**In vivo** modular control analysis of energy metabolism in contracting skeletal muscle

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We used $^{31}$P MRS (magnetic resonance spectroscopy) measurements of energetic intermediates [ATP, P, and PCr (phosphocreatine)] in combination with the analytical tools of metabolic control analysis to study *in vivo* energy metabolism in the contracting skeletal muscle of anaesthetized rats over a broad range of workload. According to our recent MoCA (modular control analysis) used to describe regulatory mechanisms in beating heart, we defined the energetic system of muscle contraction as two modules (PCr-Producer and PCr-Consumer) connected by the energetic intermediates. Hypoxia and electrical stimulation were used in this *in vivo* study as reasonably selective modulations of Producer and Consumer respectively. As quantified by elasticity coefficients, the sensitivities of each module to PCr determine the control of steady-state contractile activity and metabolite concentrations. The magnitude of the elasticity of the producer was high (4.3 $\pm$ 0.6) at low workloads and decreased 5-fold (to 0.9 $\pm$ 0.2) at high workloads. By contrast, the elasticity of the consumer remained low (0.5–1.2) over the range of metabolic rates studied. The control exerted by each module over contraction was calculated from these elasticities. The control of contraction was found on the consumer at low workloads and then swung to the producer, due to the workload-dependent decrease in the elasticity of producer. The workload-dependent elasticity and control pattern of energy production in muscle is a major difference from heart. Since module rate and elasticity depend on the concentrations of substrates and products, the absence of homeostasis of the energetic intermediates in muscle, by contrast with heart, is probably the origin of the workload-dependent elasticity of the producer module.

Key words: control coefficient, elasticity coefficient, metabolic regulation, modular control analysis, muscle energetics, $^{31}$P magnetic resonance spectroscopy.

INTRODUCTION

In skeletal muscle, as in heart, contraction is powered up by the $\Delta G_p$ (Gibbs free energy of ATP hydrolysis) available at actomyosin ATPase levels. In the absence of changes in regulatory external effectors, both rates of ATP supply and ATP demand depend on the concentration of their substrates/products ATP, ADP and P, The concentration of ATP remains fairly constant during muscle contraction, and [ADP] remains low and undetectable by non-invasive techniques such as $^{31}$P MRS (magnetic resonance spectroscopy). As long as the cytosolic creatine kinase reaction remains close to equilibrium, PCr (phosphocreatine) concentration reflects the status of energy balance within the entire myocyte and over all the fibres in the studied muscles [1,2]. Since energy production and energy consumption during muscle contraction are, respectively, responsible for increasing and decreasing PCr concentration, $^{31}$P MRS assessments of PCr levels are representative of cellular energetic intermediates, and have been widely used to study the behaviour of the energetic system of contraction in heart as well as in muscle [3–9].

Recently, our group proposed a new experimental approach to describe control and regulatory mechanisms of energetics in intact beating hearts, based on the development of the MoCA (modular control analysis). Heart energetics was defined as a two-module system. Modules respectively produce (so-called Producer) and consume (Consumer) energy and are connected by PCr concentration [10]. Central to this approach are the elasticity coefficients of the ATP/PCr-producing and ATP/PCr-consuming modules to PCr concentration [10]. Indeed, elasticity values in such a modular system quantify how the system is maintained in a steady state. Elasticities also allow us to quantify how the effects of an external effector signal/molecule that change the steady state are transmitted through the intermediate [10–13].

It is worth noting that heart is capable of dramatically altering its overall energy flux with only minimal changes in the concentrations of energetic intermediates [14]. Homoeostasis of the intermediates in heart is likely the consequence of a perfectly balanced parallel activation of ATP supply and ATP demand [14,15] as demonstrated in intact hearts stimulated by either calcium [10] or adrenaline [16]. By comparison, an unbalanced activation could thus be suspected in skeletal muscle [5,15,17], since the transition from low to high work intensity is consistently accompanied by a decrease in level of PCr and an increase in the connected intermediates (free creatine, ADP and P,) [3,4,7,9,18,19]. These changes in the energetic intermediates may in turn impact the kinetics of the modules. Therefore it appears that the *in vivo* determination of the elasticities of ATP/PCr-producing and -consuming modules over a wide range of activity is of great interest in skeletal muscle.

