セラピューティックフォーラム
特 別 講 演

Exercize Therapy for Heart Failure Patients

Pr Alain Cohen-Solal*

I will start only by reminding that in the definition of heart failure, we have both the term "heart" and "periphery" (Table 1). Because in general, a good definition of heart failure is "the inability of the heart to deliver a cardiac output sufficient to meet the needs of the periphery, not only at rest but also during exercise". So there is a tight coupling in the definition between the heart and the periphery. And often people neglect the role of the periphery in the symptoms of heart failure. And we will see now in the next minutes that this role is very important and this is mainly the rationale for the exercise therapy in heart failure.

(Table 2) We will see successively the rationale of exercise training in this patient, what are the main inclusion criteria, the result of the studies, what were the protocols that were used, how to select the patients, and also some unsolved issues.

(Fig. 1) First, I would like to remind you that contrary to general belief, there is no clear relation between the alteration of the left ventricle function here expressed by the depressed ejection fraction on one side, and the exercise capacity of the patient reflected here by the peak oxygen consumption on the y-axis. There is really no significant correlation. So you cannot predict the exercise capacity of the patient based on the rest ejection fraction.

And you can see for example that here you have ten patients with an ejection fraction of ten percent with a very different exercise capacity. It is likely that, for example, these patients need perhaps cardiac rehabilitation and perhaps these patients do not need as more (much) as these ones, cardiac rehabilitation.

(Fig. 2) Because in order to explain this discrepancy, we have to consider the chain of transport of the oxygen in the body. In the body, when we perform an

*Service de Cardiologie, Hopital Beauj, Paris, France

Table 1 Heart failure : defintion

Inability of the *heart* to deliver a cardiac output sufficient to the needs of the

→ coupling heart/periphery
→ dynamic state

Table 2 Exercise Training in CHF

- Rationale
- Inclusion criteria
- Main results
- Ancillary results
- Protocols
- Selection of the patients
- Unsolved issues

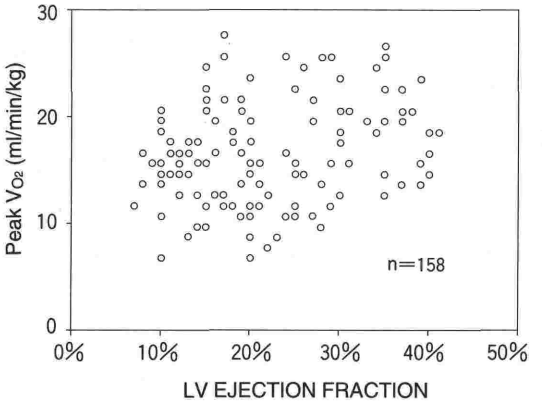


Fig. 1

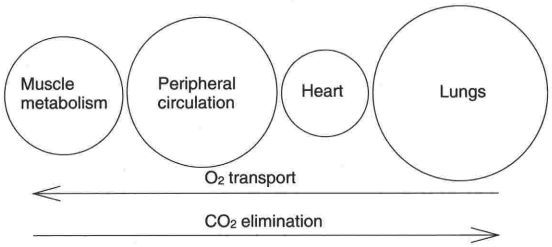


Fig. 2 The O_2/CO_2 transport chain

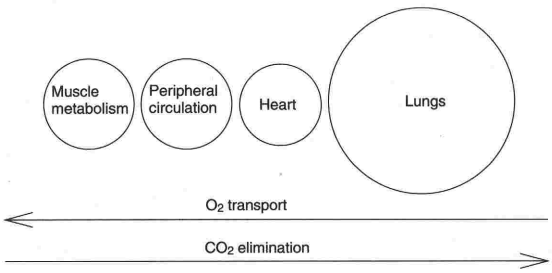
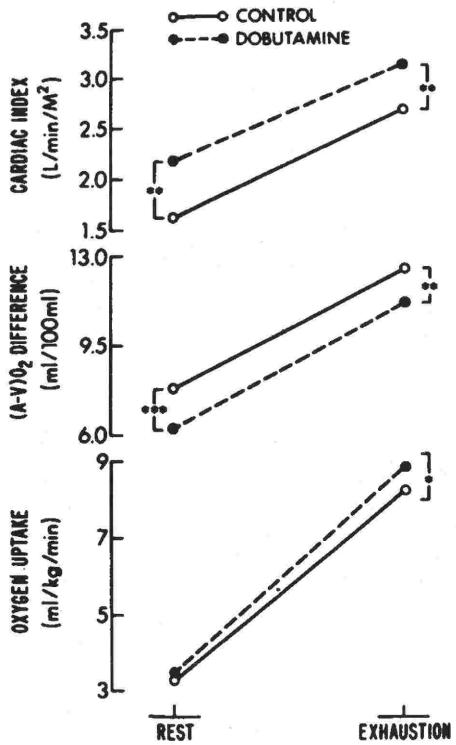


Fig. 3 The O_2/CO_2 transport chain in CHF

exercise, we transport oxygen from the lungs to the muscle and we reject CO_2 from the muscle to the lungs. And I have depicted some spheres, some rounds that depict the capacity of one organ to delay it or to accept, to increase its capacity in order to meet the exercise response. And as you see the reserve of the lung is very high, the capacity of the peripheral dilation to dilate is very important in a normal subject as well as it is the capacity of the muscle metabolism to increase. But the limited parameter here is the heart. So in the normal subject, the ability to increase cardiac output is the limiting factor to exercise.

(Fig. 3) In patients with heart failure, obviously the ability to increase cardiac output is limited. But we have learned in recent years that other factors also play an important role and as you can see, the alteration of the peripheral circulation and of the muscle metabolism seems to play a role at least equal to that of the heart, in the limitation of oxygen transport and in the increase in oxygen transport and the elimination in CO_2. So in the five next minutes, we will say some word about these abnormalities of the periphery, namely the muscle and the vessel

(Fig. 4) I will show you three examples. For example, one can imagine that when we increase acutely cardiac output in a patient, we shall increase acutely exercise capacity. This is not true. Here is an example of a patient with a reduced cardiac output at rest and exercise, and a very limited peak oxygen uptake. When you increase acutely by dobutamine cardiac output at rest and at peak exercise, you see that you have very little increase peak V_{O_2}. This means that the increase in cardiac output probably was not increased in direction to the muscle or was not correctly utilized by the muscle. This means that the periphery here limited the ability of the heart to deliver an increased cardiac output to the periphery.



D'après CS Maskin, Am J Cardiol, 1983

Fig. 4

(Table 3) So what are these peripheral abnormalities? There are formalities both at the level of the vessel which is mainly an abnormality of flow mediated vasodilation and also abnormalities of the muscle that we will discuss.

(Fig. 6) For example, it has been shown in recent

Table 3 Peripheral Abnormalities

- *Vascular abnormalities*
  - flow-mediated vasodilatation
- *Muscular abnormalities*
  - quantitatives
  - qualitatives
    - shift in fiber typology
    - mitochondrial metabolism abnormalities

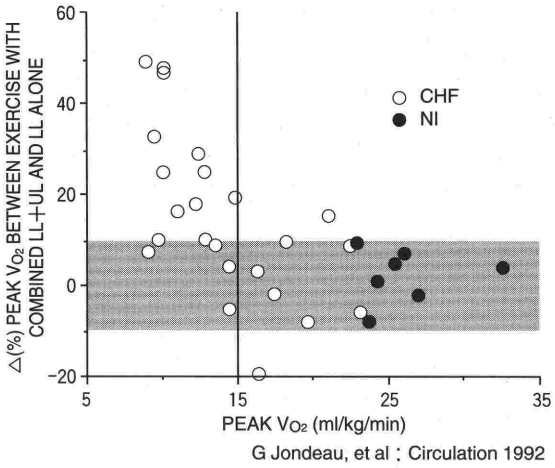


Fig. 5

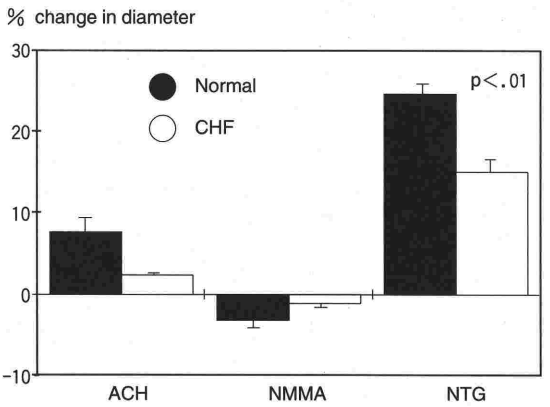
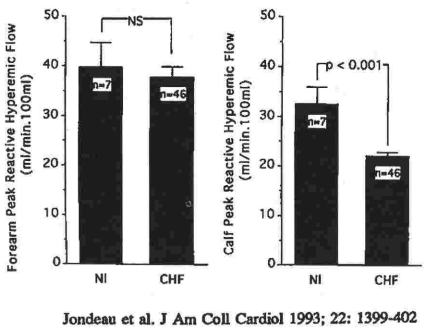


Fig. 6 Large vessel responses to intra-arterial infusions



Jondeau et al. J Am Coll Cardiol 1993; 22: 1399-402

Fig. 7

years that the ability of the vessel within the muscle of the patient with chronic heart failure to dilate in response to an injection of a substance like acetylcholine which increases flow dependent vasodilation is decreased in patients with heart failure. Here is the Response Unit Study and Drexler following intra-arterial infusion of acetylcholine in normal subjects and in patients with heart failure, you note a clear decrease of this flow-mediated vasodilation in patients with heart failure. Note also that although this response is markedly dependent on the endothelium, it seems that so the response to an endothelium-independent vasodilator such as nitroglycerin is also slightly reduced in patients with heart failure as compared to normal subjects. Thus, the ability of the vessel in the muscle to respond to any stimuli seems to be decreased in patients with chronic heart failure.

