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Possible effects of fatigue on muscle efficiency

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ABSTRACT

The efficiency of energy transduction is defined as the ratio of the work done by a muscle to the free energy change of the chemical processes driving contraction. Two examples of the experimental measurement of muscle efficiency are: (1) the classical method of Hill which measures the value during a steady state of shortening, (2) measuring the overall efficiency during a complete cycle of a sinusoidal process, which comes closer to the situation during natural locomotion. The reasons why fatigue might lower efficiency are the following. (1) The reduction in PCr concentration and increase in Pi and Cr concentration which are characteristic of fatigued muscle, reduce the free energy of PCr splitting. This will reduce the efficiency of the recovery process. It is not known whether the efficiency of the initial process is increased to compensate. (2) There is a general conflict between efficiency and power output when motor units are chosen for a task or when the timing of activation is decided. During fatigue more powerful units have to be used to achieve a task which is no longer within the scope of less powerful units. (3) The slowing of relaxation that is sometimes found with fatigue may make it impossible to achieve the short periods of activity required for optimum efficiency during rapid cyclical movements. A reason why fatigue might increase efficiency is that muscles are thought to be more efficient energy converters when not fully activated than when fully active. Full activation is often not achieved in muscle which is considerably fatigued. Available observations do not allow us to find where the balance between these factors lies. The conclusion is thus that experiments of both the types discussed here should be performed.

Keywords muscle efficiency, muscle fatigue.

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As far as I have been able to discover there exists no detailed study of the experimentally measured efficiency of energy conversion by isolated muscle during the onset and recovery from a reversible state of fatigue. Therefore this article will be devoted largely to reviewing those very few studies which have touched on the matter experimentally, expounding why such a study might be worthwhile and explaining those factors that could be expected, according to current understanding, to lead to a reduction in efficiency of energy conversion during fatigue, and also some factors which might produce the opposite effect.

DEFINITIONS OF EFFICIENCY

Thermodynamical efficiency (Eff_T) will be used here in the usual thermodynamical sense to describe the ratio of the work done by muscle over a certain period to the free energy change of the driving chemical reactions that have occurred over that same period. Because by definition the driving processes are those which provide the free energy which is converted to work, the efficiency can never exceed unity. The work done will mean the net work done, calculated as the integral of the force exerted, with respect to length change, over the period of interest. This period can sometimes include a time during which the muscle is lengthened under load. During this time of stretch, energy put into the muscle from an external source may be stored, for example in stretched elastic structures within the muscle–tendon complex. If all of this work is returned at a later stage during the period of work integration then there will be no effect from this storage and return of energy on the overall thermodynamical efficiency measured for the whole period. However if only a part of the stored energy is returned the overall efficiency will be diminished. Authors who wish to study the efficiency of this storage and return of mechanical energy

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by muscle tendon complexes, have sometimes used different conventions for calculation of work done, in which negative work (work done on the muscle by stretching it) is either ignored, or included as part of the free energy driving the overall processes. These conventions can be useful where the focus of the study is the energy storage process but are not suitable when, as here, the intention is to concentrate on the overall conversion of energy from chemical to mechanical form.

The nature of the driving reaction in muscle will be different according to the length of the period being considered. In general during short periods (a few seconds) the net chemical change occurring in the tissue will be the splitting of phosphocreatine to creatine and inorganic phosphate. For longer periods a part or all of the net chemical free energy change will have been provided by either glycolysis or oxidation of substrates.

In order to provide a numerical value for Eff_T the nature and the extent of the driving processes have to be known. In our experiments we have usually estimated the extent of the reactions from measurements of the total energy output as heat plus mechanical work. We denote the ratio of work done to energy output as Eff_H. As we have generally studied short periods of time using muscle that cannot resynthesize PCr quickly, we consider that the chemical source of the energy output will be predominately PCr splitting. For this reaction, under the conditions in unfatigued muscle, the free energy change will be close to -48 kJ mol^{-1} (Kushmerick & Davies 1969) and the enthalpy (heat + work) output about -34 kJ mol^{-1} (Woledge & Reilly 1988). Thus the free energy change occurring is 1.4 times the measured energy output. However not all of this energy has come from phosphocreatine splitting by the myofibrils; a part of it will have come from the PCr splitting consequent to calcium pumping by the sarcoplasmic reticulum. It is well established that the rate of this process corresponds to about 30% of the isometric energy production, and a lesser proportion of the energy output during shortening (Lou *et al.* 1997). Thus if it is desired to obtain the thermodynamic efficiency (Eff_T) of the myofibrils themselves, from the operational quantity (Eff_H) two corrections must be made. Firstly the free energy must be calculated from the heat + work, secondly the energy used by the SR pump must be subtracted.