For this purpose, we developed a non-invasive experimental set-up providing simultaneous *in vivo* assessments of PCr content and contraction force from electrically stimulated rat muscle. Plantar flexor muscles of intact anaesthetized rats were interrogated by a two-probe ($^1$H and $^{31}$P) set-up providing muscle imaging at rest, and muscle content of phosphorylated intermediates during sustained contractions. The experimental design was defined in the frame of MoCA: the Consumer module contains all the reactions that consume ATP/PCr in contracting myocytes, and...
the Producer module grouped the reactions catalysed by mitochondria and glycolysis together with substrate delivery to contracting muscles. Under steady-state conditions, the selective modulation of ATP/PCr production required by MoCA was achieved by changing the oxygen concentration in the gas mixture inhaled by the rat. The other required modulation, namely ATP/PCr consumption, was carried out by decreasing the electrical stimulation of plantar flexors. The energetic flux through this two-module system is represented by the ATP turnover rate. In contracting muscles during sustained submaximal exercise, the ATP turnover rate is a direct function of the work rate by contraction [20]; therefore the latter can be used as an index of the former [21].

We carried out in vivo the analytical study by MoCA of energy metabolism in contracting muscle over a broad range of metabolic rates. The full MoCA analysis provided a complete integrative description of the behaviour of muscle energetics for each individual animal tested. In agreement with previously modelled elasticities [5], we demonstrate here that the sensitivity of (mitochondrial) ATP/PCr production in vivo decreases as a function of activity in skeletal muscle.

METHODS

Animals

Female Wistar rats weighing 280–340 g were used according to the guidelines of the National Research Council’s Guide for the Care and Use of Laboratory Animals. Rats were housed in an environmentally controlled facility (12 h/12 h light/dark cycle, 22°C), and received water and food ad libitum.

Rats were anaesthetized by continuous inhalation of a gas mixture containing 1.5% isoflurane delivered in a face mask during a 90 min period corresponding to the duration of the experiment inside the magnet and then housed back in their environmentally controlled facility.

Muscle stimulation

Plantar flexor muscles of rats in supine position were stimulated (3 Hz; pulse duration: 220 μs) directly with transcutaneous surface electrodes located at the knee and heel levels [18] and connected to a Compex 2 stimulator (Compex Medical SA, Ecublens, Switzerland). Current intensity was set to 4 mA (low workload), 5–6 mA (moderate workload) and 7–8 mA (high workload). MRS acquisition was synchronized to electrical stimulation. Electrically stimulated regions of the plantar flexor group were assessed by $T_2$-mapping MRI (magnetic resonance imaging) [18]. Transverse relaxation time constants ($T_2$) were measured using an imaging CPMG (Carr-Purcell-Meiboom-Gill) pulse sequence (64 echoes; echo time 7.3 ms; repetition time 2000 ms). $T_2$ maps indicated that the mixed-gastrocnemius muscle responded to electrical stimulation over the range of stimulations used (Figure 2).

$^{31}$P MRS

Rats were placed in a supine position into a supraconducting magnet (4.7 T; 47/50 Biospec Avance magnetic resonance system (Bruker, Karlsruhe, Germany). The foot was positioned on the ergometer pedal and the hindlimb was immobilized so that the lower limb was centred inside a 30 mm diameter $^1$H Helmholtz imaging coil tuned to the $^1$H frequency (200.3 MHz).

A circular home-built transmit–receive probe (18 mm) was placed horizontally under the calf and was tuned to the $^{31}$P frequency (81.1 MHz). Field homogeneity was achieved locally in a $20 \times 20 \times 20 \text{mm}^3$ voxel by using the water proton resonance, with typical line widths of 30–35 Hz.

$^{31}$P FIDs (free-induction decays) (100 μs rectangular pulse, 60° flip angle at the centre of the coil; 40 accumulations; 2.8 s recovery time; 3.3 kHz spectral width; 1024 data points) were acquired in 112 s blocks throughout the experimental protocol.

After Fourier transform, the NMR spectra were then routinely deconvoluted into Lorentzian lines (Igor Pro; WaveMetrics, Lake Oswego, OR, U.S.A.). The PCr, P, and $\beta$-ATP peak areas were calculated and were converted into concentrations using $[\text{ATP}]=8.2 \text{ mM}$. Intracellular pH was determined by using the chemical shift of P, relative to PCr.

