentration:

catabolism=1.a. concentration*(.....)

from this it is easy to see that in the mentioned part of the body, HERMANSEN and STENSVOLD´s results will differ greatly from results from tests starting with resting lactate values, specially at low lactate concentrations:

H andS: always catabolism=22*(.....)
our tests: e.g. catabolism=1*(.....)

for this part of the body, Herm. and Stensv. data could then be

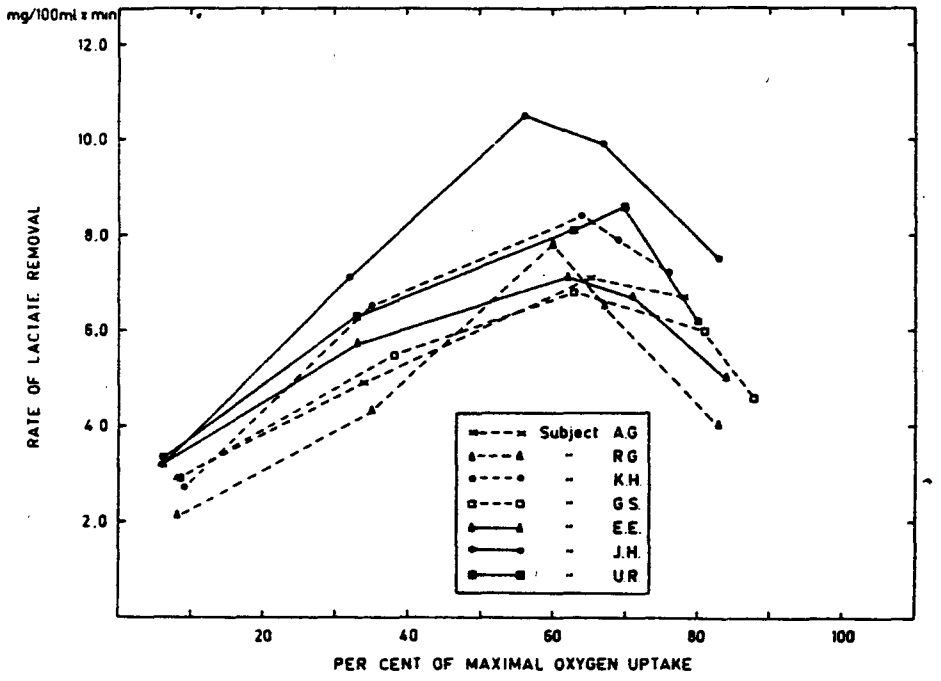


Fig. III-6-7. Rate of lactate removal in relation to relative work load (Hermansen) (1972).

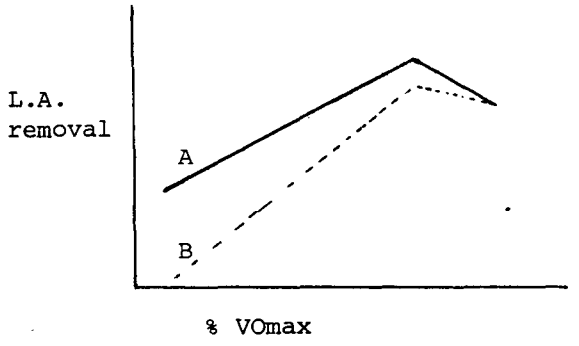
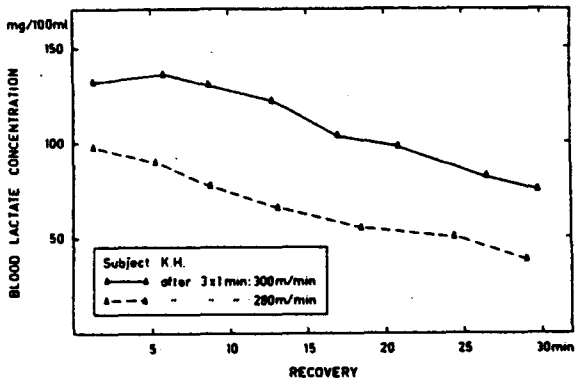


Fig. III-6-8. A Hermansen and Stensvold's results
B corrected values

Fig. III-6-9. (Hermansen).

Blood lactate concentration for one subject in the recovery period after 3 maximal work bouts of different intensity (*i.e.* 300 m/min upper curve, and 280 m/min lower curve).



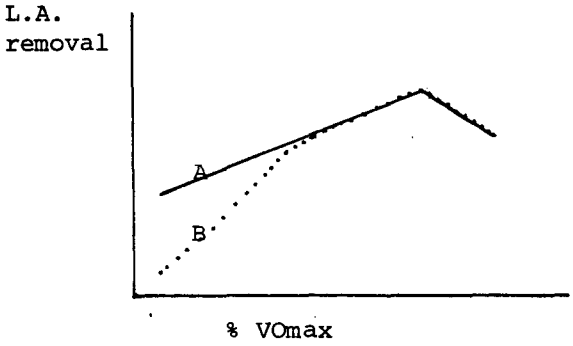


Fig. III-6-10. A Hermansen and Stensvold's results
B corrected values

recalculated by correcting them for lower lactic acid concentrations (see fig. III-6-8)

But besides the question of the relative importance of the mentioned body part, there is also the question as to whether catabolism stays linearly related to lactic acid concentration up to the highest concentration values. According to Herm. and Stensv. ,this is not the case for the splanchnic organs (see fig. III-6-9). It should be remarked that they measured in this case catabolism in recovery, which might differ from catabolism in activity. They suggest that lactate uptake by the splanchnic organs will increase with increasing arterial blood lactate concentration up to a critical value (40-50 mg/100 ml.=about 5 mmol/litre, Herm. and Stensv.) where the maximal enzymatic rate in the cells will be reached. But as splanchnic blood flow is reduced in exercise and as muscle blood flow is increased in exercise, the question is still open if a similar effect of a maximal influence of lactate concentration on catabolism is present in the muscles too. If this would be the case, Herm. and Stensv. results should be recalculated in a way presented in fig. III-6-10, reaching much earlier values equal to Herm. and Stensv. Results than we saw in fig. III-6-8.

As I could not find any information on this point there are still two possibillities for the interpretation of Herm. and Stensv. results. Personally I prefer the last interpretation, suggesting a maximal lactate concentration influence for all catabolism sites (possibly by a saturation of the involved enzymes. It should be noted that this will not necessarily produce a maximal catabolism as catabolism can still increase in speed e.g. by increased temperature), although I have no evidence for this.

Summarising the information I decided to:

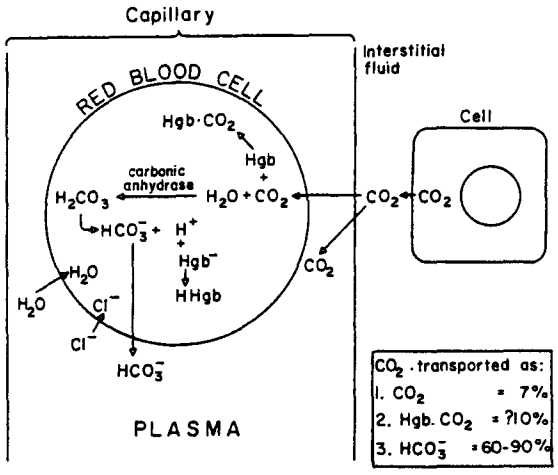
1. let catabolism approach production values at low work rates to stop the netto "over" production,
2. to limit organ catabolism to 150 mg/minute (ROWELL),
3. to reduce catabolism above 63 percent of Vomax,
4. to create a maximal catabolism value of 0.8 mmol/second.

To achieve this I changed the catabolism description in:

```
        X=TPH*10.-69.
        Y=C29*RLACT
        ORGCAT=Y*(X*.8612+.0232*2.**((8.-TPH)*3.33))
A       X=ORGCAT-.3*FT/.016667
        IF (X.GT.0.0) ORGCAT=.3000*FT/.016667
        X=QA/FT
B       CALL FUNCTN (X,CATOX,FUN2,10)
        CATMUS=Y*CATOX
        Z=ORGCAT+CATMUS
C       IF (TO2PR.LT.(FITNS-8.0)) Z=TO2PR*.04

NEW NAMES:
ORGCAT=ORGAN CATABOLISM (LIVER AND KIDNEY)
QA/FT=OXYGEN CONSUMPTION
CATOX=OXYGEN CONSUMPTION-MUSCLE CATABOLISM RELATION
```

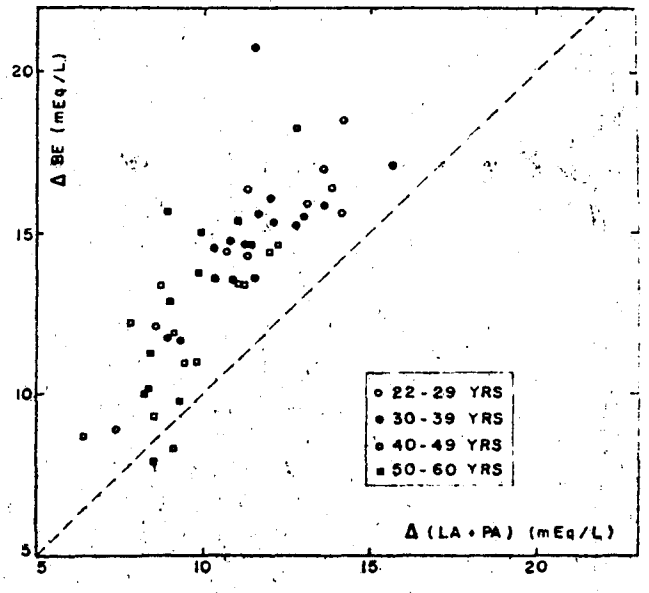
CATMUS=MUSCLE CATABOLISM
FITNS=FITNESS (33.0)

in which A limits organ catabolism (2) and B deals with point 1,3 and 4. C lowers catabolism, influenced by lower tissue oxygen pressure (DICKINSON).
Data for subroutine FUNCTION were calculated from functions with shapes equal to the function for lactic acid production, with the restrictions mentioned above.



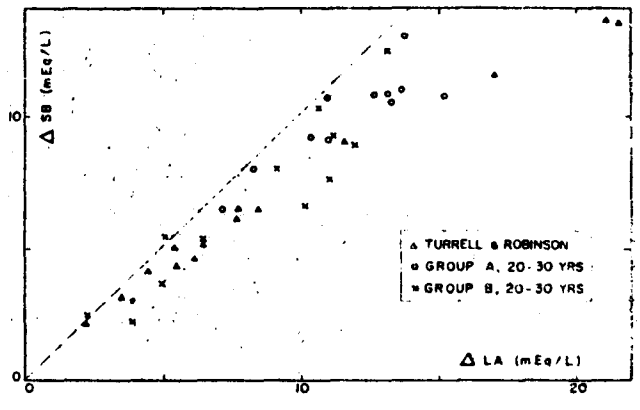
Transport of carbon dioxide in the blood.

Fig. III-7-1. (Guyton1971).



Ordinate: changes of base excess after maximum work in all subjects of group A. *Abscissa:* changes of lactate plus estimated pyruvate in the same experiments; see text for the method of estimating pyruvate. Each point indicates a single work experiment. Line of equality (broken line) at 45°.

Fig. III-7-2. (Bouhuys1966).



Ordinate: change in standard bicarbonate after maximum work in all subjects between the ages of 20 and 30. *Abscissa:* change in blood LA content for the same experiments. Data in other subjects not shown to avoid crowding the graph. Data of Turrell and Robinson (24) are shown for comparison.

Fig. III-7-3. (Bouhuys1966).

III-7 BUFFERS

Whenever lactic acid is produced it will influence pH. The body, in an effort to prevent any pH changes will try to buffer the lactic acid. The possible buffers are:

-bicarbonate
-haemoglobine
-plasma proteins

All these substances are also involved in the transport (and buffering) of carbondioxide. see fig. III-7-1.

A quantitative estimation of the sum of changes in bicarbonate, proteinate and haemoglobinate base, is possible by determining the base excess value of the blood. (BOUHUYS 1966). But this is not representative for the buffering of lactic acid alone, as there are other acids (pyruvic acid) which will also claim a part of the buffer capacity.

At low work rates with low lactic acid concentration, bicarbonate is the most important buffer. At high work rates respectively high lactate values haemoglobinate and proteinate become more important, as can be concluded by comparing fig. III-7-2 with fig. III-7-3.