(Fig. 7) This was elegantly shown also four years ago in a study by Girard Jondeau in New York who assess the reactive hyperemic bloodflow in the forearm and in the calf, in the lower limb, in normal subjects and in patients with heart failure. You can notice that the decrease in the reactive hyperemia was mainly observed in the calf and not in the forearm. This seems to mean that this abnormality or vasodilation is more marked in the lower part of the body than in the upper part. One can imagine that this is due - because patients with heart failure are deconditioned and do not use their lower limbs as often as they use their arms. And the vasodilator capacity of the vessels of the arms is less altered than that of the legs. This may support the use of training in this patient to improve the vasodilator capacities of the vessels within the calf.

(Fig. 8) The second culprit is probably the muscle.

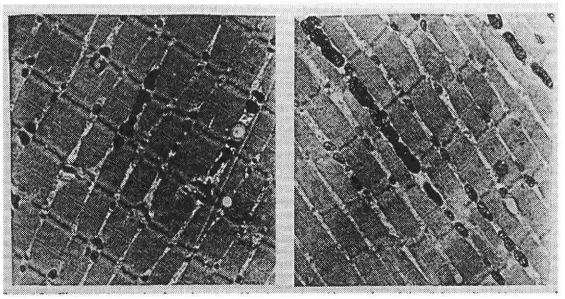
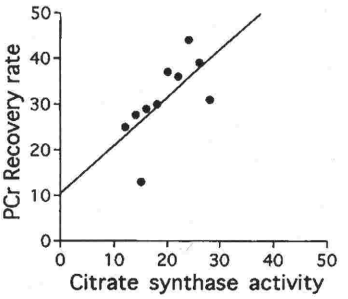


Fig. 8



KK Mc Cully et al. J Appl Physiol 1993; 75: 813-9

Fig. 10

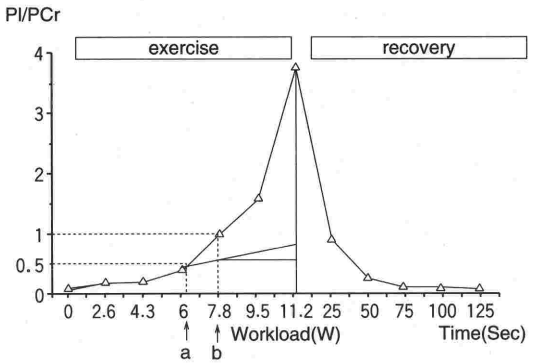


Fig. 9

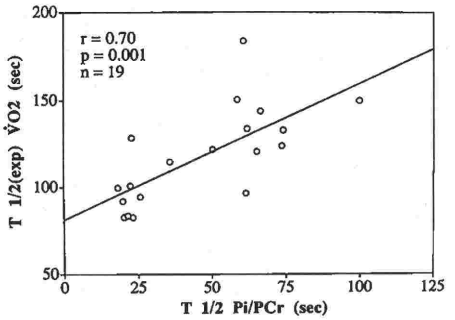


Fig. 11

We know that patients with severe heart failure have some atrophy of the muscle, have sometimes cachecia with increase in cytokin such as tumour necrosis factors, that result in cachecia. And when you perform electron micrography of patients with severe heart failure for example on the left, and a normal subject on the right, you can see that the enzyme activity within the mitochondria, which is shown here in black, is reduced in patients with heart failure compared to normal subjects.

That is to say, the number - the enzyme, the oxidative enzymes - are decreased in patients with heart failure compared to normal subjects without change in glycolytic enzyme. And this results in a shift in the typology of the fibers within the muscle with a decrease in Type 1 and 2A fibers and an increase in Type 2B fibers.

(Fig. 9) We can also assess this by performing anama spectroscopy of 31 phosphorus during exercise and during recovery, and you can assess during exercise and recovery the ratio of anorganic phosphate divided by creatinine phosphate. And you know the kinetics of recovery of creatinine phosphate is related to the metabolic state of the muscle.

(Fig. 10) There is a close relationship between the PCr recovery rate and the citrate synthase activity within the muscle as shown by the group of McCully.

(Fig. 11) And we have some years ago correlated the half-time of recovery of creatinine phosphate after exercise in patients with heart failure and we have found that it was decreased in relation with the half-time of recovery of oxygen uptake after exercise.

(Fig. 12) And as you can see, the more severely reduced is the peak exercise capacity of the patient, the more prolonged is the recovery of the creatinine phosphate within the muscle after exercise. This means probably that all these patients have intrinsically an abnormality of their muscle metabolism that

probably can be ameliorated by training.

(Fig. 13) And finally, the group of Mancini in Philadelphia elegantly showed that improving blood flow within the muscle is not sufficient to improve muscle metabolism. They have assessed the muscle oxygenation during exercise by infrared spectroscopy in normal subjects, there, and in patients with heart failure. And you can see that for a similar level of muscle de-oxygenation, patients with heart failure exhibit a greater decrease in creatinine phosphate than normal subjects. This means that the abnormalities of muscle metabolism seems to be not solely related to reduced bloodflow, but also to other mechanisms.

(Table 4) So the consequences of this abnormality of muscle metabolism are changes in fibers typology with an increase in Type IIB fibers, an increase in lactate and protons production, leading to an early anaerobic metabolism during exercise, early fatigue, decreased force and perhaps occasional dyspnea.

(Table 5) And concerning the mechanism leading to this muscle metabolism abnormality, we have no clear explanation. One can suggest three possibilities. The first, all these are only secondary to chronic bloodflow reduction, some others evoke the possibility that patients with heart failure have generalized myopathy within the heart as well as within the muscle. But a third possibility is that de-conditioning presented by most of the patients with severe heart failure, plays by itself a role in this muscle abnormalities.

(Fig. 14) An example here is given by a study performed in France where this group has compared the profile of creatinine phosphate during exercise in patients with heart failure there, in trained subjects there, and in normal but sedentary subjects. And you can see that sedentary subjects have a profile of

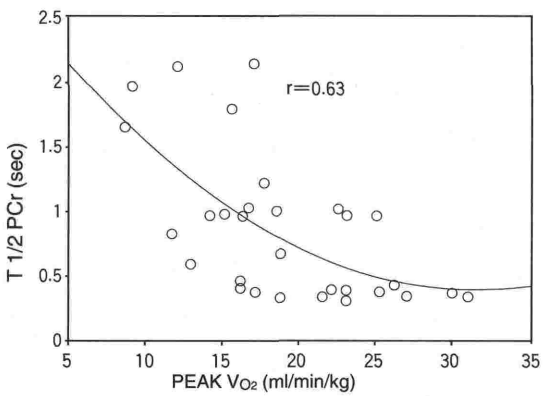


Fig. 12 Role of oxydative metabolism

Table 4 Abnormalities of muscle metabolism Consequences

⟶	change in fibers typology (Ⅱb↗)
⟶	increase in lactate and H+ production
⟶	early anaerobic metabolism, fatigue, decreased force
⟶	dyspnea ?

Table 5 Muscle metabolism abnormalities : Mechanisms

- Chronic blood flow reduction
- *Deconditioning*
- Generalized myopathy

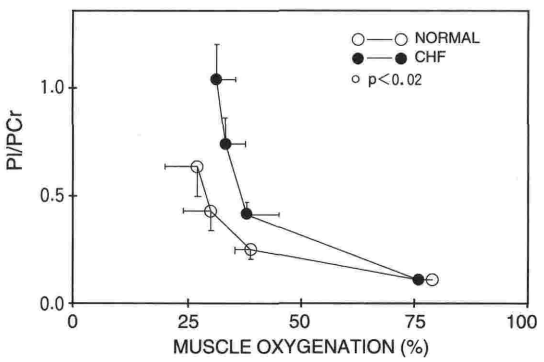
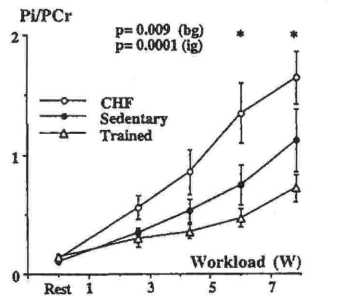


Fig. 13



Z Chati et al. Am Heart J1996; 131: 560-6

Fig. 14

creatinine phosphate depression during workload that is intermediary between patients with heart failure and trained subjects.

(Fig. 15) So after this introduction, we can now - after this rationale for the possible use of training in patients with heart failure, what is known now about training in these patients? We have few studies on this therapy. One of the first studies was an unblind study conducted by the group of Martin Sullivan in Duke, Carolina, US In a small group of patients with severe heart failure, they compared the response before and after I think three months of training recording the hemodynamic profile. You can see here that training resulted in an increase from here to here in peak oxygen consumption with very limited and insignificant increase in peak cardiac output. So it seems that the increase in peak Vo_2 was mainly due to changes in the periphery because peak Vo_2 was not markedly changed. And this is the case because as you can see, the artero-venous oxygen difference was significantly increased after training than before training.