Contraction measurements

Contraction resulting from muscle electrical stimulation was measured with a home-built ergometer consisting of a foot pedal connected to a hydraulic piston. A hydraulic circuit filled with water connected the piston to a force transducer (MLT0699 + Powerlab; ADInstruments, Bella Vista, Australia), which was placed outside the magnet. The pedal was adjusted so that the foot was perpendicular to the leg. Changes in pressure induced by pedal stroke were recorded every 5 ms. The magnitude of strokes was computed as a function of time (Igor; Wavemetrics) to provide the contraction signal. Since only relative changes (in percentage) in contraction are required for MoCA, contraction force was expressed as the voltage delivered by the sensor (μV, see Figure 3).

The modular system

We defined the system of contraction as two modules, Producer and Consumer, connected by the phosphorylation potential ($\Delta G_p$) as represented by [PCr] in our conditions [10,16,22]. By grouping reactions and reactants into large modules connected by a small number of explicit intermediates, complex systems are thus simplified [13,23]. The behaviour of the system was studied over a wide range of steady states achieved by a sustained steady level of electrical stimulation. The elasticity coefficients of Producer and Consumer were determined under each given steady-state condition. The typical design of each experiment is described in Figure 1. Two $^{31}$P-MR spectra (spectra 1 and 2) were acquired before muscle stimulation began to assess [PCr]$_{0}$ ([PCr concentration at rest]). During spectra 3–12, muscle stimulation was progressively increased up to the desired current intensity, and hypoxia was gradually initiated by reduction of the FiO$_2$ (inspired fraction of oxygen) of breathed gas to 9% O$_2$ (in N$_2$). The system reached thus a hypoxic steady state where the producer is inhibited for several minutes by hypoxia (spectra 14–18). During spectrum 19, hypoxia was stopped; the rat then inspired air and the system achieved quickly the so-called ‘reference’ steady state (absence of modulation, spectra 20–24). The consumer elasticity was calculated from relative changes in steady levels of PCr and contraction between ‘reference’ and hypoxic conditions (Figure 3). During the last steady-state period, the electrical stimulation was decreased by 1 mA to lessen energy consumption, while FiO$_2$ was purposely maintained at 0.21 (ambient air). The steady values during this stage when compared with ‘reference’ were used for the calculation of the producer elasticity (Figure 3). The elasticity coefficients in each individual animal were quantified by dividing the relative change in contraction by the relative change in [PCr] [10]. The single-experiment determination of the elasticities developed here allows the determination of the control distribution for each animal.
In vivo modular control analysis of muscle energetics

Figure 1  Experimental protocol

Two $^{31}$P spectra were obtained from plantar flexor muscles at rest and then muscles were electrically stimulated for approx. 1 h. After a 20 min period, modulations around the ‘reference’ steady state were achieved, beginning with the steady state under hypoxic conditions (low supply, 9% O$_2$); then, after the switch to normal air, the reference conditions were maintained for 12 min. To achieve the ‘low demand’ episode, the consumer was modulated by a slight decrease in electrical stimulation. Simultaneous measurements of $^{31}$P spectra and muscle contraction during modulation of the steady state allowed calculation of the elasticity coefficient of each module. The value for $n$ depends on the desired imposed workload (see the Methods section).

Figure 2  $^1$H-MRI study of the lower hindlimb of the anaesthetized rat placed in the experimental set-up

Left panel: typical $T_2$-weighted image obtained from the axial view at rest. Middle panel: $T_2$ maps obtained immediately after a typical steady state under low electrical stimulation; right panel: high electrical stimulation. The whiter parts (arrows) in the middle and right panels as compared with resting conditions show the contracting regions of the muscles in response to electrical stimulation.

Statistics

Results are presented as means ± S.D. Elasticity and control coefficients at low, moderate and high work rates were compared using one-way ANOVA. Significant differences were considered at $P < 0.05$.

RESULTS AND DISCUSSION

In the present study, we experimentally apply for the first time metabolic control analysis in vivo to study non-invasively the behaviour of energy metabolism in contracting skeletal muscle on an anaesthetized rat. The analysis was carried out using controlled electrical stimulation to provide a wide range of steady muscle activity. Our experimental two-probe set-up ($^1$H and $^{31}$P) also allowed the application of a specific MRI technique ($T_2$ mapping) dedicated to identify the contracting regions inside the studied muscle group [18]. Figure 2 shows typical axial $T_2$ maps from the rat lower hindlimb obtained at rest (left panel) and immediately following low (middle panel) and high (right panel) steady stimulated contraction. Although this technique did not indicate which precise fibres were contracting, the images in Figure 2 clearly show that only gastrocnemius mixed muscles responded to the electrical stimulation in the current experimental set-up.