There is also a difference in buffer capacity between muscle tissue and blood. According to SAHLIN (1978) and MADER (1979), muscles have a buffer capacity of 68 SLYKES (=68meq/litre/pH) concerning the fluid part, and of 52.5 SLYKES/kg. total muscle with a fluid content of 77 percent.

Apart from this, there is the buffer capacity of split creatine-phophate at high work levels, but this can not be quantitatively estimated.

Blood buffer capacity at a haemoglobine concentration of 16-17 percent is about 40 SLYKES. which is about 30 percent lower than muscle fluid buffer capacity. These values, together with the maximal pH decrease values (7.0-6.3=0.7 for muscle and 7.4-6.85=0.55 for blood (MADER)) result in a maximal lactic acid concentration of 52.5*0.7=36.7 mmol/kg for the muscle and of 40*0.55=22 mmol/kg for blood. This is in accordance with the findings of JOHRFELDT (1978), who actually finds higher muscle lactate concentration. Causes for the presence of the difference are already discussed in the chapter on lactic acid.

In MACPUF. the lactic acid influence on buffer quantity is presented as:

TC3MT=TC3MT+.....-V*.4
TC3MT=tissue pool of standard bicarbonate
V=change in lactic acid amount.

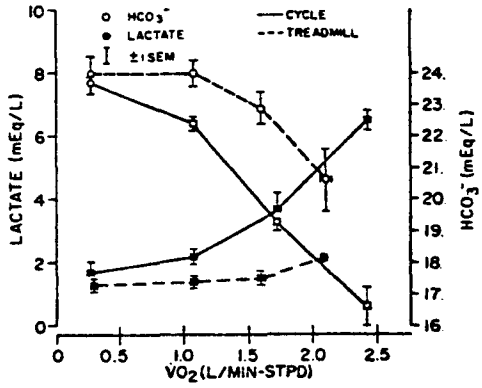
If bicarbonate would have been the only buffer, there would have been a one to one relation between delta lactate and delta bicarbonate. Incorporating the influence of other buffers and of intracellular buffering, Dr. DICKINSON chose for a 1 to 0.4 rela-

tion,which means that 1 mol lactate will force 0.4 mol bicarbonate to be removed.

Comparing this value with results from BOUHUYS (1966) ,MADER (1979) and WASSERMAN (1973), it seems to be an underestimation of the effect of lactate generation on bicarbonate removal. From their results, a ratio of 1 mol lactate to 0.7 or 0.8 mol bicarbonate would seem more realistic. In relation to results of KOYAL, also the absolute bicarbonate values remain too high in exercise(bicycle, see fig. III-7-4). From these results, a ratio of 1 to 1 would seem to be acceptable. In MACPUF however, similar results where obtained by changing the lactate/bicarbonate ratio in 1 to 0.65 . This showed more acceptable bicarbonate values (KOYAL 1976). Other effects where: lower pCO2, pH and lactate values, and higher minute ventilation , mainly at work rates above 225 watts.

At this point I must remark that I did not do many simulations on this subject, and as changes had great influences all over the model, the validity of the value of 0.65 is not yet clear.

FIG. 1. Comparison of minute ventilation ($\dot{V}_E$), tidal volume (V_T) and breathing frequency (f) between cycle ergometer and treadmill exercise at various levels of O_2 uptake ($\dot{V}O_2$).



Arterial lactate and bicarbonate (HCO_3^-) during cycle ergometer and treadmill work at several levels of O_2 uptake ($\dot{V}O_2$).

Fig. III-7-4.
(Koyal1976).

III-8 VENTILATION

Although my investigation of ventilation was far from complete, I had to stop due to lack of time. Nevertheless I want to give some comments on this subject, as it might be interesting to continue the investigations at a later date.

The ventilatory response to physiological changes in macpuf is split into:

- -a- a representation of the ventilatory response to arterial carbondioxide pressure,
- -b- control of ventilation by a central brain hydrogen ion receptor,
- -c- a representation of ventilatory response to hypoxia, presented as a relation of ventilation to arterial oxygen saturation,
- -d- a central neurogenic drive to ventilation.

Then, in the summation of these effects, they are related to barometric pressure and body temperature. When we compare ventilation-work rate curves from literature with MACPUF results, we find an important difference. Research literature shows a non-linear increase of ventilation above the anaerobic threshold value(CLARK 1980,DAVIS 1979,IVY 1980). Macpuf shows a non-linear increase of ventilation at much higher values. Dr. Dickinson mentioned in his book that in exercise, PaCO2,PaO2 are only little changed and that the fall of bicarbonate concentration and pH resulting from accumulation of lactic acid is quite inadequate to bring about the large increases in ventilation observed. Therefore he introduced part -d- of the description of ventilation which may be considered most important for exercise simulations.

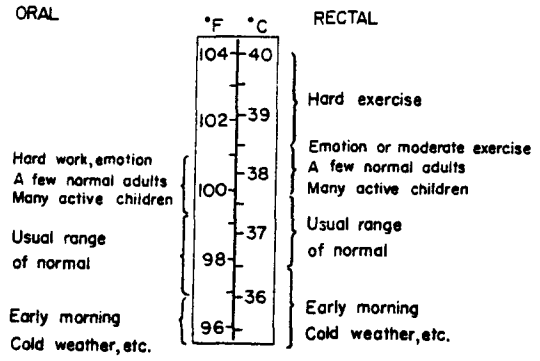
```
C7=CONSO*PD*.00081*(TEMP-26.)**1.05
C68=FT*3000./(PD+200.)
C46=CZ*.78*((C7*.00051)**.97+.01)
XRESP=DAMP(C46,XRESP,C68)
TOTAL VENTILATORY STIMULUS=.....+XRESP....

CONSO=RESTING OXYGEN CONSUMPTION
PD=METABOLIC RATE
TEMP=BODY TEMPERATURE
FT=FRACTIONAL TIME INTERVAL
CZ= MANUAL CONTROL FACTOR IN PERCENTAGE OF NORMAL
```

The expression given subsequently for the total ventilatory stimulus incorporates C46, specifying the central neurogenic drive as almost linearly proportional to oxygen consumption. For moderate exercise, MACPUF produces an increase of ventilation of 2.1 litres/minute for each 100 cc. of increase in oxygen consumption, which was measured by COTES in 1966. However for exercise values above the anaerobic threshold, ventilation is too low.

One important cause for this may be found in the body temperature. Macpuf does not change body temperature actively in exercise,although the body temperature will increase in reallity.

(see fig. III-8-1). A body temperature change of 1 degree (from 37 to 38 degrees CELSIUS) in MACPUF at a work rate of 180 watts produces a delta ventilation of 58.1-46.0=12.1 litres/minute. This shows quantitatively the importance of the influence of body temperature on ventilation(which influence will not only be on ventilation). Nevertheless this cannot be expected to be a complete explanation for the absent start of non-linearity in ventilation at the point of the anaerobic threshold. This must then also be caused by the influence of carbon dioxide,lactic acid, pH, or bicarbonate.

Some alterations on this point that I investigated did not yet show any results. For this reason it might be interesting to study some other formulations of ventilatory control in order to get more information on this point. E.g. Swanson and Bellville, 1974; Yamamoto and Hori, 1971; Grodins, Buell and Bart, 1967.



Estimated range of body temperature in normal persons.

Fig. III-8-1
(Guyton1971).

IV GOODNESS OF FIT

To get a notion of the validity of a model it is necesary to compare model input/output values with real input/output values(research literature). In the ideal situation, input/output pairs of the model and the real system will be equal. However, this will very seldom be the case. This does not imply that unequality of input/output pairs means that the model cannot be useful. Whenever input/output pairs do not show equality, it is necessary to find a criterion for determination of how well the model and the real system agree.

As in this study, mostly transients and not steady states are inveatigated, it is not possible to use e.g. multiple regression or correllation tests. Instead of these there are several possibilities from which one can choose.
If p(t)= model value on point "t" - real value on point "t", we can use:

Table 1 Some Common Norms

Criterion	Definition of Norm
Maximum	$\|\rho\| = \max \{\rho(t) \mid t \in \text{dom}(\rho)$
Integral absolute	$\|\rho\| = \int_{\text{dom}(\rho)} \|\rho(t)\| \, dt$
Integral square	$\|\rho\| = \int_{\text{dom}(\rho)} \rho^2(t) \, dt$

then it is also possible to reduce the area in which P is calculated (dom (P)). This is of importance when the model was designed to simulate e.g. asymptotic values (see fig. IV-1). In this case

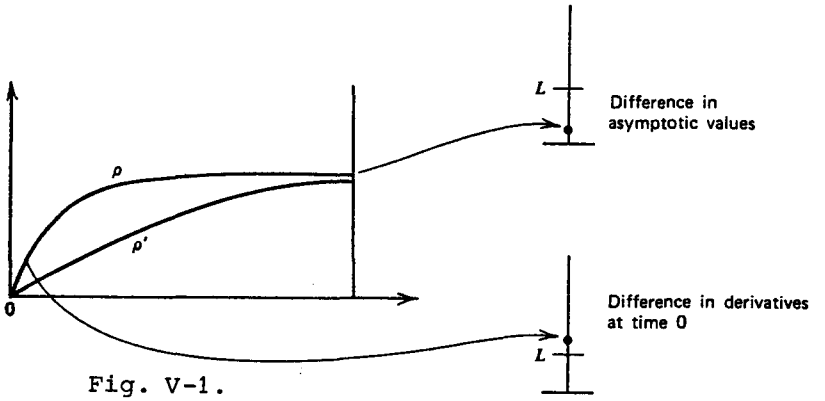


Fig. V-1.
Two ways of measuring the distance between trajectories. (Zeigler 1976).

the first part of the curve is not important for the determination of the goodness of fit. The value the norm P is allowed to reach in order to accept the model (acceptance level) has to be defined by the investigator. Besides these norms it is also possible to

accept a model if its results remain within the range of measured values of the real experiment. This range can be caused e.g. by interindividual variations of the tested subjects, but also by errors in the measurement of output or input factors.

This last method cannot be used for MACPUF simulations as most research literature does not give the error range of their data. Further it did not seem realistic to define a norm value at this point as I had very little experience, regarding the validity of such a norm.
Nevertheless I did introduce a performance index; generally to create a criterion to compare one simulation with another. For this I choose an integral square error, related to the square value of the real data:

$$\text{PERFORMANCE INDEX} = 1 - \sqrt{\frac{\int \{A(t)-B(t)\}^2 \, dt}{\int \{A(t)\}^2 \, dt}} \times 100\%$$

A(t)=literature data
B(t)=simulation data
t= simulation time
P=100 means that simulation results are identical to real data.

The performance index was introduced in MACPUF at the end of the main programme, in subroutine PERFO and in function SUMPF.

V FINAL SIMULATIONS

All simulations were started with a ten minute period of rest, to assure that a steady state was present at the start of the test.

Diverse datasets (P.T.T., WASSERMAN) showed a higher oxygen consumption at rest than MACPUF did. This could be due to the fact that in B.G.D./P.T.T. tests, the tested subjects did not have complete rest before the test started; but I think that even more important is, that in all tests (at B.G.D./P.T.T. As well as those mentioned in research literature), the apparatus to which the tested persons are connected will always create a light stress situation for the subjects, resulting in a higher resting metabolism (BOCK 1928). For this reason, I increased metabolic rate in macpuf (initial 100 percent of resting metabolism)to 178 percent , during the 10 minute rest simulation (this results in a oxygen consumption of about 450 cc per minute).

The simulated tests were:

I Wasserman and Whipp '73 cycle ergometer.

A 25 watts/minute 0-175 watts.
B 25 watts/4 minutes 0-150 watts.
C 135 watts constant load test for 9 minutes.

In these tests, the measured parameters were: in A and B blood lactate concentration and arterial bicarbonate, and in C arterial bicarbonate concentration and respiratory quotient.

II B.G.D./P.T.T. tests.

A 15 watts/minute increments, 0-270 watts.
B 25 watts/minute increments, 0-300 watts.

Both tests I and II were simulated with various fitness values (31, 33, 35, normally 33). This was done to check if the fitness parameter in macpuf was able to influence simulation results in the right manner (fitnessfactor above 33 simulates decreased fitness, below 33 increased fitness).
Tests I and II were also simulated with the original model, in order to be able to compare these results with results from the present model.

III Constant load test series (fitness 33).

Twenty minutes at loads of 80, 100, 120, 140, 160 watts. Although there were no data present to compare these results, they can be used for the evaluation of the different test methods.

IV Incremental test, 15 watts/minute with constant tissue R.Q.