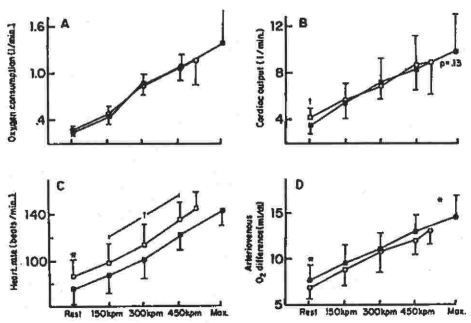
So this study first showed that the beneficial effect of training seems to be due mainly to changes in the periphery than to changes in cardiac hemodynamics. Note however that for a similar increase in cardiac output, patients with heart failure always exhibited a lower heart rate at each stage, as can be observed after training in athletes. That is to mean that at each stage, stroke volume was increased, but as you can see, cardiac output was not significantly increased at each level of submaximal exercise.

(Fig. 16) They showed also that leg bloodflow was significantly increased as was also leg oxygen delivery.

And you can see there was also a slight reduction in peripheral vascular resistance within the leg that was above the line of significance.

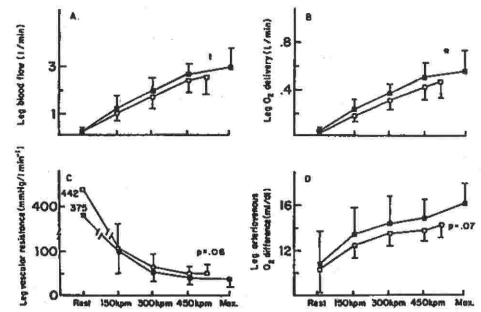
(Fig. 17) What was very significant was a significant decrease in arterial lactate throughout exercise in the blood as well as in the femoral vein.

(Fig. 18) These others - this was the response during a graded maximal exercise - the others also examined the response during a constant workload submaximal exercise. And the effect was probably more clear during this type of exercise. Here on the y-axis you have the time of exercise, as you can see at each level of exercise, after training, you have a decrease in heart



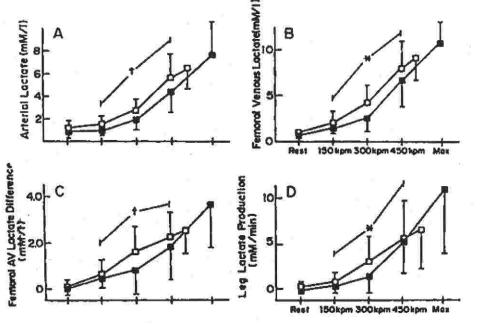
D'après Sullivan, Circulation 1988, 78, 506-15

Fig. 15



D'après Sullivan, Circulation 1988, 78, 506-15

Fig. 16



D'après Sullivan, Circulation 1988, 78, 506-15

Fig. 17

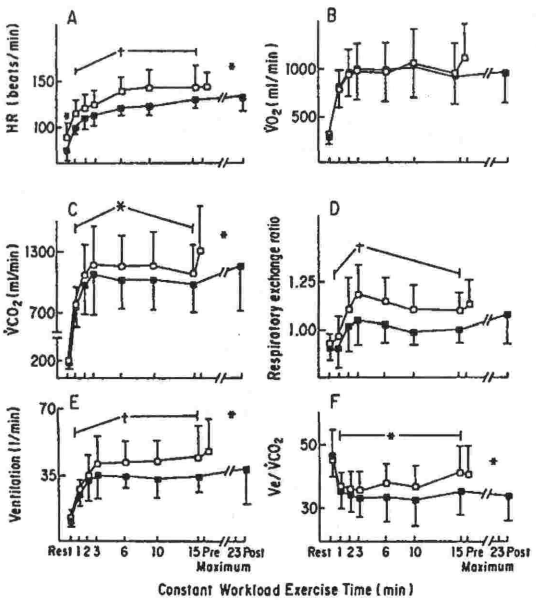
rate. And also you have what is, I think, more interesting is also a decrease in ventilation at each level of exercise. This means that for performing the same task, the same workload, patients hyperventilated less. And this is probably beneficial for the point of view of quality of life and of symptom.

They also assess the respiratory exchange ratio, that is the ratio of VCO_2 by V_{O_2}, that was also significantly decreased by training. So they found in this first study that the improvement in exercise capacity was not mainly due to an increase in cardiac output, but was mainly due to, first, a change in the artero-venous difference in oxygen, a decrease in the arterial within the femoral vein and the circulating blood, and also a change in the pattern of ventilation suggesting that for, at this time, an unknown reason, the patient needed to hyperventilate less, either because of a decrease of pulmonary congestion or because of an improvement in oxygenation of the muscle during exercise.

(Fig. 19) There was at this time some concern about the potential risk of performing exercise in patients with heart failure, especially when the heart failure was due to a large myocardial infarction. There was at this time a study by Jett in Canada that showed that after training in patients after a large myocardial infarction, there was an increase in ventricular volume suggesting that training was deleterious in these patients. One has to note that this study was performed before the time of the use of ACE inhibitors in these patients. We had also some studies performed in animals with also poor results. This was a study by the group of Gaudron in East Germany, a very elegant study, where he performed a myocardial infarction in rats - an arterial myocardial infarction - and he assessed the diastolic pressure/volume relationship here in rats. In normal rats here. In rats with heart failure here, due to myocardial infarction, and in these rats, after a program of training, and as you can see in this study, training seems to have a deleterious effect by shifting the pressure/volume relationship on the right side of the slide suggesting a deleterious effect on remodeling.

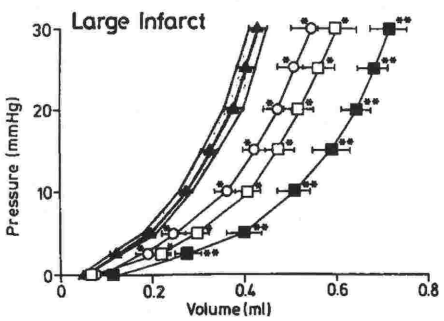
One has also to say that the program of training that these poor rats had to do was very dramatic. These rats had to swim about ten hours per day and I think that it is very difficult for these poor rats to perform such a training program. So there was some debate regarding the safety of training after myocardial infarction.

(Table 6) But there were two studies that were recently performed. The first study was an Italian study, the EAMI Study, which was a control study performed in nearly 100 patients after an arterial acute



MJ Sullivan et al. Circulation 1989; 79: 324-9

Fig. 18



P Gaudron et al. Circulation 1994; 89: 409-12

Fig. 19

myocardial infarction. Training was started four to 8 weeks after myocardial infarction. Patients have very limited heart failure. They were in NYHA Class Ⅰ or Ⅱ, and they had an ejection fraction greater than 25%, and 33% of them had an ejection fraction of less than 40%.

You know that less than one-third of them were on ACE inhibitors and most of them were on β blockers. The training program consisted of six months at 80% of maximum predicted heart rate. And they showed that the end-diastolic volume increased from 60 to 61 ml/m^2 in the training group, whereas it increases more in the control group. So this study did not find a deleterious effect of training compared to a control group in these patients.

I have to say that, as you can see, in this program patients have a very mild left ventricle dysfunction and ejection fraction was always greater than 25%, and they were poorly limited on exercise capacity. Recently the same group reported the ELVD Study, that is, the Exercise Left Ventricular Dilatation study in a similar population but with an ejection fraction that was more reduced, and they also found in this study that training did not affect left ventricular remodeling. On the contrary, it seems that in these patients training tended to stop LV dilatation. On the contrary, in the control group, left ventricular dilatation seems to progress.

(Table 7) And there was recently a study that was performed by Paul Dubach when he was in the United States. It is an interesting study because left ventricular geometry was assessed by a very nice technique, magnetic resonance imaging (MRI) in patients with moderate heart failure, as you can see, ejection fraction was 38 on average. Mainly patients after myocardial infarction. Here again as you can see, there was not a very severe LV dysfunction. What you can see is that the end-diastolic volume after exercise does not seem to increase more in the training group than in the control group. This was true for the end-diastolic volume and also for the end-systolic volume. There was also no change in left ventricle mass.

So it seems that training does not adversely affect LV remodeling after myocardial infarction. But in my opinion we need further studies to definitively confirm this point.

(Table 8) So in conclusion of this part of the talk, we can say that training seems not to affect left ventricle geometry without change in volume or in wall thickness. Regarding systolic function at rest, training induces in these patients reduction in heart rate and

Table 6 EAMI

Controlled study
n=95
Ant AMI (4-8 w), NYHA Ⅰ-Ⅱ, FEF>25% (33%EF<40%),28%ACE-Ⅰ, 7%diuretics et 70%BB
Readaptation : 6 m at 80%max predicted HR
EDV : from 60±14 to 61±16 ml/m^2 (vs from 63±16 to 66±20 in control group)
Expansion index : from 1.08±0.1 to 0.98±0.4 (vs from 1.1±0.1 to 0.98±0.4 in control group)
Group with EF<40%: condition, indentical in the 2 groups

JACC 1993 ; 22 : 1821-9

Table 7 MRI measures of ventricular volume and mass initially (pre) and after (post) the study period

	Exercize Group		Control Group	
	Pre	Post	Pre	Post
End-diastolic volume, ml	187±47	196±35	179±52	180±51
End-systolic volume, ml	118±41	121±33	119±54	116±56
Ejection fraction,%	38.0± 9	38.2±10	37.0±10	38.3±13
LV mass end diastole, g	185.4±35	184.2±32	164.0±29	162.0±33
LV mass end systole, g	179.4±39	182.2±27	161.0±26	159.3±32

None of the differences within or between groups were statistically significant.