Determination of elasticity coefficients

In the formalism of MoCA and more extensively in metabolic control analysis, the correct determination of elasticities must obey some rules: only the intermediate and the flux must vary freely, while other parameters such as external effector molecules...
Table 1  Average PCr, pH and contraction values during steady-state modulations as a function of muscle workload

Steady-state conditions are described in Figure 1. Values are means ± S.D. The different workload conditions were achieved by controlled electrical stimulation: low (4 mA), moderate (5–6 mA) and high (7–8 mA) stimulations respectively. Modulations were tested by using one-way ANOVA and post-hoc Tukey HSD (honestly significant difference) tests.

<table>
<thead>
<tr>
<th>Workload</th>
<th>Cytosolic pH</th>
<th>PCr reference (% of rest)</th>
<th>PCr (mM)</th>
<th>Contraction (μV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low supply</td>
<td>Reference</td>
</tr>
<tr>
<td>Low (n = 7)</td>
<td>7.01 ± 0.04</td>
<td>77 ± 3%</td>
<td>16.7 ± 2.1†</td>
<td>20.2 ± 1.8</td>
</tr>
<tr>
<td>Moderate (n = 17)</td>
<td>6.98 ± 0.03</td>
<td>60 ± 4%</td>
<td>10.7 ± 2.4†</td>
<td>16.3 ± 1.4</td>
</tr>
<tr>
<td>High (n = 9)</td>
<td>6.96 ± 0.04</td>
<td>44 ± 4%</td>
<td>9.6 ± 2.5</td>
<td>12.4 ± 1.0</td>
</tr>
</tbody>
</table>

* P < 0.05, between low supply and reference.
† P < 0.05, between low supply and low demand.
‡ P < 0.05, between low demand and reference.

Figure 3  Typical PCr and contraction records carried out to calculate producer and consumer elasticities in a single animal

Muscle contraction and 31P MRS spectra were measured simultaneously during modulations of the steady state. Magnetic resonance spectra were analysed to assess steady values of energetic intermediates. The magnitude of the contraction signal was averaged over the corresponding period of time. Relative changes in contraction and [PCr] in response to modulations of the steady state provided all the required data for the calculation of the elasticities.

or signals must remain unchanged. The present non-invasive MRS experiments in vivo could therefore be considered as a preliminary crude method, since modulations of the steady state by hypoxia and electrical stimulation might not be perfectly specific. Hypoxia evidently affects the PCr-producing module via selective mitochondrial inhibition, resulting in both [PCr] decrease and consequent contraction decrease (Table 1 and Figure 3). However, the modulation of the consumer module by changing electrical stimulation may be less selective: some cytosolic factors, e.g. intracellular calcium pulses, might impact the producer module to some extent. It is worthy of note that, in contrast with cardiac muscle, wherein direct activation of Producer by calcium has been demonstrated, [Ca2+] changes may likely be of minor concern in the interpretation of skeletal-muscle results. This is illustrated by the dynamics of [PCr] and oxygen consumption in perfused cat soleus (oxidative muscle) as compared with biceps brachii (dominantly glycolytic muscle) [2]: a post-exercise overshoot of [PCr] was detectable only in soleus, but not in biceps brachii, indicating the persistence of the activation of PCr production only in the electrically stimulated fully oxidative muscle. \( T_2 \) maps indicate that only gastrocnemius muscle groups are stimulated in the present study. Since the rat gastrocnemius is not a fully aerobic muscle [24], the direct activation of PCr production by slight changes in electrical stimulation is minimized. A strong additional argument comes from the integration of a broad range of experimental data from skeletal muscle into a dynamic computer model of oxidative phosphorylation and ATP usage [15,17,25]. Indeed, to fit with experimental data, the model predicts the absence of direct activation of PCr production in electrically stimulated muscle [17].