This test with constant tissue R.Q. was done for evaluation of

the importance of T.R.Q. changes on one hand and of metabolic acidosis on the other for the non linear changes of VCO2 and R.Q. in ramp tests (see also chapter III-4).

VI RESULTS

See also RESULTS IN TABLES and fig. VI-1 - VI-11.

I WASSERMAN AND WHIPP

In all the simulated tests (25 W/min., 25 W/4 min., 135 W const. load) we find the best overall results at a fitness factor value of 35. This indicates that the subjects, used in Wasserman's test, have a lower fitness than the "average" subject presented by MACPUF. The changes in MACPUF were aiming at a maximal oxygen consumption of 3.5 litres per minute (fitness 33.). So, Wasserman's subjects should have a lower VOmax than 3.5 l/min.. Unfortunatly the authors have not given this information explicitly in the article I used. They only stated that their subjects were between 17 and 91 years old and were predominantly sedentary, but included fit subjects as they became available for the study, which indeed indicates a VOmax below 3.5 litres/minute.

When we use the 4 mmol/litre lactate concentration value to locate the anaerobic threshold, we find that it is reached during the 125 Watt work increment, both in the 25 Watt/min. test and in the 25 Watt/4 min. test (fitness 35.). At the start of the 125 Watt work bout, lactate value in the 25 W/4 min. test is higher than in the 25 W/min test.
In the data from Wassserman, this tendency is even more strongly present, resulting in a lower A.T. in the 25 W/4 min. test (A.T. reached in the 100 Watt work bout; it should be noted that WASSERMAN and WHIPP calculated the A.T. using respiratory parameters as VE and VCO2).

Using the 2 mmol lactate concentration value, we find that A.T. is reached at the end of the 75 Watt work bout for the 25 W/min. test and in the 75 Watt bout for the 25 W/4 min. test.

From the 135 Watt constant load test results, we can see that this work rate in MACPUF lies above the A.T., as lactic acid concentration keeps increasing. This is in accordance with the results from the 25 Watt/min. and the 25 Watt/4 min. test.

Comparing simulation results with results produced by the original model, we see that regarding the two 25 Watt increment tests, mainly the performance value for lactate has been improved. The fact that HCO3- performance index has not changed greatly, caused by the changes in lactate metabolism, is due to the change in lactate buffering by bicarbonate.
In the 135 Watt constant load test, an improvement of the respiratory quotient performance index compared to the original model is present.
For other parameters the performance index cannot be calculated as there are no data present.

II B.G.D./P.T.T. tests

In the B.G.D./P.T.T. tests, best results are achieved with fitness factor 31., indicating increased fitness and therefore VOmax of the simulated subject can be expected to be higher than 3.5 litres/minute. This is known to be so for subject WO., who showed to have a VOmax above 4.0 litres (see data 25 Watt/min. test). For the second subject, KE., VOmax is not measured to be above 3.5 litres per minute, but regarding heart rate at 3.5 litre VO2 in the 15 Watt/min. test it can be expected that VOmax of KE. will be above 3.5 litres (e.g. in a 50 Watts/min. test).

Compared to the original model, the main improvements have been made in VCO2 and R.Q.. These two parameters are closely correllated, and their improvement will be mainly achieved by the changes in lactate metabolism, tissue R.Q., and bicarbonate buffering. Minute ventilation (VE) and breathing frequency (AF) were only slightly improved. On lactate concentration and cardiac output there were no data available.

From the 4 mmol/litre blood lactate concentration, the models A.T. was determined. In the 15 Watt/min. test it was reached in the 165 Watt work bout; in the 25 Watt/minute test in the 175 Watt work bout (fitness 31.).

Using the 2 mmol lactate concentration value, A.T. was reached in the 135 Watt work bout for both 15 W/min. tests and at the start of the 150 Watt bout in the 25 Watt/min. test with subject WO..

A.T. determined from non-linearity of respiratory parameters was located at:

	VE	VCO2
KE. 15 W/MIN.	120	90
WO. 15 W/MIN.	120	120
WO. 25 W/MIN.	125	125

III CONSTANT LOAD TESTS

From the series of constant load tests, A.T. was determined, using the definition that A.T. is passed when lactate does not reach a steady state.this was the case above work loads of 120 watts (fitness 33.), thus we can state that in this case A.T. is reached at 120 Watts.

IV 15 WATT/MINUTE INCREMENTAL TEST, TISSUE R.Q.=0.8

The result of this test compared with results from the 15 Watt/min. test with influence of metabolic rate on tissue R.Q., indicate that in the model, the influence of metabolic acidosis and tissue R.Q. changes on respiratory quotient (and VCO2) are almost equal. this means that food utilisation has a

50 percent influence on R.Q.(and VCO2).

VII DISCUSSION.

For the location of the anaerobic threshold I preferred the absolute values of 2 and 4 mmol/litre. According to KEUL (see chapter III-5-1) this method is acceptable in this case (besides the method of calculation of increase in angle) as the lactate data from Wasserman's tests were average values for a large group of persons (85)and as values in MACPUF are aiming on the simulation of an "average" subject. Nevertheless I think it would be very interesting to do further investigations on the subject of anaerobic threshold determination with the calculation of the angle of increase in relation to interindividual differences. Especially to investigate the relation between this method of anaerobic threshold determination and the way of testing (work pattern).

In the simulation results we find, in agreement with research literature, a general tendency that anaerobic threshold determination results are influenced by the work pattern of the used test. The anaerobic threshold (for ramp tests) determined at the 2 and 4 mmol/litre lactate concentration value as well as the A.T. determined by VE and VCO2 measurements is highly correllated with the value of the increments in load, as well as with the duration of the work at each load.
Comparing simulation results of fitness 33. of all tests with each other, we find A.T.'s e.g. at the 4 mmol lactate value as presented below:

TEST	A.T.
CONST.LOAD	120 WATTS
15 W/MIN.	150-165 WATTS
25 W/MIN.	150-175 WATTS
25 W/4 MIN.	125-150 WATTS

If we look at this information out of the point of view of work physiology with its interest in endurance capacity for very long work bouts (8 hours), the best A.T. value is the one determined in the constant load test (see also chapter I).

Comparing the constant load A.T. value with the other A.T. values from ramp tests we see that the ramp test A.T. values will be overestimations of the real endurance capacity. The shorter the work bouts at each load and the higher the load increments, the lower the lactic acid accumulation will be (KOYAL 1976). This indicates that if we want to use ramp tests for A.T. determination, with the 4 mmol. lactate value, we have to take account of the time constants of the various body reactions (VO2, oxygen transport by blood, metabolism rise, lactate transport into blood etc.).

From the diverse simulation results, concerning 4 mmol lactate as parameter for A.T. determination I concluded that in ramp tests using lactate as parameter for A.T. determination, it would be best to use small increments (maximal 15 watts) during work bouts of at least 4 minutes.

A disadvantage of such a test would be the duration, e.g. a test of 0-210 watts would take 14*4=56 minutes. This is not

acceptable as this duration would influence test results (see III-4-2 food utilisation). Therefore it will be advisable to locate A.T. roughly with use of the subjects medical history or e.g. with a 25 watt/min. test (knowing that this will produce an overestimation), and then start the 15 watt/4 min. test at a work level not too far from the estimated A.T..
This test (e.g. 75-165 watts) reproduced in the model the results of a test starting at 0 watt load. This indicates that "skipping" the first increments does not influence A.T. determination in a 15 watt/4 min. test (under the condition that ca. three increments remain before A.T. is reached).

The value of VCO2 and R.Q. as parameter for anaerobic metabolism was estimated by comparing model results without tissue R.Q. changes (and thus only metabolic acidosis influence on R.Q.) with model results with both tissue R.Q. and metabolic acidosis influence. The result that T.R.Q. accounts for about 50 percent of the R.Q. (vCO2) changes implies that in ramp tests, a non-linear increase of R.Q. (vCO2) could easily be caused by, or at least be partially due to, a non-linear increase of tissue respiratory quotient.
This does not mean that R.Q. and VCO2 are not usable as parameter for A.T. Determination, as a correllation between them has already been found, but it shows that factors as food influence (diet, time between meal and test, metabolic deviations) are more important for both absolute values of R.Q. and VCO2 and their changes in time, and that they should be handled more carefully than generally assumed. It is therefore advisable to use more parameters for A.T. determination than R.Q. and VCO2 alone.

The A.T. values determined from VCO2 point also in the direction of the problems mentioned above; the A.T. value of subject KE. in the B.G.D./P.T.T. test differs greatly from the expected value, regarding the A.T. determined by lactate concentration and VE. Comparing the A.T.'s calculated from VE with the A.T.'s calculated with lactate concentration, we see that the VE values are generally lower than the 4 mmol lactate values, and that they seem more closely related to the 2 mmol lactate concentration values (the start of metabolic acidosis).

	2 MMOL	4MMOL	VE	VCO2	CONST. LOAD
W/W 25/4MIN	75	125	100	100	90
W/W 25/MIN.	75-100	125	100	100	90
WO. 25/MIN.	150	175	125	125	140
WO. 15/MIN.	135	165	120	120	140
KE. 15/MIN	135	165	120-135	90	140

When we compare these values with A.T. values calculated from constant load test simulations (for Wass. and Wh. fitness 35., for B.G.D./P.T.T. fitness 31) we find the best results from the 2 mmol/litre value. The 4 mmol value overestimates (as discussed above) and the VE and VCO2 values underestimate the A.T..
Regarding the disadvantages of a 15 Watt/4 min. test, as mentioned above, making a shorter test with higher increments preferrable, these findings indicate that in such a test A.T. should be calculated from the first rise of lactic acid concentration in the

blood (2 mmol), and possibly from the related first decrease in HCO3- concentration. This first rise of lactic acid concentration is in the simulations closely related to the first non linear increase of VE.
But although minute ventilation has improved compared to the original model, it deviates still too much from realistic values to draw conclusions from the observed behaviour.
It can only be suggested that VE may be preferrable as parameter for A.T. determination to the 4 mmol lactate value, for short steep ramp tests.
it would be interesting to do further investigations , e.g. on the relation of VE and the 2 mmol lactate value, as (in case such a relation is present) VE measurements have the advantage above the lactate measurements of being a non invasive method.
Summarising one might conclude that the problems mentioned above are possibly for a great part solvable when more information on the time constants of the various body systems is available.

The behaviour of lactic acid metabolism has, compared to the original model improved greatly. The accumulation of lactic acid in the model, in relation to the work pattern is now generally in accordance with results from research literature. At this point it should be remarked that the improvement of lactate metabolism is the result of improvement of the production/catabolism ratio, and that this does not necessarily imply that absolute production and catabolism values have become more realistic. In the model, the improvement of lactate metabolism is primarily due to the changes in lactic acid catabolism, which seems, regarding model results as well as research literature results, to play a more important part for lactate metabolism than often assumed.
This would imply that fitness differences are not only caused by differences in lactate formation but also by differences in lactate catabolism. Another indication for this is that it appears to be possible to simulate increased and decreased fitness by changes of the fitnessfactor, and that this factor influences both lactic acid production and catabolism. Possible causes for the differences in lactate catabolism were already discussed in chapter III-5.
From model results,lactic acid concentration seems to be a reasonable parameter for anaerobic threshold determination, although for the individual A.T. determination, the absolute 2 and 4 mmol/litre values are questionable (see chapter III-5-1)

Fig. VI-1. I=recent model, II=original model, III=literature data.