Dubach P, et al : Circulation, 1997, 95, 2060-7

thus an increase in stroke volume without change in cardiac output. And at maximal exercise, a slight increase in maximum heart rate and stroke volume, leading to a small - very small increase in cardiac output.

What about now the effects of training on diastolic function in this patient? We have a very limited data about this subject.

(Fig. 20) One of these was given by a work by Belardinelli but is not, can be open to some criticism. We assessed peak feeling rate during each workload of exercise, before and after training, in a group of patients with chronic heart failure. And this author seems to find that training increased peak feeling rate in patients compared to the state before training. However it is difficult to say to what an increase in peak feeling rate corresponds. Is it beneficial? Is it deleterious? An increase in peak feeling rate can be due to an acceleration of relaxation which is good for the left ventricle. But it can be also due to an increase in arterial pressure which is not good for the left ventricle. So we need other studies using more sophisticated methods to really understand what is the effect of training on the diastolic function of the left ventricle in these patients.

(Fig. 21) It was finally in 1991 that was performed, the first control study. This was performed by the group of Andrew Coats in London. It was a small study in a group I think of less than twenty, I think twelve patients, with chronic heart failure - with very severe heart failure because the ejection fraction on average was less than 20%. And these patients underwent after randmization six months of training first in the department of cardiology, and after at home on bicycle, and six months of detraining. And what he observed for the first time was clearly that training improved in all patients the exercise capacity assessed by the peak exercise time or the peak oxygen consumption. And that when the patients stopped training, in all patients, there was a decrease in peak exercise capacity.

In this study as well as in most of all the subsequent studies, the improvement in exercise capacity brought by exercise training in these patients, was about an increase of twenty percent of peak V_{O_2} or of exercise duration.

(Table 9) I won't discuss all the studies that have been performed but I will concentrate on some of them. This was a study performed in Finland recently, published in Chest last year. It was a program of 6 month training, a control program, and you see on this table that whereas peak V_{O_2} increases moderately from

Table 8 Effects of cardiac training on LV function

- Geometry :
  no change in volume and thickness
- Systolic funtion
  rest : reduction of HR, augmentation of SV, CO unchanged
  maximal exercise : augmentation of max HR, SV ±, increase in CO
- Diastolic function ?

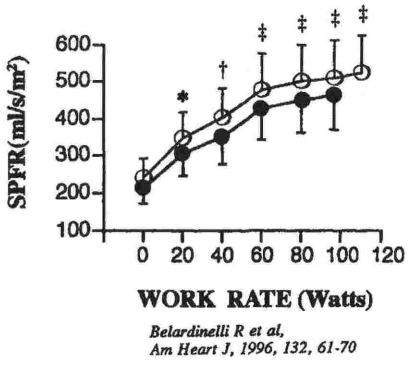


Fig. 20

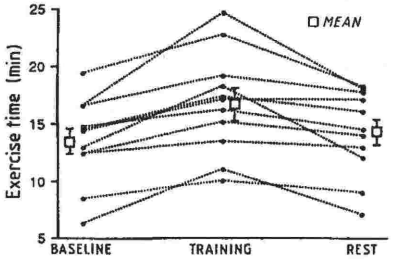


Fig. 21

19 ml/min/kg to 21 or 22, there was a more pronounced increase in the anaerobic threshold which increased from 10.5 to 12.3. And also in maximal workload. Note also that the duration of exercise was, of sub-maximal exercise, was also markedly increased starting from 14 minutes and reaching 27 minutes.

So it seems that training improves more sub-maximal exercise capacity here depicted by the duration or the anaerobic threshold than the peak exercise capacity. But you will consider as I have, that sub-maximal capacity is more important for the daily life of the patient than peak exercise capacity. Note also in this table, two things. First is that this improvement in sub-maximal capacity was accompanied, was associated with an improvement in the functional class of the patient.

And note also that most of the benefit was already observed after only 3 months of training. Other studies seem to show that the benefit may be observed after 6 weeks or 2 months. So I don't mean that there is no benefit, no need to sustain training after six months. But it seems that the maximal of the effect can obtained after only two or three months of training.

(Fig. 22) As I said there seems to be an improvement in sub-maximal exercise capacity. In his study Coats and his co-workers showed also that throughout exercise there was a significant reduction in minute ventilation in these patients suggesting that the patient feels better during exercise and were less obliged to hyperventilate during exercise than before training. This is obviously a beneficial effect of training improving the dyspnea of the patient throughout exercise.

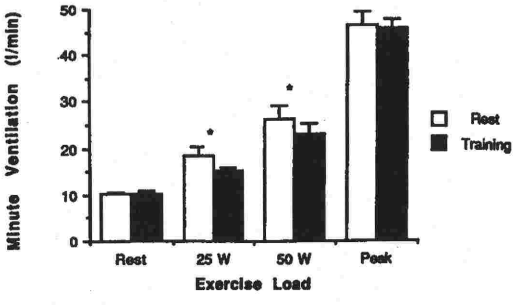
(Fig. 23) So what are now the mechanisms by which training have a beneficial effect in these patients? We have seen that these effects seems to be mainly due to an effect on the periphery, and we can speculate that it is due an improvement in both abnormalities that we have seen in the beginning. Abnormalities of vasodilations and abnormalities of the muscle metabolism. It has been known for a long time that training

Table 9 Effects of training

	0	3m	6m
Duration submax ex (min)	14.7±2.0	27.8±2.7†	27.0±2.8†
Max workload (W)	118±10	140±13†	137±12†
Peak Vo_2 (ml/min/kg)	19.3±1.6	21.7±2.3	21.7±2.5
Anaerobic threshold	10.5±0.8	12.7±1.0*	12.3±1.2*
NYHA Class	2.5±0.1	1.9±0.2*	1.9±0.2*

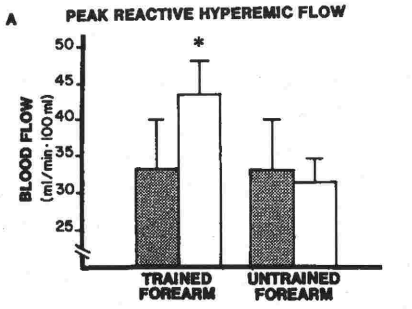
†$p<0.01$; *$p<0.05$

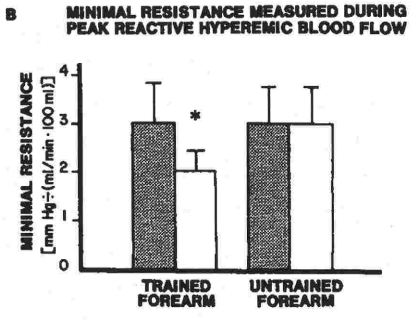
K Kiilavuori et al. Chest 1996; 110 : 985-91



AJS Coats et al. Circulation 1992; 85: 2119-31

Fig. 22





Sinoway et al., 1987

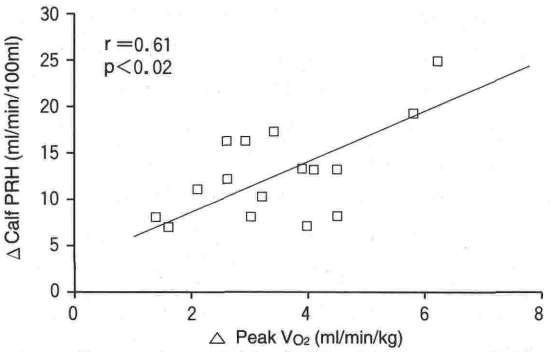
Fig. 23

improves the vaso-dilatory capacity of the vessel. This is an old study by the group of Sinoway ten years ago. A very nice study, where they assess peak reactive hyperemic flow in a normal patient when they train only one arm and they compare this to the other arm. As you can see, after training, peak reactive bloodflow markedly increased only in the trained arm. It really doubled without change in the untrained arm. And this was due to a clear decrease of the minimal resistance measured during the hyperemic bloodflow in the arm that was trained, compared to the untrained arm. So training improved locally the vasodilatory of the muscle of the territory that is subjected to training.

(Fig. 24) This was a study performed very recently. It was the group from Kelly that performed exercise training at a very low level (we will discuss this point after) in patients with severe heart failure. And it says that changes in peak V_{O_2} after training and also the change in calf reactive hyperemic bloodflow after training. And you can see a very nice correlation between the improvement in calf peak reactive hyperemic bloodflow after training, and the increase in oxygen consumption after training. So this seems to mean that part of the improvement in peak V_{O_2} after training is due to an improvement of the vasodilatory capacities of the vessel within the muscle.

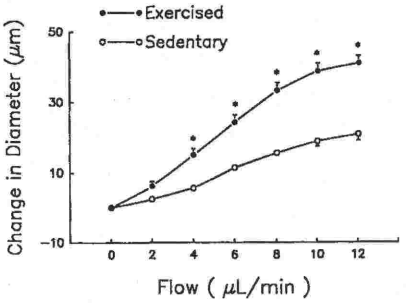
(Fig. 25) What is the cause of this improvement in vasodilation? You know, as me (I do), that this is probably due to an improvement in flow-dependent vasodilation. There are numerous studies in the literature regarding the effect of training on the flow-dependent vasodilation on isolated vessels in animals. This is one example of this study. It was performed by the group of Koller who have a large study on this topic, and you see the changes in the diameter of a vessel submitted to an increase in flow within the vessel before and after training. You see that the training in these animals resulted in a sharp increase of flow-induced increase in diameter in these animals. And this is also probably observed in men with heart failure.