We may therefore consider that the present in vivo application of MoCA to skeletal-muscle energetics might be a crude method and the experimentally determined values of the elasticity coefficient would be approximated. However, we assume that under our conditions, this would not change the general conclusions (see below), and the development of a quantitative approach in vivo, even based on a crude method, seems yet to be advantageous [5,6,26].
The intermediate

In the energy metabolism of contracting skeletal muscle, the true intermediate between production and consumption is the phosphorylation potential $\Delta G_p$. A direct measurement of $\Delta G_p$ in vivo is difficult. Although $\Delta G_p$ can be calculated from MRS of phosphorylated intermediates and pH, errors in the detection of $P_i$, PCr and each ATP peak sum up in this calculation. Thus we based our analysis on [PCr] changes, taking into account the reliable signal-to-noise ratio obtained in vivo with our set-up (Figure 3). Furthermore, the phosphorylation potential depends on the concentrations of ATP, ADP, P, and $H^+$, which are all directly related to PCr concentration and therefore changes in PCr directly reflect changes in $\Delta G_p$. Since only relative changes in the intermediate (and flux) are considered in the MoCA, PCr may be used as a representative of $\Delta G_p$ in the present study [10]. Under our conditions, changes in $[H^+]$ have negligible effects on $\Delta G_p$ (e.g. a decrease in muscle pH by 0.15 only corresponds to less than 2% change in $\Delta G_p$), and the negligible effect of pH on myosin has been demonstrated in skeletal muscle at physiological temperatures [27]. At last, muscle pH was assessed in our MRS experiment in vivo, and values reported in Table 1 show only very small changes in pH over the workload range tested. In conclusion, in vivo MRS assessments of PCr changes are relevant to study the kinetic response of the PCr Producer and PCr Consumer.

Experimental elasticities and muscle activity

Quantifying elasticity coefficients in the frame of MoCA requires the simultaneous measurements of relative changes in [PCr] and in contraction power output. This was achieved here in vivo as illustrated by typical $^1$H-MR spectra and contraction measurements presented in Figure 3. Such a typical experiment was repeated under various levels of electrical stimulation, thus allowing the quantification of elasticity coefficients over a wide range of skeletal-muscle activity. The activity has been scaled according to the steady-state level of [PCr] relative to [PCr] at rest, since a strong correlation has been demonstrated between this parameter and the relative workload in human muscle [4]. The PCr level varied from 82% at the lowest workload to 38% [PCr], at the highest workload. Experimental values for [PCr] and contraction were arbitrary grouped as low, moderate and high levels of muscle activity. Activity-specific averaged values of PCr and contraction are presented in Table 1. These values are only indicative, since the present study was designed to allow single-animal comprehensive MoCA analysis, so that elasticity coefficients were actually calculated for each animal. Therefore between-animal variability, as indicated by S.D. in Table 1, does not interfere with the calculation of elasticities. Averaged individual elasticities measured experimentally are reported in Table 2. The statistical analysis indicates that the Producer elasticity to PCr decreased more than 5-fold from low to high workloads (from −6.7 to −0.3). The Consumer elasticity to PCr was much lower than that of Producer and remained roughly unchanged ($\pm 1.0$) when the workload changed. Figure 4 shows the results from individual experiments and provides a clear picture of the activity-dependent value of the Producer elasticity to PCr and of the roughly constant Consumer elasticity to PCr. Taking into account these marked differences in elasticity values, and the strong effect of muscle activity on the producer elasticity, even the crude method developed here in vivo provides for the first time a clear picture of the behaviour of the energetic system in contracting skeletal muscle in the in vivo integrative context.

### Table 2 Elasticity and control coefficients as a function of muscle workload

<table>
<thead>
<tr>
<th>Workload</th>
<th>Elasticity</th>
<th>Control by...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Producer</td>
<td>Consumer</td>
</tr>
<tr>
<td>Low (n=7)</td>
<td>$-4.3 \pm 1.7^{+} \pm 0.6 \pm 0.3^{+}$</td>
<td>$11 \pm 3^{+} \pm 89 \pm 3^{+}$</td>
</tr>
<tr>
<td>Moderate (n=17)</td>
<td>$-1.6 \pm 0.9$</td>
<td>$0.5 \pm 0.3$</td>
</tr>
<tr>
<td>High (n=9)</td>
<td>$-0.9 \pm 0.6$</td>
<td>$1.2 \pm 0.4^{+}$</td>
</tr>
</tbody>
</table>

* $P<0.001$ between low and moderate.
* $P<0.001$ between low and high.
* $P<0.001$ between high and moderate (except consumer elasticity $P<0.05$).