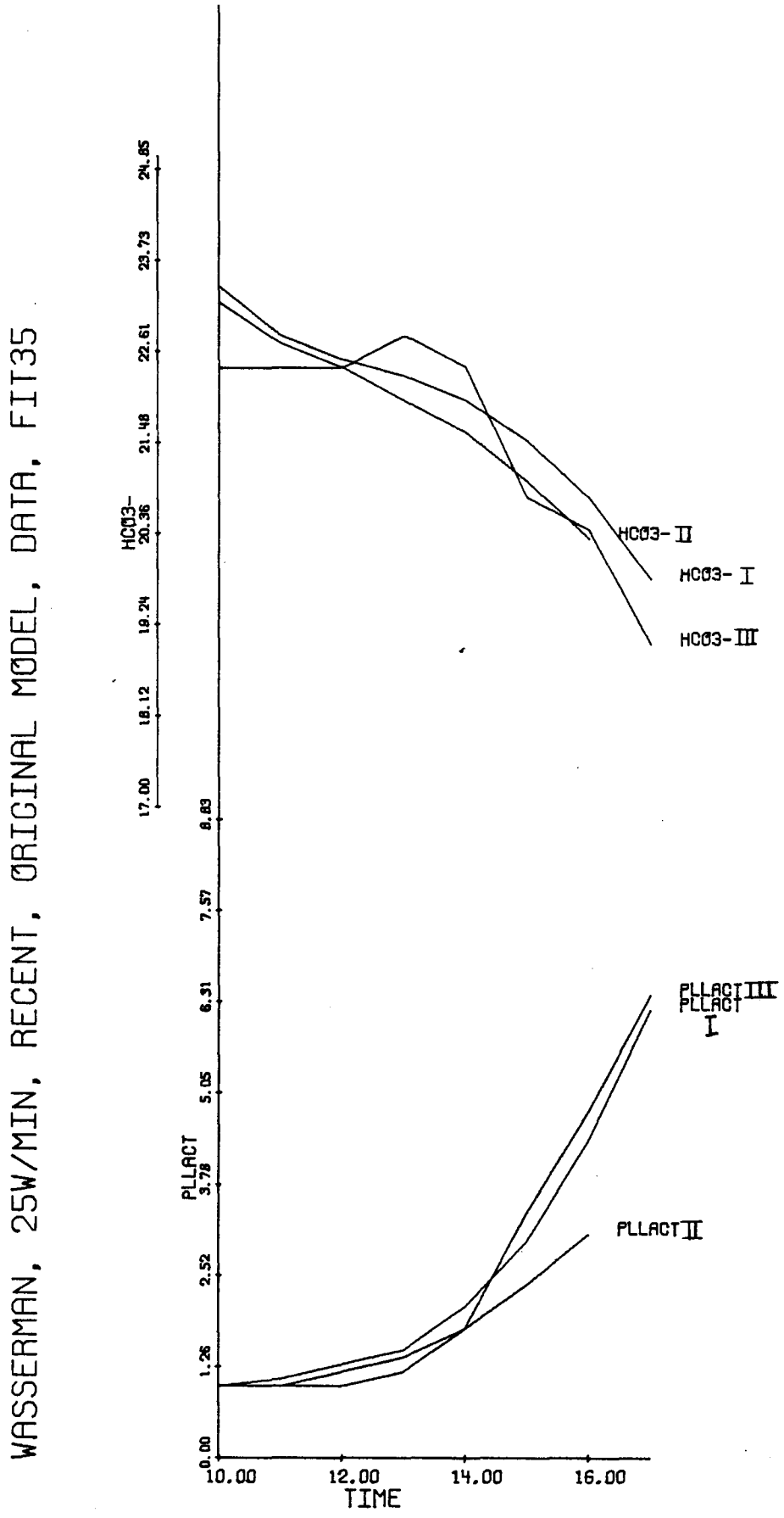


FIG. VI-2.

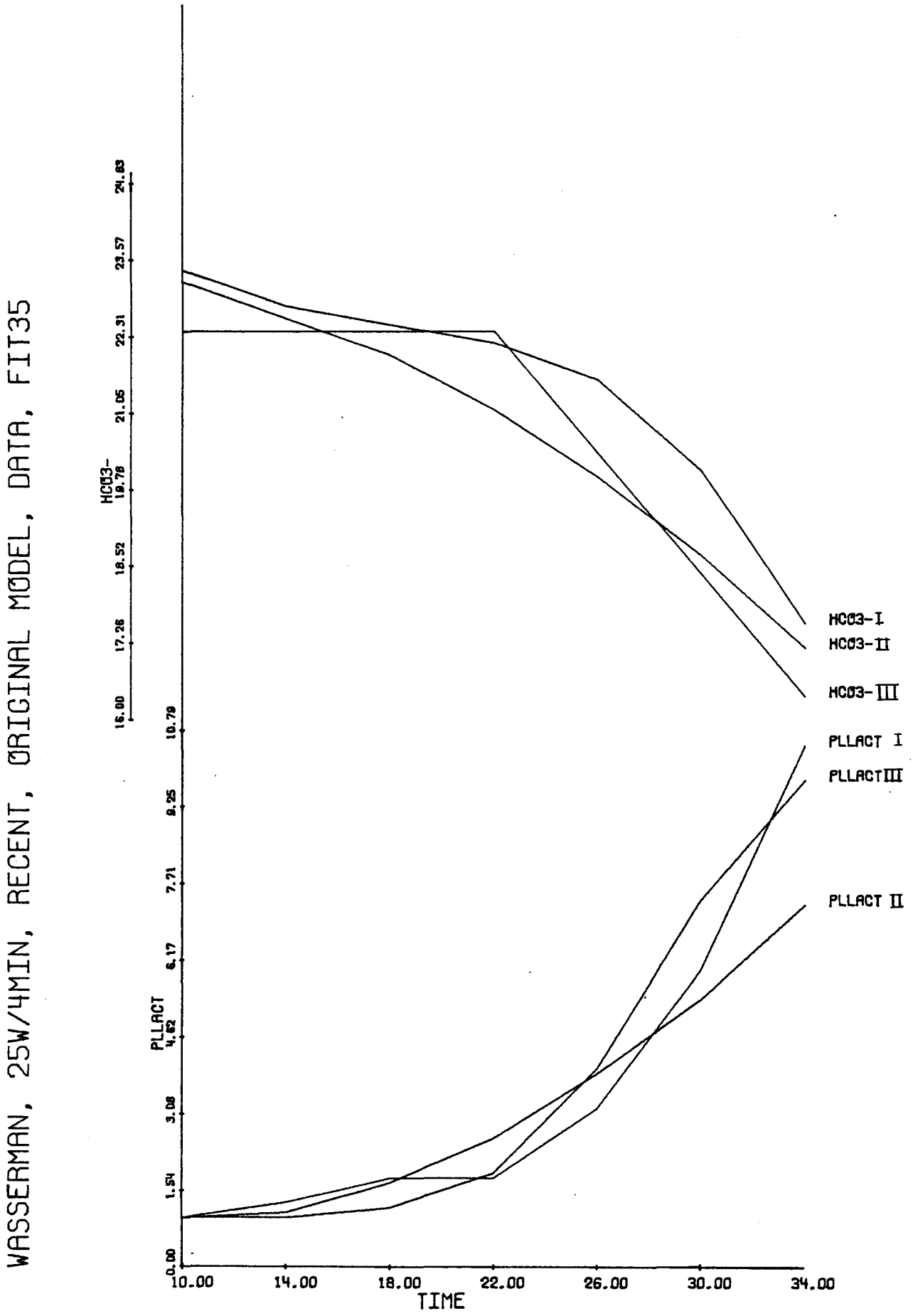

WASSERMAN, 25W/4MIN, RECENT, ORIGINAL MODEL, DATA, FIT35
HCO3-
16.00
17.26
18.52
19.78
21.05
22.31
23.57
24.83
PLLACT
0.00
1.54
3.08
4.62
6.17
7.71
9.25
10.79
10.00
14.00
18.00
22.00
26.00
30.00
34.00
TIME
HCO3-I
HCO3-II
HCO3-III
PLLACT I
PLLACTIII
PLLACT II

Fig.VI-3

WASSERMAN, 135 WATT CONSTANT LOAD TEST;
I=RECENT MODEL, II=ORIGINAL MODEL, III=LITERATURE DATA.
(FITNESS 35)