(Table 10) I am sorry because this Fig. is in French but it is easy to understand. It was the preliminary data shown by the group of Kelly that has been published



Demopoulos et al, J Am Coll Cardiol, 1997, 29, 597-603

Fig. 24



A Koller et al. Circ Res 1995; 76: 544-50

Fig. 25

Table 10 ENTRAINEMENT ET FONCTION ENDOTHELIALE

	Pre-training	Post-training	
NTG 10^{-7}	1.52±0.20	1.87±0.13	p = ns
NTG 10^{-6}	2.50±0.30	3.20±0.30	p = ns
Ach 10^{-6}	1.39±0.16	2.35±0.04*	
Ach 10^{-5}	3.10±0.50	6.60±0.80**	

*p<0.05 ; **p<0.02

n=6

Débit de l'artère humérale (ml/min/100 ml) mesuré par pléthysmographic avant et après 4 semaines d'entrainement

Yuen JL, et al : J Am Coll Cardiol, 1993

this year where patients with heart failure were submitted to a program of training. And they assess the flow of the brachial artery by plethysmography before and after four weeks of training. And they assessed first, the response to intra-arterial nitroglycerin at two of those age and also of acetylcholine at two of those age. Notice that training did not seem to

markedly improve the response of the vessel to nitroglycerin which is an independent and endothelium in the dependent vasodilatory response.

There is a small increase you can see in the diameter of the vessel, but it was not significant in this study. But what is more clear is that you have a clear increase in the response of the diameter following acetylcholine injected after training compared to before training at two dosages. You can see here, you go from 1.29 to 2.35 and at higher dosage from 3.1 to 6.6, so more than 100 increase after training. And this was after only four weeks of training and it was an artery of, it was training of the forearm and it was the flow of the brachial artery.

(Fig. 26) And very recently also and of the very important group, the group of Helmet Drexler in Hamburg in Germany show also similar results. Can you focus a little more please? They assessed the change in diameter in the forearm of the patient with heart failure in response to acetylcholine by the technique of echo tracking. You the technique of echo tracking allows us to measure very precisely the diameter and the wall thickness of a very small vessel. As you can see, with training there was a clear increase in the percent change in diameter of this vessel after training and with a return to normal value with a withdrawal of training. So clearly, training markedly improves flow-dependent vasodilation.

(Fig. 27) This fig. is very preliminary but I have got it just before leaving Paris because it is as of yet unpublished. It was presented at the American Heart Meeting and European Society Meeting and will be published in circulation in a few months. It was a very nice study published by a group of Yuen who studied rats who had heart failure due to a large myocardial infarction. And they assessed the response of the vessel within the muscle of these rats in response to an increase in bloodflow. So this is the response of the artery of the Sham rats. In response to an increase in bloodflow, you see a slight increase in the diameter of the vessel. When the rats had severe heart failure, here in blue, you can see that the increase in blood within the vessel did not induce any change in the diameter of the vessel. So a clear alteration in the flow-dependent vasodilation.

And they submitted this animal to two strategies. First, training, and second, a treatment by ACE inhibitors. And you can see that training, in red, improved the flow-dependent capacity of the vessel but did not normalize it, whereas treatment with an ACE inhibitor normalized and even improved the flow-dependent vasodilation. So this study of animals confirmed that training improved flow-dependent vasodilation in the muscles but to a much lesser extent that can be done by a treatment with an ACE inhibitor.

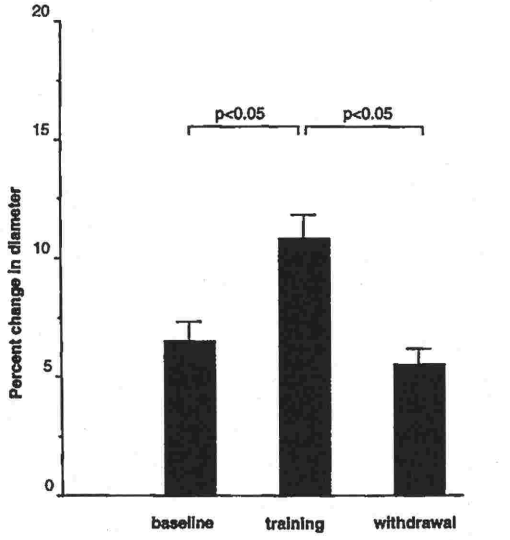


Fig. 26

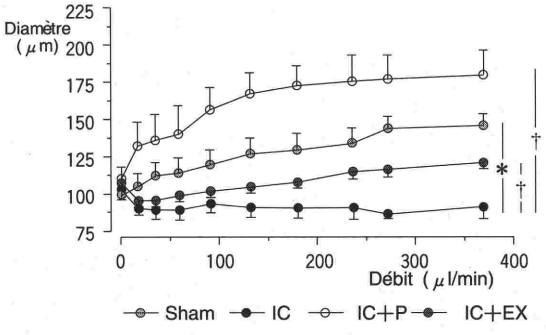


Fig. 27 Dilatation Débit-Dépendante

(Fig. 28) The effect of training on the muscle is also beneficial. This is a study of Hambrecht in Germany published two years ago, and if you remember the first fig, you can notice obviously that you have an increase here in the number of mitochondria after training. This is before training and this is after training. And here are the mitochondria marked by some colouration that figures the cytochrome c oxidase that is an enzyme of the Krebs cycle.

(Fig. 29) This author will perform a program of training in patients with heart failure observed a clear improvement in peak V_{O_2} that could reach 12 ml/min/kg. As you can see also a very nice correlation between the improvement in oxygen uptake brought by training and the increase in the volume of the mitochondria containing the cytochrome c oxidase positive, that is to say, the mitochondria that were reached in oxidative enzyme, there was a very close relationship between the increase in discolouration and the increase in peak V_{O_2}.

(Fig. 30) This was regarding the mitochondria regarding the functional consequences of this, various studies using animal spectroscopy have also shown that training of one limb markedly improves the metabolic response of this muscle. You have here the slope of the change in Pi/PCr ratio during an increase in workload in the forearm of the patient with heart

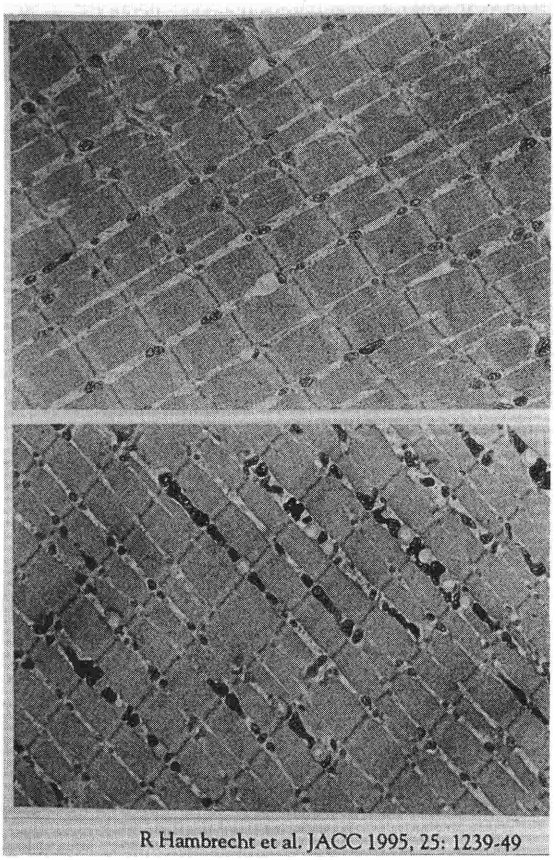
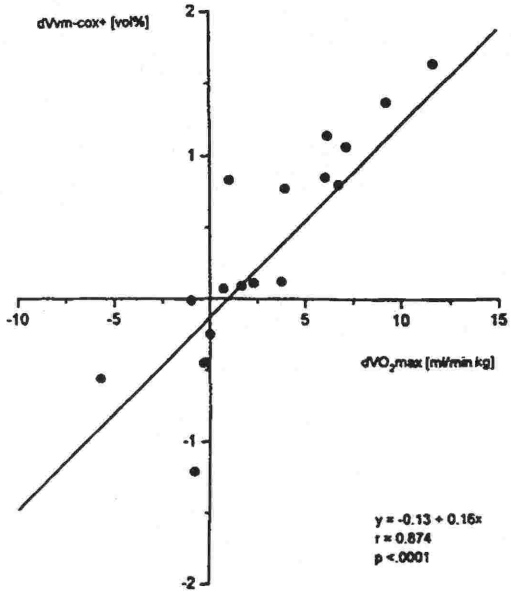
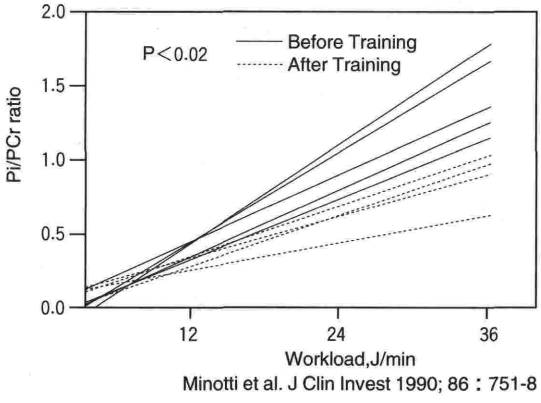


Fig. 28



R Hambrecht et al. JACC 1995, 25: 1239-49

Fig. 29



Minotti et al. J Clin Invest 1990; 86 : 751-8

Fig. 30

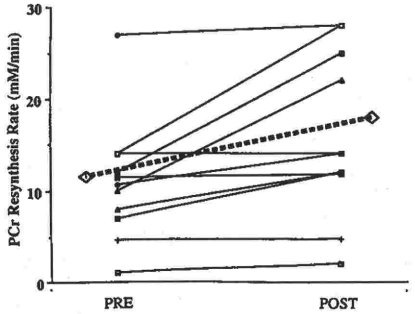
failure, here, before training. And this patient underwent I think 8 weeks of training of the forearm. As you can see after training for the same level of workload, the patient had less depression in creatinine phosphate suggesting an improvement in muscle metabolism.