The shift in kinetic control over contraction

The respective control coefficients of the producer and the consumer were calculated from the above elasticity coefficients as allowed by MoCA [10]. Therefore we can describe how control over contraction is distributed under our conditions. The major finding here is that the control distribution is not unique but depends on muscle activity, in agreement with previous predictions [5]. The change in the control distribution was almost completely accounted for by the decrease in the producer elasticity. At low activity, the producer had a very high elasticity and consequently very low control (10%) over contraction (Table 2 and Figure 4B). Under these conditions, energy consumption mainly set by the activity of the AM (actomysin)-ATPases and SR (sarcoplasmic reticulum)-ATPases controls the contraction (90%), i.e. ATP turnover. At moderate activity, due to the elasticity decrease, the control of the producer module over the contraction increased but remained low (25%), whereas the control by consumer module shifted down to 75%. Under high activity conditions, where PCr depletion was above 50%, the control distribution changed dramatically: the producer rather than the consumer had dominant control over contraction. It was even observed in some animals that the energy production controlled almost totally (>80%) contraction (Figure 4B). Again, it is unlikely that approximations in the experimental determination of elasticity due to our in vivo method can modify the control pattern to a large extent.

Conclusion

For the first time, the behaviour of the energy metabolism in contracting skeletal muscles under steady-state conditions has been quantified here experimentally in vivo in anaesthetized rats. Despite the difficulty in applying strictly selective modulations of energy production and consumption in vivo skeletal muscle, the values of the elasticity coefficients indicate clearly how the steady state of contraction is maintained in skeletal muscle over a wide range of metabolic rates. We highlighted here the low sensitivity of the energy-consuming ATPases to reactants at every metabolic rate as compared with energy production and concluded therefore that, over the range of activity studied here, the activation of myosin is strongly dependent on the direct stimulation by calcium. By contrast, the oxidative phosphorylation processes included in the Producer module appeared highly reactive to small changes in the intermediates at low skeletal-muscle activity, so that feedback metabolic activation is one possible (although not exclusive) mechanism of activation for energy production. This mechanism is far less efficient in activating energy production at higher levels of muscle activity, as indicated by the activity-dependent decrease in the producer elasticity, not observed in the heart [10,14,28].

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It appears crucial to understand the mechanisms underlying the observed changes in the Producer elasticity with activity in skeletal muscle but not in heart. In heart, due to the perfectly balanced parallel activation of energy supply and energy demand by external effectors [10,14,16], [PCr] (as well as the other energetic metabolites and ΔG∗) does not change as a function of contractile activity.

As concentrations of all reactants remain constant, the local kinetic response of each connected module is constant as well. By contrast, the decrease in [PCr] in skeletal muscle when activity increases illustrates substantial changes in all reactants, likely due to unbalanced activation. We hypothesize here that the producer elasticity dependence on activity could be due to these changes in reactant concentrations highlighted by MRS assessments of PCr levels (Table 1). By contrast with the absence of modification of consumer response to the intermediates, results indicate that producer module kinetics shows substrate saturation (probably by creatine) so that its response to substrate changes decreases at high workload and the elasticity decreases to the low values observed.

As we still did not test the regulatory effect of any effector on the system (the effects responsible for a change in the steady state in the formalism of MoCA), no conclusion can be made about the regulation of muscle energetics in vivo. The magnitude of respective activations of energy supply and energy demand when muscle activity increases [16] cannot be detected by our measurements of elasticity and flux control coefficients. To date only approaches in silico have provided insights into intact skeletal muscle [15,17,25,29,30], while experimental evidence was obtained recently in intact heart [10,16].

We anticipate that the application of MoCA analysis will be of great interest for integrative biology studies of healthy or pathological muscles, since it allows deciphering the biochemistry of energy transfer into the physiology of muscle cells. At this stage, the application of MoCA to skeletal-muscle energetics in vivo may be considered as a semi-quantitative approach, because of methodological limitations, but could well be an advance in relation to purely intuitive considerations. Other semi-quantitative approaches have been demonstrated to be very helpful in this area [6,29]. MoCA has the potential to highlight defects/adaptations in the energy transfer system on the basis of elasticity changes. It is unknown to date whether physical activity, chronic hypoxia or pathologies have the potential to alter elasticities or whether only module activities are affected. The design and setup of the present experimental approach provide a useful tool to investigate non-invasively the primary target(s) responsible for these various alterations of muscle contraction.

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REFERENCES


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