The efficiency of a sequence of processes, each of which is driven by the next is given by the product of all the efficiencies of the individual steps in the process. In the case of muscle contraction we can thus consider the efficiency of the overall process of the provision of work from oxidation to be the product of the efficiency of the initial process (production of work from the free energy of PCr splitting) and that of the recovery process (the resynthesis of PCr by oxidative phosphorylation). Some authors have considered it useful to subdivide further the processes of muscle contraction and recovery because, of course, the actual process driving contraction is not PCr splitting but ATP splitting, with the ATP rapidly resynthesized from PCr by the creatine kinase reaction. Should the efficiency of the creatine kinase reaction also be included in the product? In fact this reaction remains close to equilibrium in muscle (Wiseman & Kushmerick 1995) which means that the free energy of ATP splitting is kept the same as that of PCr splitting by 'adjustment' of the ADP concentration. As the efficiency of a tightly coupled process is simply the ratio of the free energies of the driving and driven processes (Kedem & Caplan 1965) it follows that the efficiency of the creatine kinase reaction is always very close to unity. There is therefore nothing to be gained from these discussions by considering the free energy of the ATP splitting process, rather than that of PCr splitting, and as the concentration of the reactants and products can be measured readily for the latter but not for the former, there is much to be lost in clarity of argument by such a shift in emphasis. The free energy for the oxidative resynthesis of PCr can be calculated from the known stoichiometry and molar free energy changes (ΔG) for the driving and driven processes as follows:

$$Eff_T = (\text{P/O ratio})\ (\Delta G \text{ of PCr splitting}) \,/\, (\Delta G \text{ for oxidation per mole of O})$$

The result is about 65% for the conditions which exist in unfatigued muscle. It is possible that the value might be slightly different in different fibre types due to different metabolite levels.

EXAMPLES OF ITS MEASUREMENT OF MUSCLE EFFICIENCY

An example of measurement of maximal muscle efficiency during steady state shortening is provided in Figure 1. This unpublished experiment was performed in collaboration with Dr M. Linari in 1994, following the principle of the classical shortening heat experiments of Hill (1939). The experiment used a single frog muscle fibre mounted over a sensitive thermopile and held between a motor and a force transducer. Measurements were made of the rates of energy output as heat and as work during steady shortenings at different rates and also during isometric contractions. The results are expressed in dimensionless form by dividing velocity by V_{max}, force by Po and the energy output by the product (Po · V_{max}) Expressed in this way the results conform remarkably well to the empirical mathematical descriptions proposed by Hill, which are re-