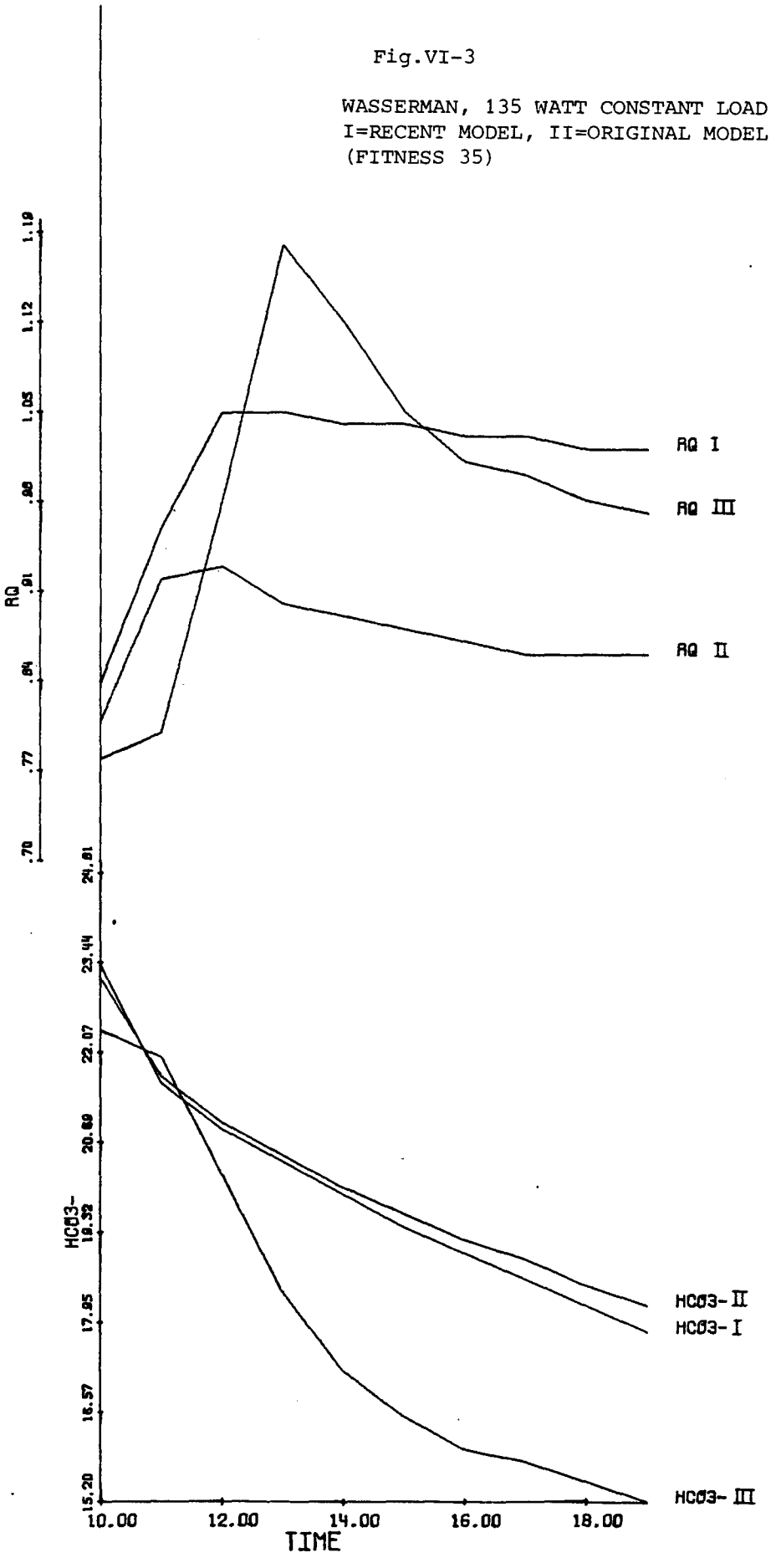
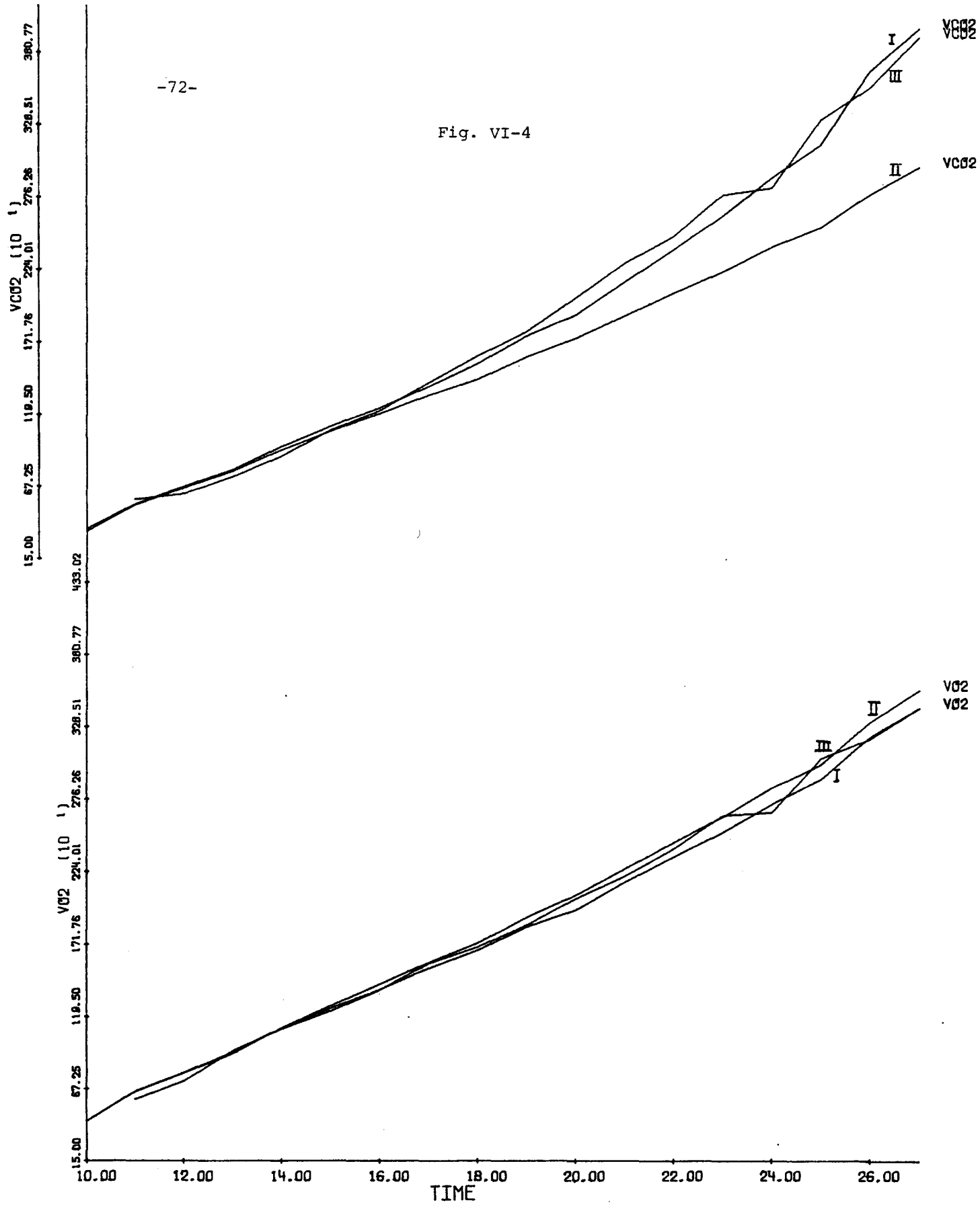
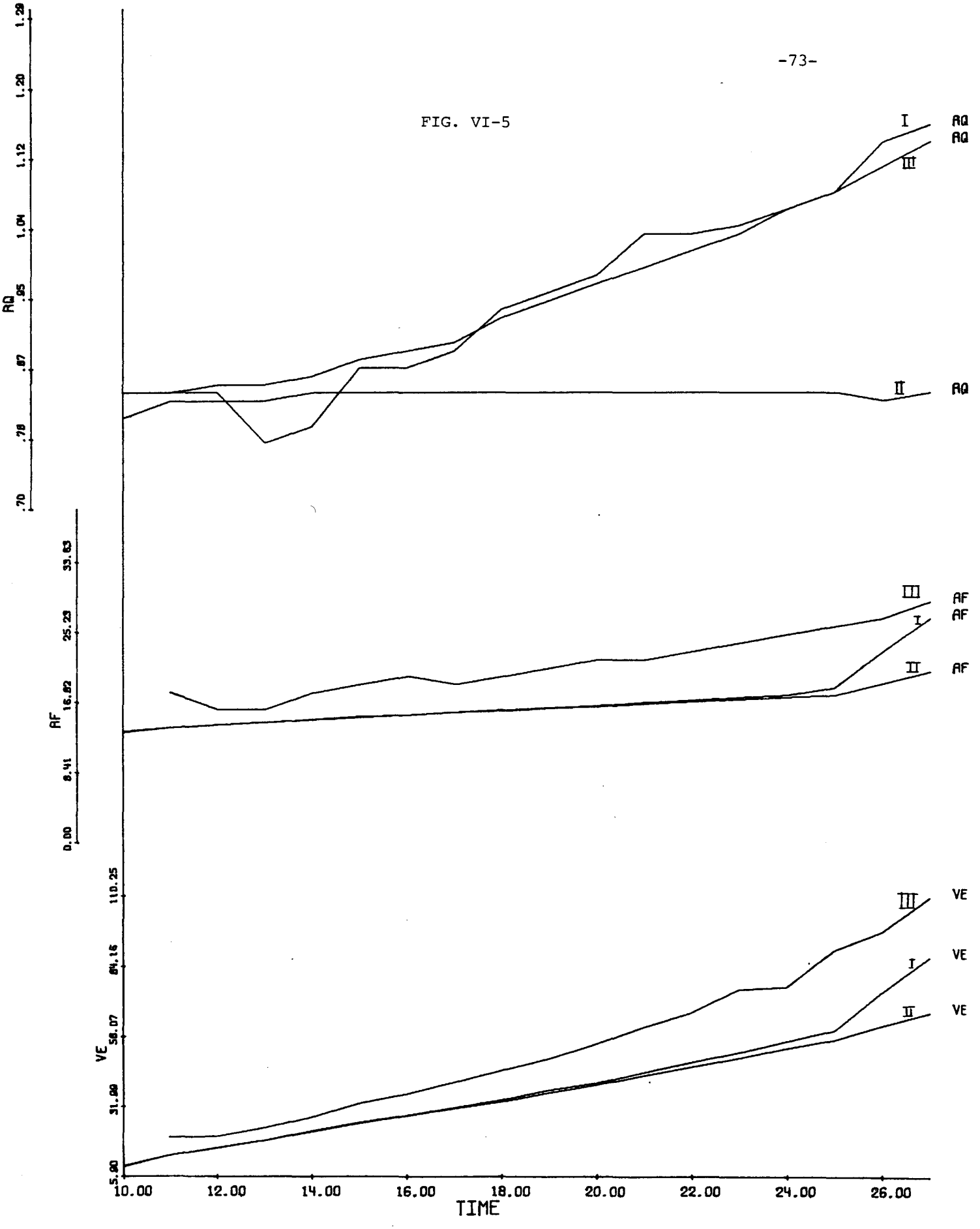


Fig. VI-4



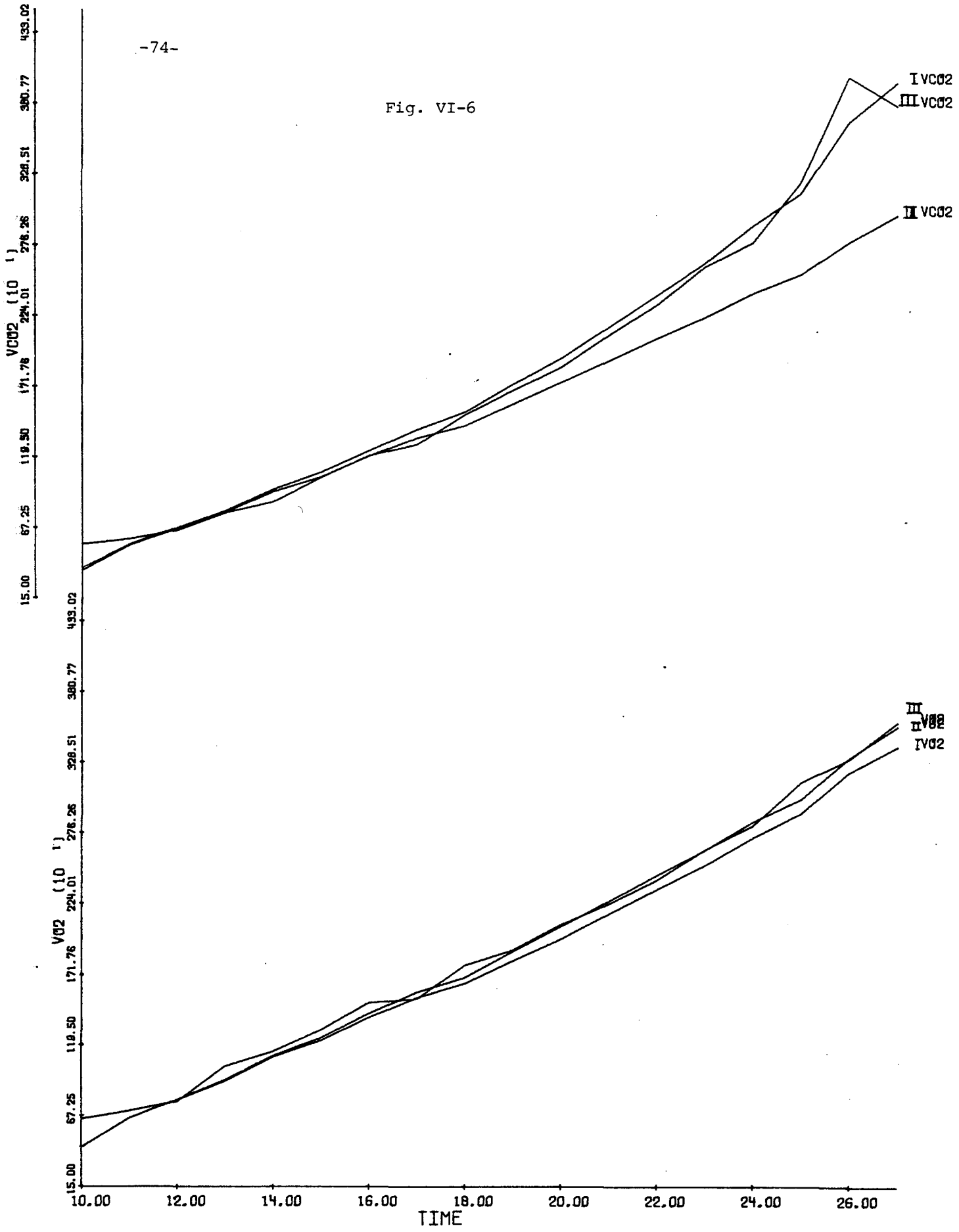
P.P.:KE., 15W/MIN, FIT31, RECENT, ORIGINAL MODEL, DATA.

FIG. VI-5



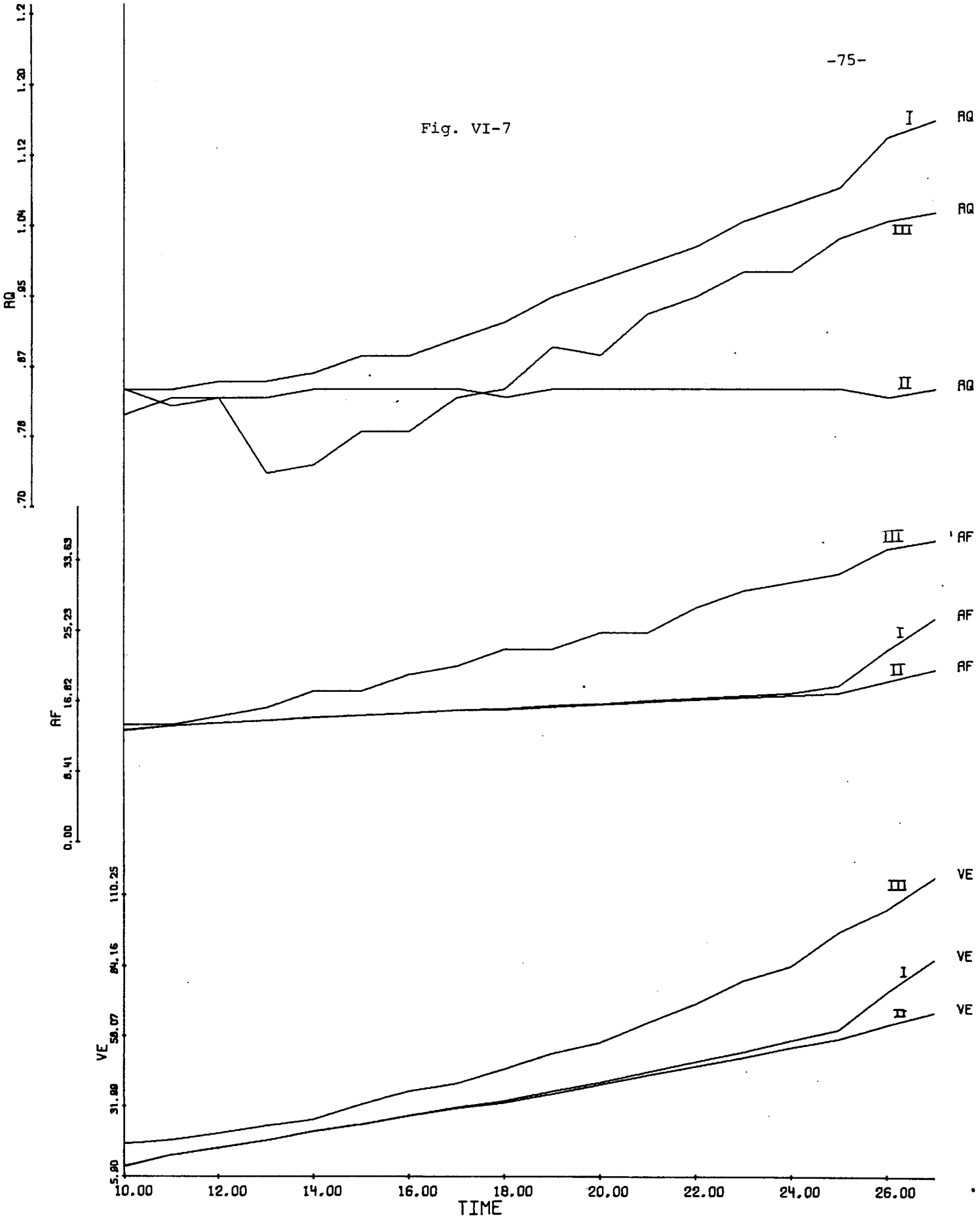
P.P. KE. 15 WATT/MIN. I=RECENT MODEL, II=ORIGINAL MODEL,
III=LITERATURE DATA. (FITNESS=31)