(Fig. 31) This is the same, the other group of John Stratton, performed a similar study in London and showed an increase in the rate of Pcr re-synthesis rate after localized training.

(Table 11) So in conclusion of this part, we can say that training has a beneficial effect on the distribution and the utilization of oxygen at the level of the vessel it results in an increase in flow-mediated vasodilation. Perhaps I have not talked of this because it is controversial of some remodeling of the vessel wall, and perhaps in an increase in muscle capillarisation that is demonstrated in a normal subject but not yet in patients with heart failure. Within the muscle it results in an increase in muscle mass, a modification in fiber typology with an increase in fiber Ⅰ and Ⅱa and an increase in oxidative capacities without change in glycolytic capacities.

(Fig. 32) Training has other effects in these patients that are poorly studied at this time. For example, this was a study performed I think in Netherlands where this group showed that a normal subject training significantly increased the level of Interleukin 6 (IL-6), and we know now that cytokins probably play an important role in the pathology of heart failure. Whether this is observed also in patients with heart failure. Whether it is beneficial or deleterious remains to be studied but I think there is some interesting studies to perform with cytokins.

(Fig. 33) Another very important effect is the effect of training on the autonomic nervous system. You know that in patient with very severe heart failure, there are marked alterations in the autonomic tone with a sharp increase in sympathetic drive and a decrease in vagal tone. This is for example a patient which is not in Intensive Care Unit. He is ambulatory.



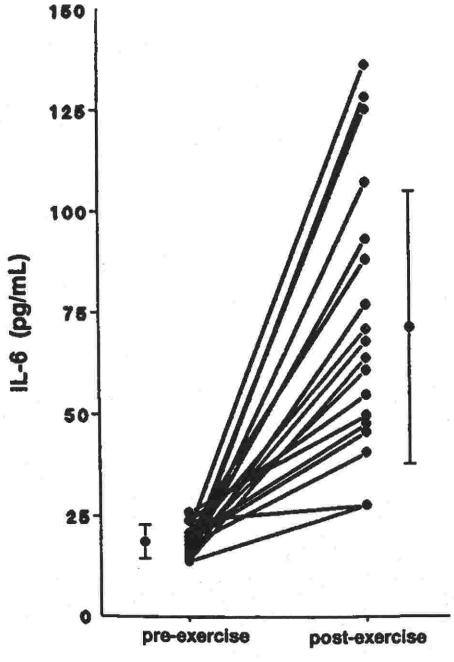
JR Stratton et al. J Appl Physiol 94, 76: 1575-82

Fig. 31

Table 11 Effects of training of O_2 distribution and utilization

Vessels
- Augmentation of flow-mediated vasodilatation
- Remodeling of vessel wall ?
- Augmentation of muscle capillarisation ?

Muscles
- Augmentation of muscle mass
- Modification of fibre typology : fibres Ⅰ et Ⅱa↗, fibres Ⅱb↘
- Augmentation of oxydative capacities, without change in glycolytic capacities



JP Drenth et al. J Appl Physiol 1995; 79: 1497-1503

Fig. 32

As you can see he is scotched. He is very, his heart rate does not change of 100 per minute. There is absolutely no change - in the viability of heart rate of this patient.

(Fig. 34) And when you perform a spectral analysis we see a very sharp peak. This patient has a very severe alteration in the autonomic nerve. This patient, I have not had the data - underwent four weeks of training with a clear, marked improvement of his heart rate viability.

(Fig. 35) Is this very important? Probably. Other groups, for example, the group of Coats, has also observed that after training in patient with heart failure you see an increase in heart rate viability that can be observed by making a spectral analysis with an increase in the bands of high frequency suggesting a decrease in sympathetic tone and an increase in vagal tone.

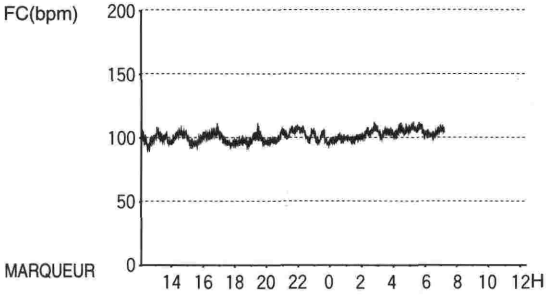


Fig. 33

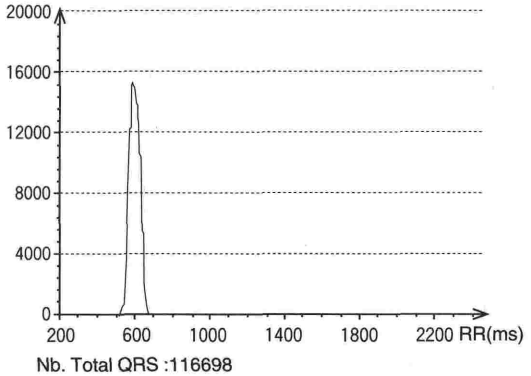


Fig. 34

(Fig. 36) Other groups, for example, the same group of Kilavuori in Finland, also reported the same data with a slight difference, that is to say, they observed a decrease in the heart in the high frequency bands after training but only during daytime without change in nighttime.

(Fig. 37) This is probably beneficial. We don't have definitive data of this, but I would like to draw your attention to this very nice study performed by all in the group of Peter Schwartz that was published three years ago. It was, I'm sorry, a study in animals. But I think it was very interesting. You know they had 39 dogs in which they performed myocardial ischemia by ligation of the coronary artery. And they performed a test of provocation to provoke ventricular fibrillation in these animals. And all these animals were susceptible, and could have provoked ventricular afibrillation that was cured by an electric shock. No, I'm sorry. Only I think eight of them were susceptible to a protocol of stimulation. Among these eight dogs that could fi-

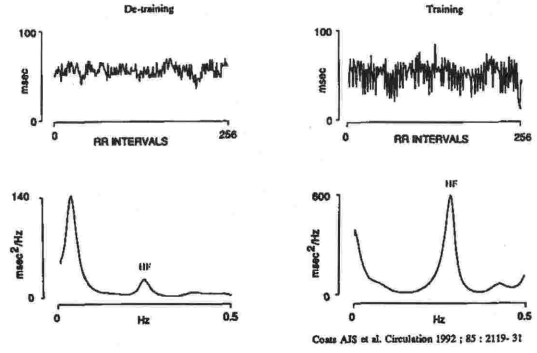
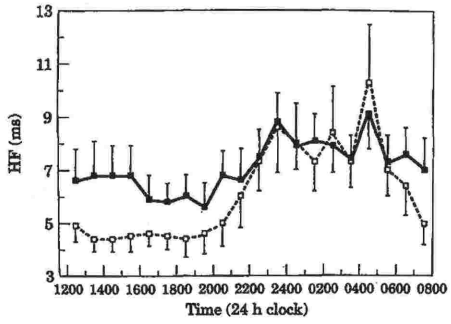


Fig. 35



K Kilavuori et al. Eur Heart J 1995; 16: 490-5

Fig. 36

brillate after provocation, five of them underwent an exercise training protocol and three of them at random rested in their cage. And as you can see, after six weeks of training all the dogs were changed and became resistant to ventricular fibrillation provoked by stimulation whereas in the three dogs that rested in their cage, the three remained susceptible to ventricular fibrillation. And when these three underwent, when two of these three underwent again an exercise training protocol, they became resistant to this. So this suggests, it is not proof, suggests that training by improving the autonomic nervous system, can perhaps reduce sudden death in patients with ischemic heart failure. But we need data on humans to confirm this.

(Table 12) So we can say that training has other effects beyond the effect on the muscle of the vessel of the heart. It does not produce excessive neurohormonal stimulation. We have seen that it decreases vagal tone and reduces the sympathetic tone. Some studies in animals, have shown an increase of the GI protein after training, an increase in the antioxidant capacities and an increase in cellular immunity. So you see there is a lot of work to be done in humans with heart failure because all of these have been observed in animals.

(Table 13) Regarding now the protocols. It is very confusing because I have listed here the studies performed to date. You see that they were all performed on a very limited number of subjects and probably all of these subjects were selected. So we don't know now if training can be a good strategy for all patients. Note that in all the studies no patient in Class 4 were involved.

And finally note that no study has a protocol similar to the other. Here is the training program fixed at 50% of maximal Vo_2, 40% only at maximal Vo_2, 70%. Here it was based on maximal heart rate. Etc., etc. Note also the variation in the duration of the training program, 3 months, 2 months, 6 months, 2 months, 1 month, 3 weeks. And also the duration of the stations, 30 minutes three times a week, 10 minutes 6 times a week, 4 hours per week, etc., etc. So there is to date, no standardization regarding the best protocol of training in these patients.