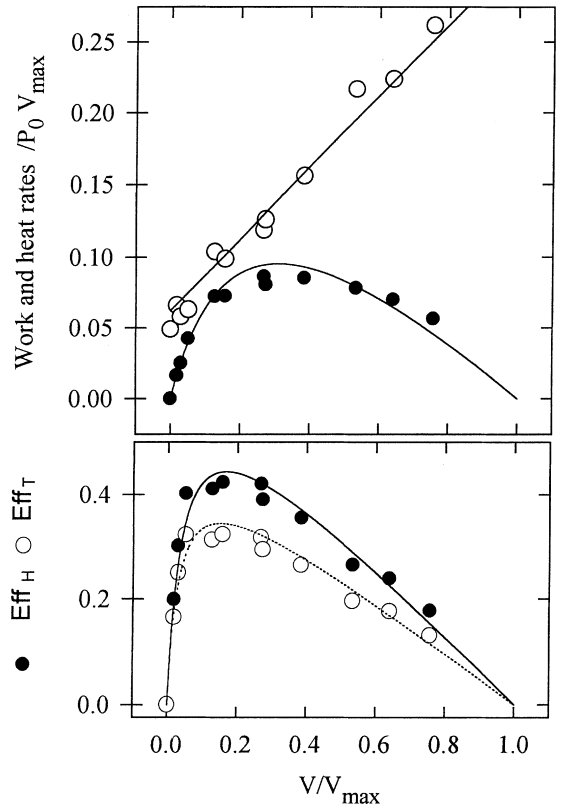

Figure 1 (a) Observation of the efficiency of energy conversion by a single frog muscle fibre undergoing isovelocity shortening. From an unpublished experiment made in collaboration with Dr. M. Linari using the methods described by Linari & Woledge (1996). Each point is the measurement from one contraction of the rate of work output (●) and of heat production (○). All measurements have been normalised by the values of the maximum force (P_0) and maximum velocity of shortening (V_{max}) of the fibre. The lines are fitted to the data using the equations shown in Fig. 2 with a value of 4 for the adjustable parameter G. (b) The efficiencies calculated as described in the text. The filled symbols and full line show Eff_H; the line is plotted from the equation in Fig. 2. The open symbols and dotted line show the effects of the conversion to Eff_T as described in the text.

expressed here by the equations shown in Figure 2 . As shown in Figure 1 these expressions can be adapted to take account of the factors discussed in the last section and provide a function for calculating the efficiency Eff_H.

Curtin & Woledge (1993a, b, 1996) adopted a different approach to the measurement of muscle efficiency. The intention was to provide *in vitro* measurements which related more closely to the probable conditions under which muscle is actually used during locomotion. From this point of view the situation in the Hill type of experiment seems very arbitrary because it concentrates the measurement of efficiency only on a part of the whole cycle of contraction and relaxation, whereas the animal's metabolism must account for the whole cost of the cycle, even though at some parts of the cycle the efficiency was perhaps low. We therefore measured the energy output, as heat and work, for the whole of a cyclical process during which the dogfish muscle fibres are stretched and then shortened following a sinusoidal time course. The muscle is stimulated for only a part of the cycle. The timing of the stimulation and the length of the stimulation period were varied to find the conditions under which either the efficiency or the power output for the cycle was the greatest. The results obtained showed that, to obtain optimum efficiency the period of stimulation needs to be kept short, in fact a single stimulus often provides the best efficiency. The reason for this result was not that the muscles absorbed work during part of the cycle when stimulated for longer, this factor was small, but that energy continued to be used after the shortening was over. Thus to get optimum efficiency for a cyclical process it is important to keep the muscles shortening, and thus able to do positive work, for the whole of their period of activity.

REASONS WHY FATIGUE MIGHT LOWER EFFICIENCY

Changes in metabolite concentration

As the driving reaction proceeds during a period of activity the free energy of the driving process will inevitably decline, because, by definition, the driving process is moving closer to its equilibrium position. The net reaction occurring during a short contraction can be written reasonably accurately (Woledge & Reilly 1988) as

$$PCr^{2-} + 0.5\ H^+ \rightarrow Cr + 0.5\ HPO_4^{2-} + 0.5\ H_2PO_4^{1-}$$

Thus in fatigued muscle the free energy of PCr splitting will be lesser because the Pi and creatine concentrations are higher and the phosphocreatine concentration is lesser than in fully recovered muscle. Any acidification that might have occurred due to glycolysis will to some extent offset these decreases in the free energy change of the reaction. Each of these changes will produce a change in the free energy of the PCr splitting by

$$RT \ln(\text{proportional change in concentration})$$

Consider the changes that will occur when a muscle which initially has 90% of its total creatine as phosphocreatine is stimulated until only 10% of the total is phosphocreatine. There will have been a ninefold change in the concentration of phosphocreatine, creatine and Pi. As $RT\ln(9) = 5586$ J mol^{-1} there will be a reduction in the free energy of PCr splitting by about 17 kJ mol^{-1} from −48 to −31 kJ mol^{-1}. If we assume, as seems reasonable, that the stoichiometry of recovery does not change when a muscle is fatigued then the efficiency of the recovery process will have