Fig. VI-6



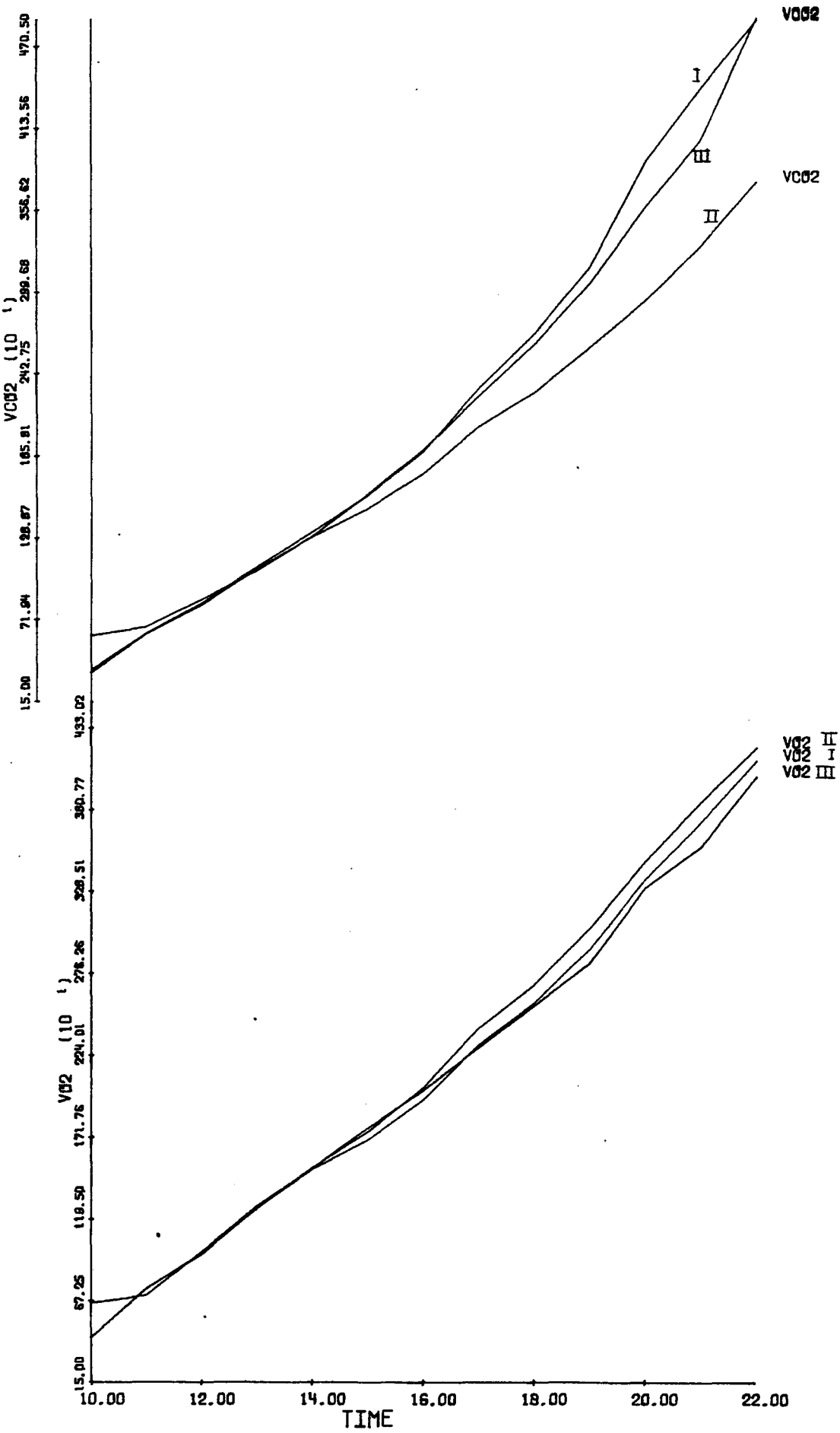
P.P.:W0., 15W/MIN, FIT31, RECENT,0RIGINAL M0DEL,DATA.

Fig. VI-7



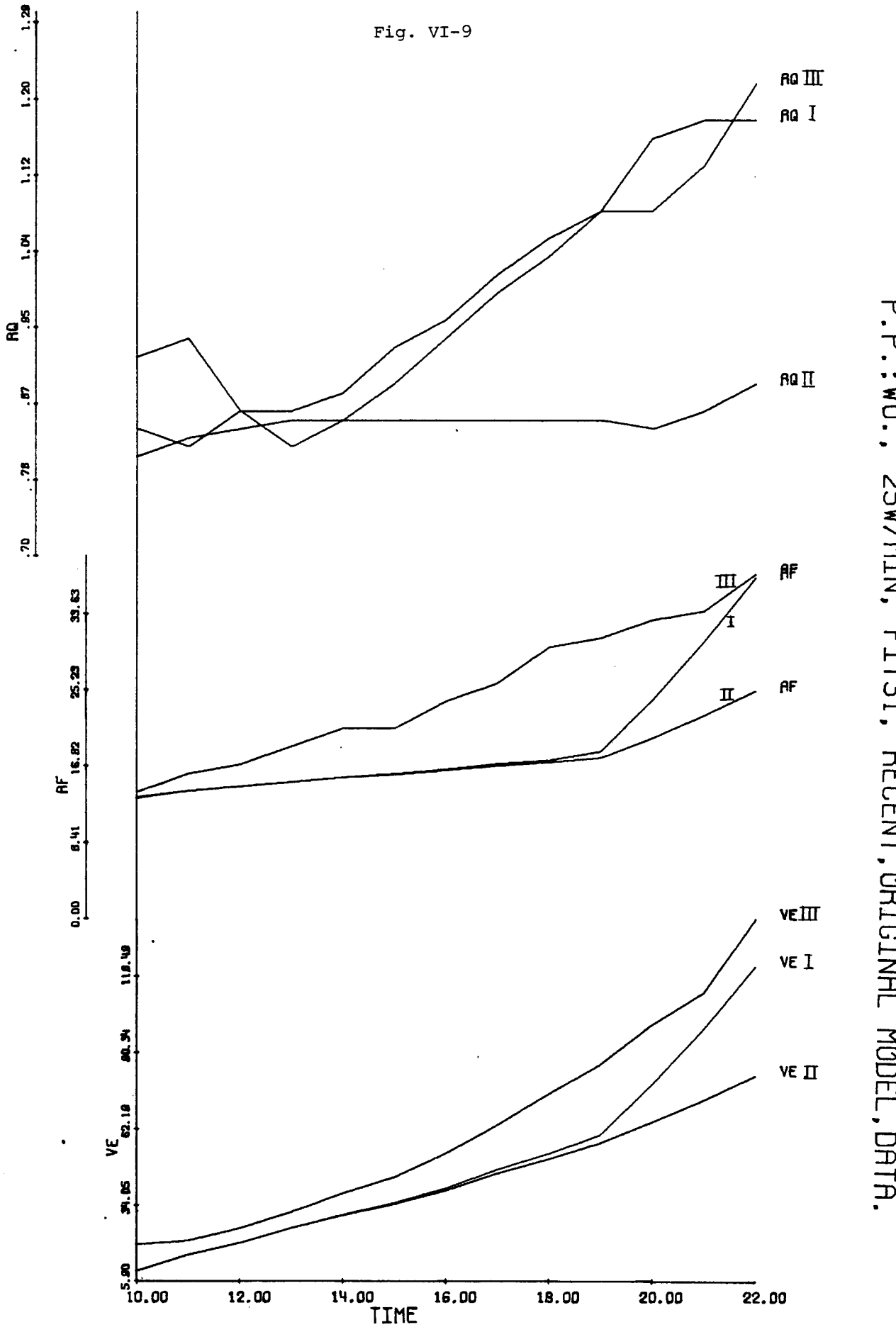
P.P.:W0., 15W/MIN, FIT31, RECENT, ORIGINAL MODEL, DATA.

Fig. VI-8



P.P.:WO., 25W/MIN, FIT31, RECENT,ORIGINAL MODEL,DATA.

Fig. VI-9



P.P.:WO., 25W/MIN, FIT31, RECENT, ORIGINAL MODEL, DATA.