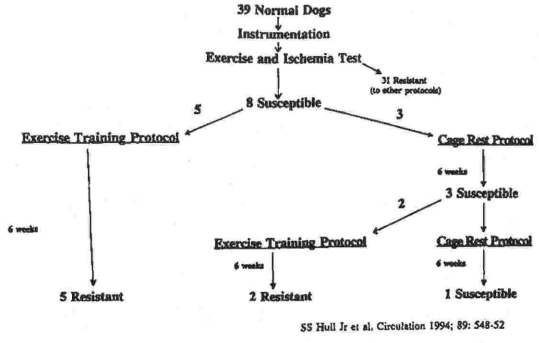


Fig. 37

Table 12 Training : other effects

- No excessive neurohormonal stimulation
- Augmentation of vagal tone, reduction of sympathetic toneh
  ⟶ reduction of arrhythmic risk ?
- Augmentation of Gi
- Augmentation of anti-oxydant capacities
- Augmentation of cellular immunity

Table 13 Studies

Kiilavuori 1996	12	II / III	24%	50−60% Vo_2m*	30' ×3	3m
Belardinelli 1995	18	II / III	30%	40% Vo_2m*	30' ×3	2m
Hambrecht 1995	12	II / III	26%	70% Vo_2m	10' ×6	6m
Adamopoulos 1993	12	II / III	24%	60/80% HRm	20' ×5	2m
Coats 1992	17	II / III	19%	60/80% HRm	20' ×5	2m
Sullivan 1989	12	II / III	24%	75% Vo_2m	4h/sem	6m
Jetté 1991	18	II / III	<50%	75% HRm		1m
Keteyan 1996	20	II / III	21%	60−80% HRR	3/w	6m
Meyer 1996	18	II / III	21%	interval train	3-5/w	3w
EAMI 1993	49	I / II	51±14	80% HR max	3/w	6m

(Table 14) In general, people use dynamic exercise protocol by making the patient run on a treadmill or cycle on a bicycle between 30 to 45 minutes per session three times a week. The duration varies from 15 days to three months with following reeducation at home. It is important that the patient continue to train at home and at a load that can be suggested to be about 60% of the heart rate reserve, or perhaps better it is our opinion, to be fixed at the level of the anaerobic threshold. It is possible that part of the poor results reported by some groups is due to the fact that the training level is too high and it is clear that these patients should train at a level that is the same or below the anaerobic threshold.

But we lack data regarding the tolerance of this protocol, whether the protocol should be individualized, this is our opinion, and whether the notion of threshold is applicable to these patients. What I mean by this is that, in normal subjects, it is generally considered that a training protocol at a level below 75% of peak heart rate does not give any beneficial effect. Probably this is not true in patients with heart failure and there are two groups, the group of Legentel and the group of Belardinelli that have shown that a training program at about 30%, 40% only of peak V_{O_2} is sufficient to elicit a beneficial effect. Other groups have proposed isometric exercise, that is to say, segmental training, that possibly has a less deleterious effect on the heart and that is probably better tolerated by the patients with the most severe heart failure.

(Table 15) I will here give the result of a study performed in the Caroliniski Institute, the famous one in Stockholm by Magnusson and co-workers, a very complicated study but I will try to explain. They used eleven patients with severe heart failure - ejection fraction of 11% in the one group and 28% in the other group, and the peak V_{O_2} between 14 and 16. There were four groups of training. One group had segmental training, extension of the quadriceps against resistance at 80% of maximal force. The extensions were performed every three seconds repeated four times, and with two minutes of rest. This protocol was repeated 45 minutes, three times per week during two months. And this was performed only on one leg. The other leg was at rest.

Another group underwent an endurance training pedaling at 75% of the maximal workload for 15 minutes, 45 minutes three times per week, during two months. That is to say, a standout protocol.

(Table 16) And you can see that the increase, look at this, in workload was, this is the endurance protocol and the strength protocol. You see the strength

Table 14 Protocols

- *Dynamic exercises* (run, cycle…)
  30 to 45 minutes per session 3 times per week
  15 days to 3 months (at home)
  at 60%of HR reserve or (better ?) at the anaerobic threshold level

  tolerance ? individualization ? notion of threshold
- *Isometric exercises* (segmental training)
  less potential deleterious effects

Table 15 High intensity segmental training in CHF

- Randomised study
- n=11, 57 y, EF 11±5%(S) et 28±9%*(E) ; V_{O_2}max 13.8± 3.3 (S) and 16.2±2.3 ml/min/kg (E).
- Segmental (S) : extension of quadriceps against resistance at 80% of maximal force; extensions every 3 sec repeated 4 times(2 min of rest).
  45 min 3 times per week during 2 months. Other leg at rest (N)
- Endurance (E) :pedalling at 65-75%of maximal workload for 15 minutes.
  45 minutes 3 times per week during 2 months. Other leg : E+S
- Evaluation of EF, V_{O_2}max, force, biopsies and MRI

G Magnusson et al. Eur Heart J 1996 ; 17 : 1048-55

Table 16 High intensity segmental training in CHF results

No change in HR or EF		
V_{O_2}max leg		
S	0.88 l/min	0.97 l/min
N	0.82	0.85
ES	0.98	1.08
E	1.02	1.05
Max workload		
S	80	85W (+10%)
E	108	124W* (+18%)

G Magnusson et al. Eur Heart J 1996 ; 17 : 1048-55

protocol increase a maximal workload from 80 to 85 watts, and the endurance protocol from 108 to 124 watts. That is to say, the endurance protocol seems to increase more the maximal workload.

(Table 17) Regarding the change in the oxidative enzyme, the citrate synthetase assessed by biopsy, strength training did not change it. And the change was observed only with endurance training, a clear increase, and with both endurance and strength training without a change in glycolytic enzymes.

(Fig. 38) Finally, some authors suggest another protocol which is what they call the interval training protocol when they perform training for one minute at a high workload and then three to four minutes workload recovery but not at 0 watts, at 50% of peak workload, the workload of recovery. And after again one minute at 100 of peak exercise capacity and four minutes of recovery. This protocol seems to yield better results than the other.

(Fig. 39) This fig. is here to show you that the group of Legemtel could achieve an improvement in peak Vo_2 despite the fact that patients were treated by Carvidilol. That is to say, one can train patients despite the fact that they received beta blockers.

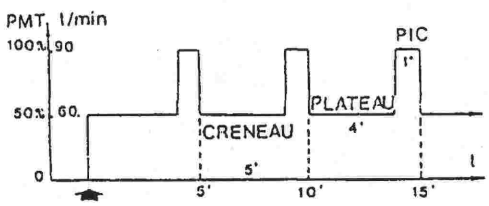
(Fig. 40) And the same group have assessed the effect of training on BNP and on pulmonary wedge pressure and left ventricular diastolic wall stress. And they found that the classical level of exercise elicited a clear increase in pulmonary wedge pressure and diastolic wall stress with also an increase in BNP and tropolyn I suggesting that the classical level of training is perhaps too elevated to patients with heart failure. But this was in a small group of patients.

(Fig. 41) And finally, the last part of my talk is to conclude in five minutes, is to say how to choose the patient to be trained. Here is the same fig. at the beginning. You see here peak Vo_2 and ejection fraction. Obviously, one has to train the patient that has the severely reduced peak Vo_2 despite a moder-

Table 17 High intensity segmental training in CHF results

"Oxydative" enzymes (citrate synthetase)		
S	-	idem
N	-	idem
ES	-	+49%*
E	-	+77%*
"Glycolytic" enzymes (LDH, PGK)		
No change		

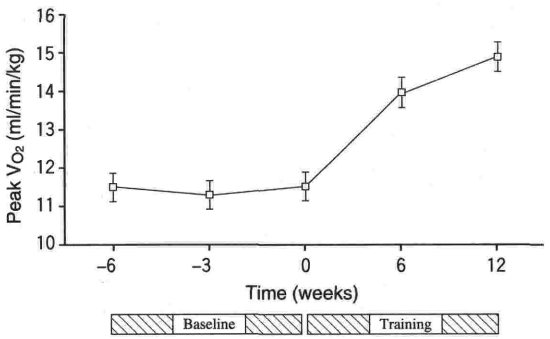
G Magnusson et al. Eur Heart J 1996 ; 17 : 1048-55



Epreuve : X Crèneaux de 5 min.

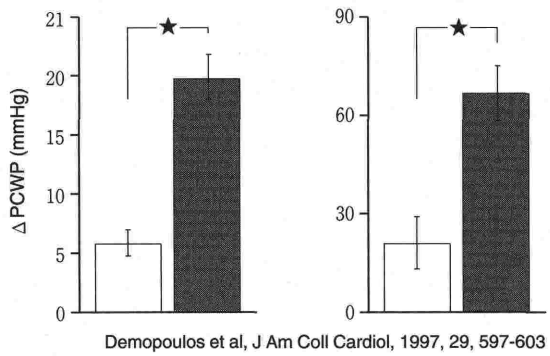
Lonsdorfer J et al
Sciences et Sport, 1989, 4, 161-4

Fig. 38



Demopoulos et al, J Am Coll Cardiol, 1997, 29, 597-603

Fig. 39



Demopoulos et al, J Am Coll Cardiol, 1997, 29, 597-603

Fig. 40

ately reduced ejection fraction. All these patients, for example, have a too limited exercise capacity compared to their ejection fraction. Probably they are de-conditioned. On the other side, these patients with a very good peak V_{O_2} probably should not be trained because they have clearly a normal exercise capacity.