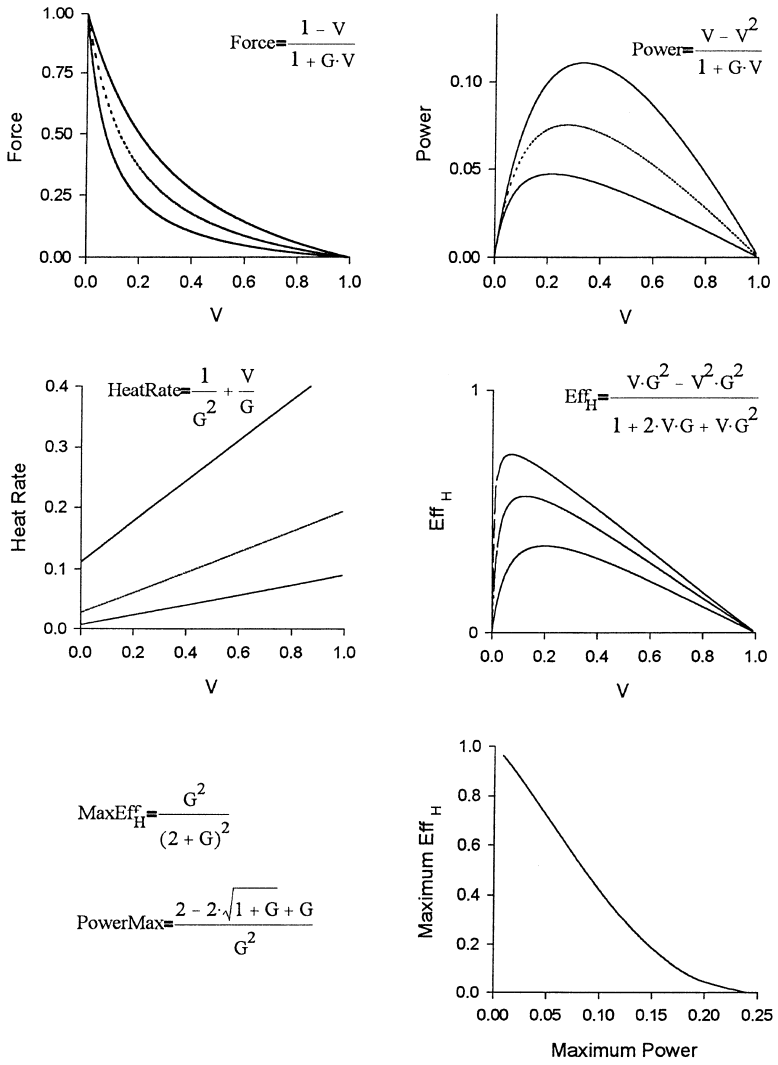

Figure 2 Calculation from the equations of Hill (1939) of the force, power, heat rate and efficiency for different values of a constant G (equivalent to Hill's P_0/a), the three values of G used here to illustrate the influence of this parameter are 3, 6 and 12. These values are in descending order for the plots of force, power and heat rate and in ascending order for the plot of Eff_H. The bottom panel shows the relation between maximum values, with respect to velocity, of efficiency and power calculated from the equations shown.

fallen from 65% to 42% and in the absence of any other change the overall efficiency will have fallen from 32% to 21%.

The above considerations make it seem likely that there is indeed a fall in the efficiency of muscle contraction with fatigue, however there could be a compensatory change in the efficiency of the initial processes which could cancel out the expected fall in the overall efficiency from the above causes. If the initial processes had a fixed 'stoichiometry' then that adjustment would occur automatically. This would be the case if the maximum work that could be obtained from the splitting of ATP (PCr) during any one cross-bridge cycle was fixed at some level well below the free energy of PCr splitting. There would then be some obligatory waste of free energy at each cycle. A reduction in the free energy available would have no effect on the mechanical output as long as this critical level was not reached. There would be a reduction in the obligatory wasted free energy which would exactly compensate for the raised inefficiency in the recovery process. Experiments by Kushmerick & Davies (1969) somewhat suggest that this might be the case. They measured the work done and the ATP used during contractions of frog sartorius muscles which were either uninhibited or poisoned with either IAA or DNFB. Measurements of metabolite concentrations confirmed that, as would be expected, the free energy change for ATP splitting was less in the poisoned muscles and allowed the actual ΔG values to be obtained. Figure 3 shows the work done by the muscles per mole of ATP split varied with the free energy. The figure also compares the results with two hypotheses:

(1) That the initial efficiency is unchanged by the poisoning. This hypothesis is shown by the sloping line passing through the origin since unchanged efficiency means a constant ratio between work done per mole of ATP splitting and the ΔG for ATP splitting.

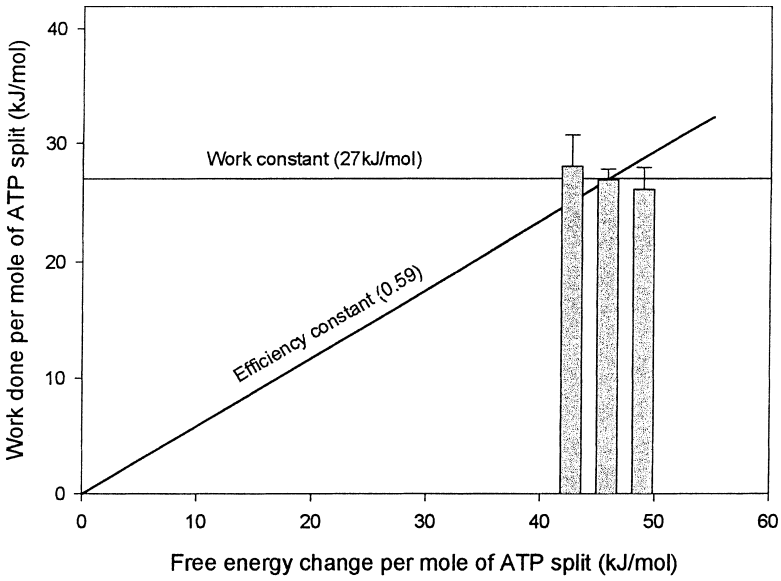

Figure 3 Measurements from Kushmerick & Davies (1969) of the work done per mole of ATP split by frog sartorius muscles. Means and SEM are shown from groups of 12 to 16 muscle pairs. The three bars (from right to left) refer to untreated muscles, to muscles treated with iodoacetic acid (which blocks glycolysis) and to muscles treated with dinitrofluoro benzene (which blocks the creatine kinase reaction). For the first and third groups of muscles the free energy of ATP splitting was calculated by Kushmerick & Davies from the chemical measurements made on the muscles. The iodoacetate treated muscles have been here assumed to have an intermediate value for the free energy.

(2) That there is a constant stoichiometry of work. This hypothesis is represented by the horizontal line. In this hypothesis the initial efficiency is not constant but the overall efficiency between work and oxidation would be unchanged, because the changes in the efficiency of oxidative phosphorylation are exactly compensated by opposite changes in the initial efficiency.

Unfortunately the results cannot decide between the two hypotheses because each line passes within one SEM of each of the three results. However the results do seem to somewhat favour hypothesis (2). By conducting an experiment with about twice the power one might be able to decide this interesting issue.

While the action of the above compensatory mechanism is feasible, observations of the effects of mild fatigue on the mechanical output of muscle show that both the force and the power output decline with exercise. Observations of the effects of changes of Pi concentration on skinned fibres seem to have provided a good parallel to these observations; thus the explanation of the first stage of force reduction on fatigue is that it is due largely to increased Pi concentration. This does not fit well with the notion of a region of insensitivity of the mechanical output of the muscle to metabolite concentration.