Fig. VI-10

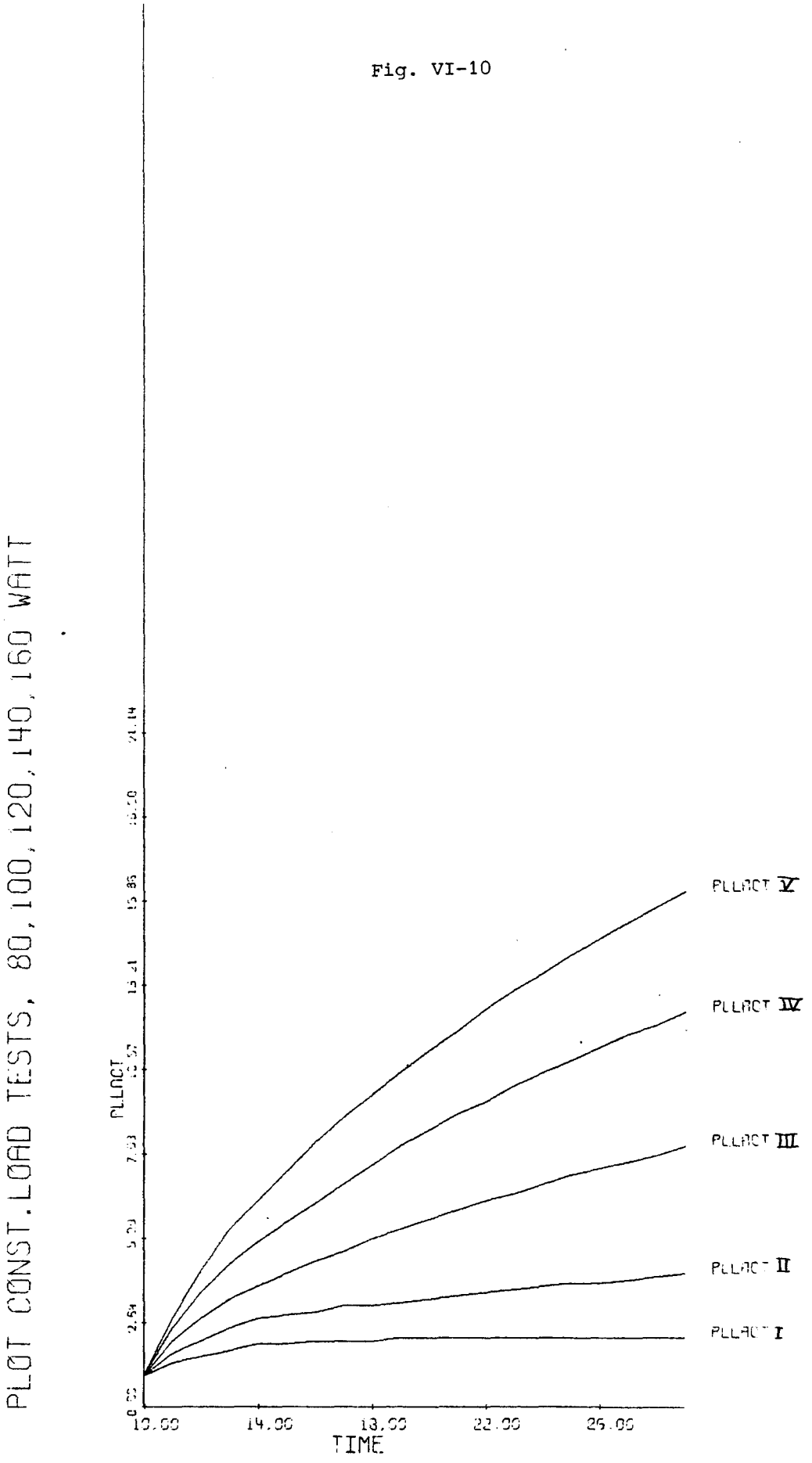
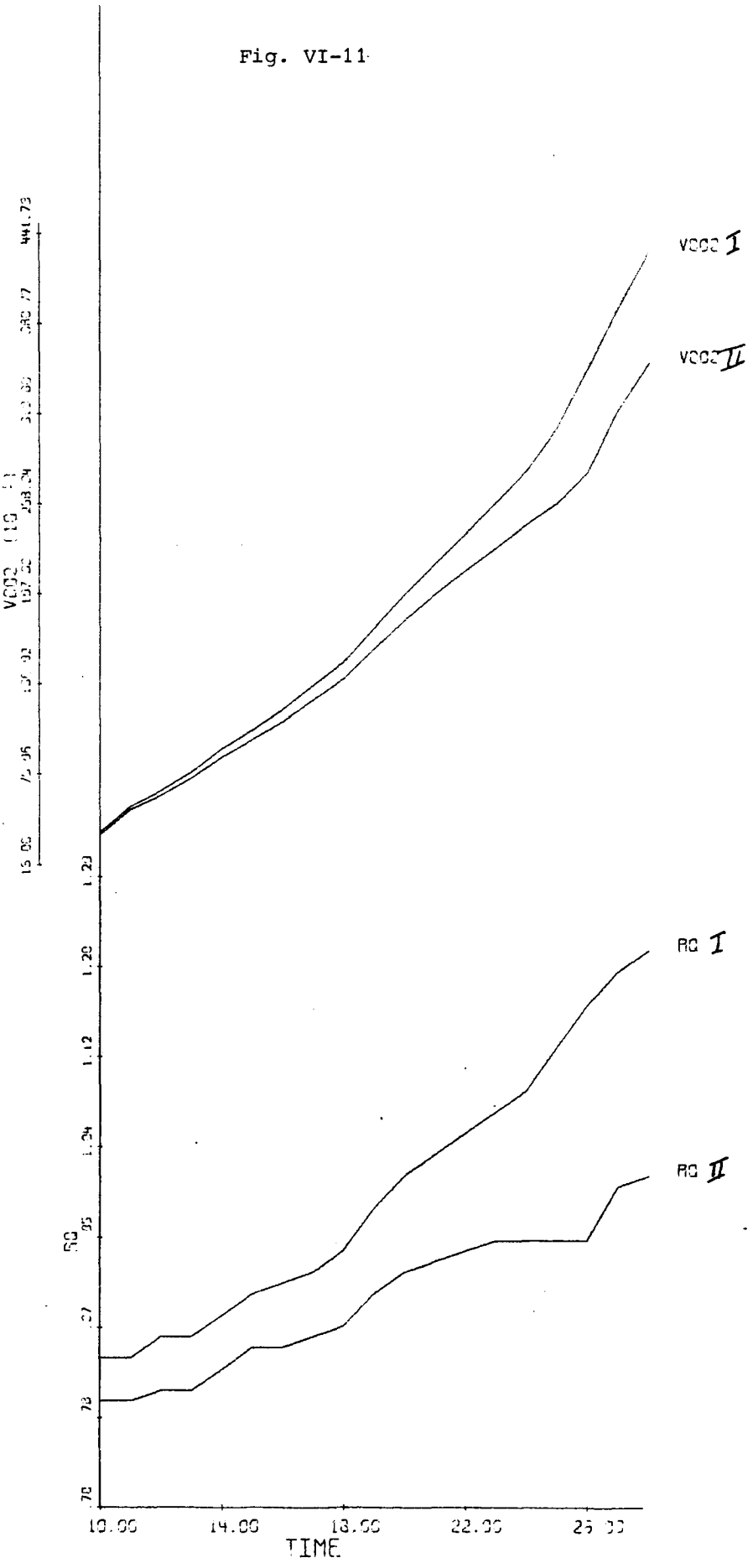

PLOT CONST.LOAD TESTS, 80,100,120,140,160 WATT
PLLACT
TIME
10.00
14.00
18.00
22.00
26.00
PLLACT V
PLLACT IV
PLLACT III
PLLACT II
PLLACT I

Fig. VI-11


15 WATTS/MIN., RECENT MODEL AND MODEL WITH CONSTANT TISSUE R.Q.
VO2 I
VO2 II
RQ I
RQ II
RQ
TIME
10.00
14.00
18.00
22.00

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

REFERENCES

Astrand, P. O., Rodahl, K., Textbook of work physiology, Mc. Graw Hill book company, New York, 1970.

Bakker, H.K., Struikenkamp, R.S., and de Vries, G.A. Dynamics of ventilation, heart rate, and gas exchange: sinusoidal and impulse work loads in man. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 48(2): 289-301, 1980.

Barter, C. E., Greville, H. W., and Campbell, A. H. Owles point, respiratory exchange ratio and blood lactate during exercise. Australian and New Zealand J. of Medicine; vol. 9 no. 4, 1979 (page 478).

B.G.D./P.T.T. ; medical department dutch P.T.T. The Hague, the Netherlands; personal communication.

Bock, A. V., Vancaulaert, C., Dill, D.B., Folling, A., and Hurxthal, L. M. Studies in muscular activity. IV. The steady state and the respitatory quotient during work. J. Appl. Physiol. 66 162-174 1928.

Bouhuys, A. J. Pool, R. A. Binkhorst, and P. van Leeuwen. Metabolic acidosis of exercise in healthy males. J. Appl. Physiol. 21(3): 1040-1046. 1966.

Buchberger J. Use of blood gas analysis for the evaluation of long-term physical efficiency in lumbermen. Int. Arch. Occup. Environ. Health 44, 45-53, 1979.

Carta, P., F. Sanna-Randaccio, M. S. Anni, G. P. Nissardi, D. Casula. Modifications respiratoires et metaboliques au cours d´exercices a charge costante a differents niveaux d´intensite par rapport au seuil anaerobique. Bull. Europ. Physiopath. Resp., 1979, 15, 171-183.

Casaburi, R. Stremel, R. W., Whipp, B. J., Beaver, W. L., and Wasserman, K.. Alteration by hyperoxia of ventilatory dynamics during sinusoidal work. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 48(6): 1083-1091, 1980.

Cerritelli, P., Pendergast, D., Paganelli, W. C., and Rennie, D. W.. Effects of specific muscle training on VO2 on-response and early blood lactate. J. Appl. Physiol. 47(4): 761-769 1979.

Clark, J. M., Sinclair, R. D., and Lenox, J. B. Chemical and non-chemical components of ventilation during hypercapnic exercise in man. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 48(6): 1065-1076, 1980.

Cohen, R. D., Yudkin, J., the contribution of the kidney to the removal of lactic acid under normal and acidotic conditions inthe

conscious rat. Clin. Sci. And Mol. Med., 48, 121-131, 1975.

Daniels, W. L., Sharp, Bascik, Kowal. Lactate accumulation in runners and non-runners during steady state exercise. Med. A. Science in Sport and Exercise, 12(2), 1980.

Davis, H. A. Blood lactate concentrations during incremental work before and after maximum exercise. Brit. J. Sports Med.: 1979,13,165-169.

Davis, J. A., Frank, M. H., Whipp, B. J., Wasserman, K. Anaerobic threshold alterations caused by endurance training in middle aged men. J. Appl. Physiol.: Resp environ. Exercise Physiol. 46(6), 1039-1046 1979.

Davis, J. A., Vodak, P., Wilmore, J. H., Vodak, J., and Kurtz, P. Anaerobic threshold and maximal aerobic power for three modes of exercise. J. Appl. Physiol. 41(4),544-550, 1976.

Davis, J. A., Whipp, B. J., Wasserman, K. The relation of ventilation to metabolic rate during moderate exercise in man. Eur. J. Appl. Physiol., 44, 97-108, 1980.

Dickinson, C. J., a computer model of human respiration, MTP Press limited, Lancaster, England, 1977.

Elridge, f. L., relationship between turnover rate and blood concentration of lactate in exercising dogs. J. Appl. Physiol. 39, 231-234, 1975.

Eykhoff, Pieter. System Identification (parameter and state estimation). John Wiley and Sons, 1974.

Evans, W. J., Skrinar, Gervino, Oliver, Phinney. Blood lactate levels at exercise intensities above anaerobic threshold. Med. A. Science in Sport and Exercise, 12(2), 1980.

Freund, H., Marbach, J., Ott, C., Lonsdorfer, J., Heitz, A., Zouloumian, P., Kehayof, P. Blood pyruvate recovery curves after short heavy submaximal exercise in man. Eur. J. Appl. Physiol.,43, 83-91, 1980.

Giminez, M., Romero Colomer, P., hennequin, R., Saunier, C. Arterial lactate levels and pulmonary haemodynamics during moderate exercise in chronic respiratory insufficiency. Bull. Physio-path. Resp., 1974, 10, 281-300.

Gimenez, M., Hennequin, R. Horsky, P., colas, Th., Saunier, C. Bull. Physio-path. Resp., 1974, 10, 463-479. Blood lactate concentration, acid base and electrolyte equilibrium during muscular exercise for 20 minutes at various loads and at the maximal power tolerated in man.

Guyton, A. C., Textbook of medical physiology, Fourth edition, W. B. Saunders Compan, London 1971.

Guz, A. Regulation of respiration in man. 1975, 303-323.

Hagberg, J. M., Hickson, R. C., Ehsani, A. A., Holloszy, J. O. Faster adjustment to and recovery from submaximal exercise in the trained state. J. Appl. Physiol.: Respir. Environ. Exercise Physiol., 48(2), 218-224, 1980.

Hagberg, J. M., Mullin, J. P., Nagle, F. J. Oxygen consumption during constant load exercise. J. Appl. Physiol.: Respir. Environ. Exercise Physiol., 45(3), 381-384, 1978.

Hermansen, L., Stensvold, I. Production and removal of lactate during exercise in man. Acta Physiol. scand. 1972, 86, 191-201.

Hermansen, L., Vaage, O., Williams, C., Helland, Nilsen, L. Glycogen synthesis and lactate metabolism during recovery after maximal exercise in man. Acta Physiol. Scand. V95, n2, pa13, 1975.

Hesser, C. M., Linnarsson, D., Bjurstedt, H. Cardiorespiratory and metabolic responses to positive, negative and minimum load dynamic leg exercise. Respiration Physiology (1977) 30, 51-67.

Hickson, R. C.,. Skeletal muscle adaptations , endurance, and frequency of training. Med. A. Science in Sport and Exercise, 12(2), 1980.

Hollman, W., Liesen, H. Uber die bewertbarkeit des lactats in der leistunsdiagnostik. Sportartzt und Sportmedizin 81973, 175-182.

Horstman, D., Patton, J., Vogel, J. Determination of anaerobic threshold from venous lactate concentration as a logaritmic function of 0/0 VO2max.

Ivy, J. L., Costill, D. L., Maxwell, B. D. Skeletal muscle determinants of maximum aerobic power in man. Eur. J. Appl. Physiol. 44, 1-8, 1980.

Ivy, J. L., Withers, R. T., Handel, v. P. J., Elger, D. H., Costill, D. L. Musle respiratory capacity and fiber type as determinants of the lactate threshold. J. Appl. Physiol.: Resp. Environ. Exerc. Physiol. 48(3), 523-527, 1980.

Jaeger, H., Selchow, B., Thiele, w. Studie zur bestimmung der dauerleistungsfaehigkeit. Zeitschrift Gesamte Hyg., 1976, 22-5, 339-342.