(Fig. 42) Another way to do it is to assess the response of cardiac output during exercise. You can do this by Doppler echocardiography during supine exercise and you can measure simultaneously oxygen uptake by gasection measurement and cardiac output by Doppler echocardiography. This is the response of a patient with severe heart failure. Note that the slope is 1.6 in this patient with heart failure.

(Fig. 43) In another patient the slope was 4, that is for us a normal value. That is to say that some patients seem to have, despite heart failure, a rather normal increase in cardiac output. It is likely that in this patient periphery is very abnormal and de-conditioning plays an important role.

(Fig. 44) Finally, it is important to understand that if you want training to be effective, you have to improve the compliance of the patients to the training protocol. This was the experience of the group of Andrew Coats, showing a clear relationship between the percentage increase in exercise time observed after training and the compliance to the training program. Clearly the best results were obtained with the patients that were more compliant to the program.

(Fig. 45) This is another study by Katherine Meyer in Germany showing something different. That is to say, the lower the peak V_{O_2} at baseline, the greater the benefit of training, that is to say, the percentage of increase in peak V_{O_2}. So it seems that the patient with the more limited exercise capacity benefits more from training.

(Fig. 46) And finally, another way to do it is to measure lactate during exercise. For example, this is the response in plasma lactate during a graded exercise

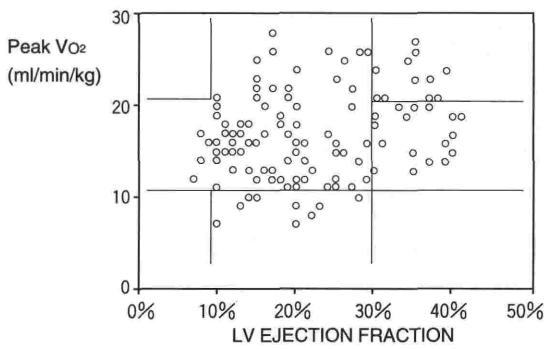


Fig. 41

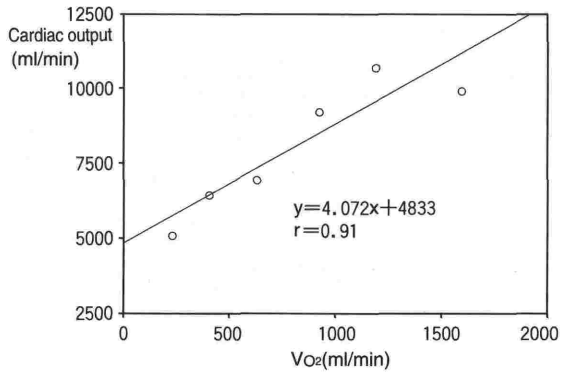


Fig. 43

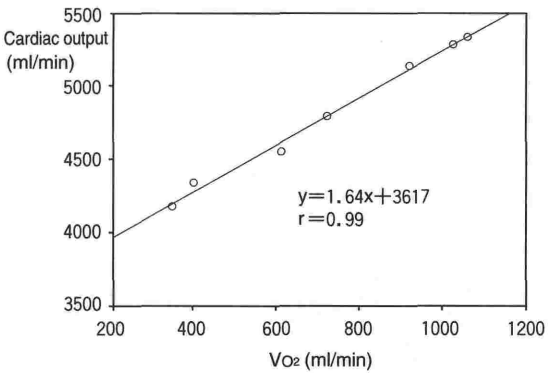
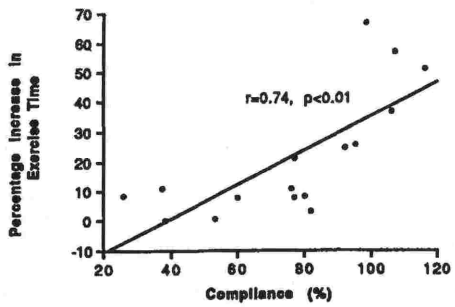


Fig. 42



AJS Coats et al. Circulation 1992; 85: 2119-31

Fig. 44

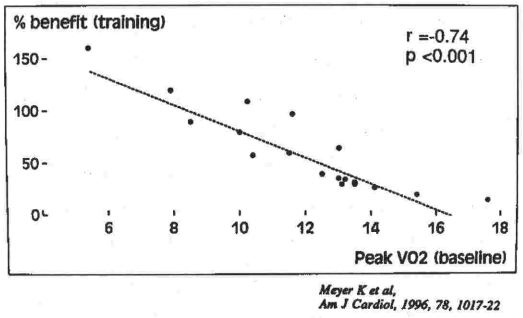


Fig. 45

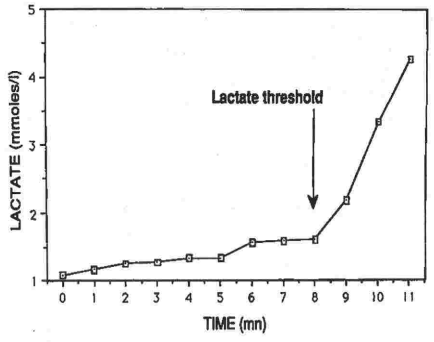


Fig. 46

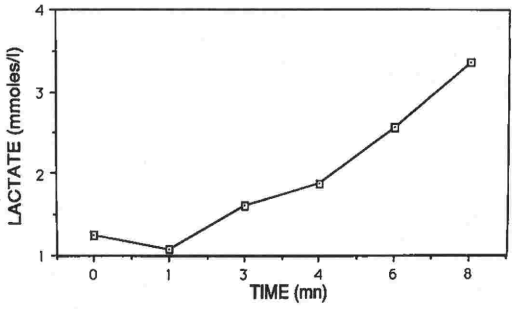


Fig. 47

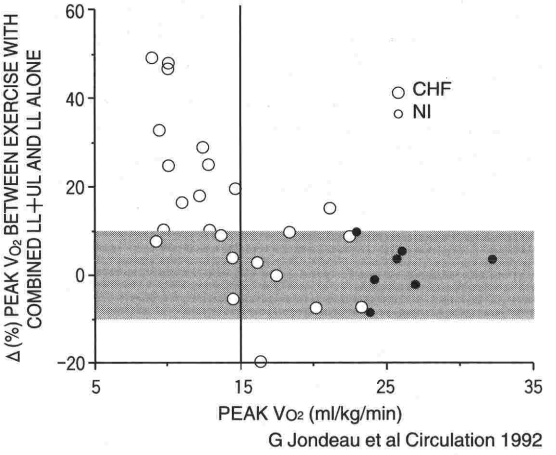


Fig. 48

in a normal subject. You can see here a clear lactate or anaerobic threshold at about 70% of peak exercise.

(Fig. 47) In some patients, you have a beginning of increase of plasma lactate since the beginning of exercise. This suggests that since the beginning of exercise, this patient produces lactate within the muscle despite a normal cardiac output probably because they have marked abnormalities of muscle metabolism that can be improved by training and one should train these patients.

(Fig. 48) And finally, a last possibility is to perform four limb exercise tests. I will explain myself. When you exercise a patient on a bicycle, and after on abicycle, and with the arms, you do not improve peak VO_2. This is the point in green. You see there is no, 0 is the change in (four legs, four arms) four limbs exercise compared to two limbs exercise. In normal subjects you do not increase peak VO_2 by adding arm exercise to leg exercise. In patients with heart failure, when you add arm exercise to leg exercise, you can improve peak VO_2 by about 40%. This means that probably in these patients when they perform cycle exercise they have a reduced functional muscle mass that can be improved by training. And all these patients probably benefit from training. Notice however that all these patients have a reduced peak exercise capacity, and that one can also consider that all patients with a peak VO_2 less than 15 can benefit from training.

(Table 18) Only I would just like to show an important thing. And this is my last fig. We are dealing with training and perhaps you say, what is the effect of training compared with drugs? This is a study performed by the group of Kostis in Chest who compared training, treatment by dioxin and placebo. Note that you have with training a marked improvement in exercise duration compared to training, to

Table 18 Results

	Training	Digoxin	Placebo	p
Weight	−5%	+0.5%	−1.5%	0.02
Exercise duration	+37%	+2%	+22%	0.04
6 min walk test	+20%	−16%	+1%	0.16
EF	−9%	+15%	−3%	0.05
A/E	+40%	−43%	−25%	0.16
Depression score	−52%	+15%	+25%	0.04
Anxiety score	−39%	+24%	+45%	0.04

JB Kostis et al. Chest 1994 ; 106 : 996-1001

Table 19 Conclusion

- Peripheral abnormalities are an important hallmark of the disease
- Their determinism may not be directly and entirely due to altered hemodynamic function
- It is possible to correct them not rapidly and more completely them with training that with drugs.

dioxin, but in this study, placebo also has some effect. But what is more important is here. Because exercise capacity is not all; quality of life in this patient is very important. Note the clear improvement in the depression score and the anxiety score brought by training compared with the deleterious effect of training and placebo. You markedly improve depression and anxiety by training, but drugs do not change this.

(Table 19) So, in conclusion, Misters and Misses, I can say that the peripheral abnormalities are an important hallmark of the disease of congestive heart failure. Their determinism may not be entirely due to altered hemodynamic function, and it is possible to correct them more rapidly and more completely with training than with drugs.