Use of high power systems for low power tasks

There exists a conflict in machines between high power and high efficiency. This can be seen in the field of the muscle motor in several ways. For example slow fibre types, which are of course less powerful, have a higher efficiency than the faster types of the same animal (in dogfish: Curtin & Woledge 1993a,b; in mice: Barclay 1994; in humans: Coyle *et al.* 1992, Horowitz *et al.* 1994). Slow species of animals are more efficient than faster species (Woledge 1968). Another example is shown by the empirical Hill relations in Figure 2 (bottom panel) which predict that increases in power produced by a straighter force velocity curve would be accompanied by decreases in efficiency. The work of Curtin & Woledge (1996) shows that when the energetics of whole cycles are considered a given muscle can be used either in a high power or a high efficiency role depending on the duty cycle. During fatigue the motor units originally chosen for the task will become unable to sustain the original mechanical power output. They will therefore have to be supplemented by others (Shinohara & Moritani 1992). If the units first used are those which are able to perform the task with the greatest efficiency then the use of other units, perhaps better suited to a higher power task will lower the efficiency.

Slowing of relaxation

That the speed of relaxation can decrease in fatigued muscle is well known (Westerblad *et al.* 1997), although this does not always happen during fatigue. When it is present this effect could lead to a fall in efficiency by the following mechanism. As already mentioned our studies on efficiency of muscles undergoing cyclical alterations of length (Curtin & Woledge 1996) have shown that, particularly when the cyclical process is rather rapid (5 Hz) the best stimulus duration for efficiency is a single stimulus. If the relaxation becomes slower because of fatigue then the twitch will inevitably become longer. As there will be no possibility of compensation for this by reduction in the stimulus duration the efficiency would seem likely to fall.

A REASON WHY FATIGUE MIGHT INCREASE EFFICIENCY

Buschman *et al.* (1995) have studied efficiency during contraction of muscle fibres which were not fully active. The results suggested that there could be a higher efficiency than that for fully active muscle. A speculative explanation of this rather surprising result would be that there is an element of competition between cross-bridges in a fully active muscle and that when the muscle is at a lower level of activation the individual cross-bridges are able to follow a path that is closer to that giving the greatest efficiency. Muscles contracting when severely fatigued are not fully active, as is demonstrated for example by the use of caffeine which can potentiate the fatigued contraction considerably, in contrast to the very small effects seen with unfatigued muscle. (Lannergren & Westerblad 1991). This might lead us to expect an increase in muscle efficiency during fatigue.

EXPERIMENTAL STUDIES OF EFFICIENCY IN FATIGUED MUSCLE

Only a few experiments have been reported which examine via muscle experiments whether there actually is a change in efficiency in fatigue. The results so far are however rather inconclusive. The experiments of de Haan *et al.* (1996) address the question directly. Efficiency was followed during a 10-s bout of electrically stimulated maximal, dynamical exercise in anaesthetized rats. ATP consumption was estimated from analysis of the muscles. The conclusion was that efficiency did not change, but the experiment does not have a very high resolution and the possibility of an appreciable change in efficiency cannot be excluded. The experiments of Moon *et al.* (1991) used fibres isolated from cod. Glycolytic recovery of the preparations was inhibited with iodoacetic acid and they were studied under anaerobic conditions. Work and chemical change were measured during a series of up to 64 cyclical contractions, which would have fatigued the muscles moderately. There was no significant change during this fatigue in the stoichiometric ratio of work done to the PCr used which averaged only about 7 kJ mol^{-1} (corresponding to an efficiency of around 15%).

There are a number of studies on human exercise which suggest that with fatigue there is a fall in the efficiency of energy conversion. These are reviewed by Gaesser & Poole (1996). In outline the observations are that when a high workload is sustained by a human subject through running or cycling the rate of oxygen consumption gradually increases beyond the time within which a plateau is reached at lower work intensities. Conversely a plateau of oxygen consumption can be sustained if the workload is progressively reduced. It has been shown that the extra oxygen uptake is taking place predominantly in the exercised limb. This has to be interpreted as a decrease in muscle efficiency probably from one or more of the three causes discussed above.

CONCLUSION

There exists quite compelling evidence that at least during high workloads, efficiency of human muscle performance falls with fatigue. The result is not unexpected in that there are a number of mechanisms known which might produce it. However there is, to date, no *in vitro* muscle experiment to provide a parallel for this observation on the exercising human. It is likely that, by using measurements of energy output as heat and work such an experiment might give a clear result. The results could be expected to throw some light on the mechanism of the effect observed in humans.

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