Jorfeldt, L., Juhlin-dannfelt, A., Karlsson,J. Lactate release in relation to tissue lactate in human skeletal muscle during exercise. J. Appl. Physiol.: Respir. Environ. Exerc. Physiol., v44, n3, 350-352 1978.

Kelman, G. R., Maughan, R. J., Williams, C. The effect of dietary modification on blood lactate during exercise. Proceedings of the physiological society, 34p-35p, 1975.

Keul, J. The relation between circulation and metabolism during exercise. Med. and Science in sports, 5, no.4, 209-219, 1973.

Keul, J., Kindermann, W., Simon, G. Die aerobe und anaerobe kapazitaet als grundlage fur die leistungsdiagnostic. Leistungssport, 8, no.1, 1978, 22-32.

Keul, J. Simon, G., Berg, A., Dickhuth, H.H., Goerttler, I., Kuebel, R. Bestimmung der individuellen anaeroben schwelle zur leistungsbewertung und trainingsgestaltung. Deutsche zeitschrift fuer sportmedizin VII/1979.

Kindermann, W., Keul, J., Huber, G. Physical exercise after induced alkalosis (bicarbonate or Tris-buffer). Eur. J. Appl. Physiol. 37, 197-204, 1977.

Kindermann, W., Simon, G., Keul, J. The significance of the aerobic-anaerobic transition for the determination of work load intensities during endurance training. Eur. J. Appl. Physiol. 42, 25-34, 1979.

Koyal, S. N., Whipp, B. J., Huntsman, D., Bray, G. A., Wasserman, K. Ventilatory responses to the metabolic acidosis of treadmill and cycle ergometrie. J. Appl. Physiol., 40(6), 864-867, 1976.

Lacour, J. R., Fladois, R. Le controle de la ventilation pulmonaire au cours de l'exercise musculaire. Bull. Eur. Physiopath. Resp. 1977, 13, 343-353.

Lemon, P. W. R., Mullin, J. P. Effect of initial muscle glycogen levels on protein catabolism during exercise. J. Appl. Physiol.: Resp. Environm. Exerc. Physiol. 48(4), 624-629, 1980.

Liesen von, H. B., Dufaux, B., Heck, H., Mader, A., Rost, R., Lotzerich, S., Hollman, W. Koerperliche belastung in training und alter. Deutsche zeitschrift fuer sportmedizin, VII/1979.

Londeree, B Ames, S. A. Maximal steady state versus state of conditioning. Eur. J. Appl. Physiol., 34, 269-278, 1975.

Mader,A., Heck, H., fohrenbach, R., Hollman, W. Das statische und dynamische verhalten des lactats und des saere-basen status im bereich niedriger bis maximaler azidosen bei 400 und 800 meter laufern bei beiden geschechtern nach belastunsabbruch. Deutsch zeitschrift fuer sportmedizin VII/1979.

Mader, A., Heck, Fohrenbach, Hollmann. Das statische und dynamische verhalten des lactats..... Fortzetsung von heft VII/1979. Deutsche zeitschrift fuer sportmedizin, VIII/1079.

Miller, D. A. A CO2 threshold mechanism in a closed loop avian respiratory system. J. Appl. Physiol.: Resp. Environ. Exerc. Physiol. 48(6), 1029-1034, 1980.

Nereaux, L. M. v., Vissers, Smolders, Binkhorst. Welke belasting

op de lopende band komt overeen met die op de fietsergometer. Ned. Tijdschr. Fysiother. 4-1977.

Niemala, K., Palatsi, I., linnaluoto, M., Takkunen, J. Criteria for maximum oxygen uptake in progressive bicycle tests. Eur. J. Appl. Physiol. 44, 51-59, 1980.

N.I.P.G., nederlands instituut voor preventieve geneeskunde. Jaarverslag 1979. Leiden.

Orr, G. W., Green, Hughson, Bennet. A computerized technique for determination of anaerobic threshold. Med. A. Science in Sport and Exercise, 12(2), 1980.

Pendergast, D., Cerritelli, P., Rennie, D. W. Aerob glycolytic metabolism in arm exercise. J. Appl. Physiol.: Resp. Environm. Exerc. Physiol. 47(4), 754-760, 1979.

Pernow, B., Wahren, J., Zetterquist, S. Studies on the peripheral circulation and metabolism in man. IV. oxygen utilisation and lactate formation in the legs of healthy young men during strenuous exercise. Acta Physiol. Scand. 1965, 64, 289-298.

Poortmans, J., Delescaille, J., Leclercq, R. Lactate uptake by inactive forearm during progressive bicycle exercise. J. Appl. Physiol. v45, n6, 1978, 835-839.

Reiterer, W. Kriterien der koerperlichen leistungsfaehigkeit. Weiner medizinische wochenzeitschrift, suppl. no.42(1977.

Riley, R. L., Cournand, A., Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J. Appl. Physiol., 1, 825-847, 1949.

Ryan, W. J., Sutton, J. R., Toews, C. J., Jones, N. L. Metabolism of infused 1(+) lactate during exercise. 1978.

Sahlin, K., Alvestrand, A., Brandt, R., Hultman, E. Acid base balance in blood during exhaustive bicycle exercise and the following recovery period. Acta Physiol. Scand. 1978, 104., 370-372.

Sanchez-medina, F., Mayor, F. Lactic acidosis and renal phospho-enolpyruvate carboxykinase activity during exercise. Biochemical medicine 14, 355-367, 1975.

Senger, H., Donath, R. Zur regulation der oxydativen substrat-verwertung im muscel bei erhohtem ATP-umsatz. Med. U. Sport XVII (1977), h12.

Stremel, R. W., Whipp, B. J., Davis, J. A., Wasserman, K. Dynamics of ventilation and CO2 output during moderate and heavy exercise. Exercise heat and sweat I 943.

S.V.R., sociale verzekeringsraad. Jaarverslag 1979. Den Haag.

Swanson, G. D. Overview of ventilatory control during exercise. Med. and Science in sports 11(2), 221-226, 1979.

Tashkin, D. P., Goldstein, P. J. and Simmons, D. H., Hepatic uptake during decreased liver perfusion and hypoxaemia. Amer. J. Physiol., 223, 968-974, 1972.

Tesch, P. A.. Muscle lactate accumulation after anaerobic training. Med. A. Science in Sport and Exercise, 12(2), 1980.

Udassin, R., Shoenfeld, Y., Shapiro, Y., Birenfeld, C., Sohar, E. Serum glucose and lactic acid concentrations during prolonged and strenous exercise in man. Americ. J. of Physical Medicine, 56(5), 1977

Ward, S. A., Whipp, B. J. Ventilatory control during exercise with increased external dead space. J. Appl. Physiol.: Respirat. Environ. Exerc. Physiol. 48(2), 225-231, 1980.

Wasserman, K., Kessel, A. L., Burton, G. G. Interaction of physiological mechanisms during exercise. J. Appl. Physiol. 22(1),71-85, 1967.

Wasserman, K., Whipp, B. J., Koyal, S. N., Beaver, W. L. Anaerobic threshold and respiratory gas exchange during exercise. J. Appl. Physiol., 35(2), 236-243, 1973.

Wasserman, K., Whipp, B. J. Exercise physiology in health and disease. Amarican review of respiratory disease ,vol.112, 1975.

Weltman, A., Katch,V. L. Relationship between the onsett of metabolic acidosis (anaerobic threshold) and maximal oxygen uptake. J. Sports Med., 19, 1979.

Whipp, B. J., Davis, J. A., Stremel, Torres, Casaburi, Wasserman. The role of the anaerobic threshold in the dynamics of O2 uptake during exercise. Med. and Science in Sports, v11, n1, p96, 1979.

Whipp, B. J., Wasserman, K. Oxygen uptake kinetics for various intensities of constant load work. J. Appl. Physiol., 33(3) 1972.

Whipp, B. J., Wasserman, K., Davis, J. A. Ventilatory control characteristics of supra-threshold exercise. Control of breathing I , 4266.

Wiswell, R. A., Girandola, Bulbulian, Simard. The effect of two houres of running on anaerobic threshold. Med. A. Science in Sport and Exercise, 12(2), 1980.

Zeigler, B. D. Theory of modelling and simulation, J. Wiley and Sons, New York, 1976.

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Date
Your reference
Our reference
Subject Macpuf

Dear Sir

As a part of my doctoral study,I am working on a 6 month project on anaerobic threshold mechanisms in bicycle ergometer exercise. In this I make use of the model "MACPUF".
As I am working with high excercise levels,I was forced to use a 1 second fractional time interval.
This is lower than the minimum fract. time int. suggested in the description of the model,so I had to investigate possible consequenses of this action.
When I looked into subroutine DELAY ,I saw that I would have to adapt it to my situation.Trying to do so,I noticed some strange behavior of the original version of this subroutine.

1. If NFT=10,the subroutine fills an array from Index to Index+NFT-1.
So it fills 10 "compartments"(one to (one+nine))
As there are only 10 compartments available,it has to READ from the next compartment in circle,which is number one.
Doing so,there whill be read the same value as was inserted in this interval,so there is no extra time delay produced.

2. In Dr.Dickinson's book about MACPUF he gives some examples about relations between FT,COADJ,and NFT.
When I inserted these values in the formula given for NFT (NFT=IFIX(13.2 sqrt(COADJ*FT))),I found results which differ from the results given in the book.

   a COADJ=5 FT=10 sec.=0.16667 min.
   NFT=IFIX(13.2 x sqrt(5 x 0.16667) = 12
   The book gives a value of 10,and this value can only be reached through the statement ,that NFT has a maximum of 10.

   b COADJ=5 FT=0.03333 min.=2 sec.
   NFT=IFIX(13.2 x sqrt(5 x 0.03333)= 5

   COADJ=1.5 FT=0.03333 min.
   NFT=IFIX(13.2 x sqrt(1.5 x 0.03333))= 2
   According to the book NFT should fall to unity in both cases.

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Date
Your reference
Our reference
Subject

Doing some calculations on the possibilities of the creation of a time delay I tried the following:

Create a 20 compartment array,
create a lineair relation between FT and NFT,e.g. NFT=IFIX(1.2 x FT)
which would give;

FT in sec.

FT	NFT	DELAY(total)
1	1	20
2	2	20
3	3	21
4	4	20
5	6	20
6	7	18
7	8	21
8	9	24
9	10	18
10	10(maximum)	20

Doing so the delay whould be about 20 sec. like Dr. Dickinson suggests in his book.
But what to do with the cardiac output?
I inserted it as a lineair relation to FT but I have no physiological arguments to do so.
At the moment I use the formula:NFT=IFIX(COADJ/5 x 1.2 x FT x 60)
shorter: NFT=IFIX(14.4 x COADJ X FT).

I would like to ask if you could give any comments on my findings and would be very gratefull if it would be possible for you to answer me soon.

your's sincerely

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30th June 1980

Dr. G. Havenith,
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Dear Dr. Havenith,

Dr. Ingram asked me to reply to your letter. I am afraid there are two sources of confusion and both are my fault. First of all, there is an error in the program itself as printed in the book in that in Subroutine DELAY on page 215, the first line of the program has a bracket in the wrong place and the bracket after 'FT' should come after'COADJ'. This means, as you correctly infer, that the DELAY will be inversely proportional to FT. The correct whole line is :
NFT = IFIX (13.2*SQRT (COADJ)*FT)

You were quite right in your calculations. The correct form of the expression makes NFT = 5 under ordinary circumstances, so that there is one 10 second delay period incorporated. When FT is reduced to 2 seconds, then NFT becomes 1. The statement about cardiac output is misleading, I am afraid, and results from the text of this part of the book having been written at a time when the function was linear in respect of cardiac output. The physiological reasoning behind using a square root term for cardiac output was that when the cardiac output is very low then many vascular beds will be shut down and the effective circulation time will probably not be very greatly diminished for that portion of the blood which is still going to perfused organs. When the cardiac output reaches 25 litres/minute, then NFT will become 10 and, as you say, the delay will disappear. This seemed to me approximately realistic. (At least, with only be 1 iteration ie 2 secs.

I am sorry for the error in the program you have and for the confusion it has produced. I think that your function is an entirely reasonable one for 1 second iteration intervals, but I would be inclined to substitute for 'COADJ/5' the square root of that expression so that with only moderate increments in cardiac output with exercise, some delay will still persist. However such approximations have to be based on reasonable physiological guesses and I should be most interested to hear in due course how the predictions measure up to observations.

(ie SQRT(COADJ/5.)

Yours sincerely,

John Dickinson

C.J. Dickinson,
Professor of Medicine.