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Intramuscular β₂-agonist administration enhances early regeneration and functional repair in rat skeletal muscle after myotoxic injury

James G. Ryall, Jonathan D. Schertzer, Tammy M. Alabakis, Stefan M. Gehrig, David R. Plant, and Gordon S. Lynch

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Ryall JG, Schertzer JD, Alabakis TM, Gehrig SM, Plant DR, Lynch GS. Intramuscular β₂-agonist administration enhances early regeneration and functional repair in rat skeletal muscle after myotoxic injury. J Appl Physiol 105: 165–172, 2008. First published April 24, 2008; doi:10.1152/japplphysiol.00317.2007.—Systemic administration of β₂-adrenoceptor agonists (β₂-agonists) can improve skeletal muscle regeneration after injury. However, therapeutic application of β₂-agonists for muscle injury has been limited by detrimental cardiovascular side effects. Intramuscular administration may obviate some of these side effects. To test this hypothesis, the right extensor digitorum longus (EDL) muscle from rats was injected with bupivacaine hydrochloride to cause complete muscle fiber degeneration. Five days after injury, half of the injured muscles received an intramuscular injection of formoterol (100 µg). Muscle function was assessed at 7, 10, and 14 days after injury. A single intramuscular injection of formoterol increased muscle mass and force-producing capacity by 17 and 91%, respectively, but this effect was transient because these values were not different from control levels at day 10. A second intramuscular injection of formoterol at day 7 prolonged the increase in muscle mass and force-producing capacity. Importantly, single or multiple intramuscular injections of formoterol did not elicit cardiac hypertrophy. To characterize any potential cardiovascular effects of intramuscular formoterol administration, we instrumented a separate group of rats with indwelling radio telemeters. Following an intramuscular injection of formoterol, heart rate increased by 18%, whereas systolic and diastolic blood pressure decreased by 31 and 44%, respectively. These results indicate that intramuscular injection can enhance functional muscle recovery after injury without causing cardiac hypertrophy. Therefore, if the transient cardiovascular effects associated with intramuscular formoterol administration can be minimized, this form of treatment may have significant therapeutic potential for muscle-wasting conditions.

METHODS

Experimental animals. All procedures were approved by the Animal Experimentation Ethics Committee of The University of Melbourne and conformed to the Guidelines for the Care and Use of Experimental Animals described by the National Health and Medical Research Council of Australia. Adult male Sprague-Dawley (SD) rats were bred and housed in the Biological Research Facility at The University of Melbourne. Rats were kept in standard cages with access to food pellets and water ad libitum and were maintained on a 12-h light/12-h dark cycle, operating in light from 0600–1800.

Determination of optimal dose of formoterol for intramuscular injection. Adult male SD rats (n = 25 rats, body mass = 300–380 g) were randomly allocated into one of five formoterol-treated groups. Rats received 0.01, 0.1, 1.0, 10, or 100 µg formoterol (in 0.1 ml saline) via a single intramuscular injection into the right extensor digitorum longus (EDL) muscle. The left EDL muscle served as the untreated control.

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SKELETAL MUSCLES CAN BE INJURED as a consequence of extrinsic events, including mechanical stress, crush, contusion, and laceration (3, 4, 13, 31); intrinsic events, such as ischemia and metabolic deficits; or diseases, such as the muscular dystrophies (18, 33). Although skeletal muscles have an intrinsic ability to regenerate after injury, repair is often slow and sometimes incomplete (9, 19, 23). Furthermore, regenerating muscles have a reduced functional capacity and can be more susceptible to reinjury (14). Thus developing safe and effective treatments that enhance muscle repair following injury would improve the quality of life for many patients.

Sympathomimetics such as β₂-adrenoceptor agonists (β₂-agonists) have therapeutic potential for conditions in which muscle wasting and weakness are indicated. These agents increase muscle size and strength of healthy muscle fibers and enhance the rate of muscle repair following injury (1, 8, 26, 27). In previous studies using β₂-agonists to induce muscle growth, high doses have been administered systemically over a period of weeks, either orally, via intraperitoneal injection, or by subcutaneous infusion (6, 21, 26, 27). However, these routes of administration, combined with the high doses of these agents and the lengthy treatment periods required to elicit skeletal muscle hypertrophy, have been associated with cardiovascular side effects (especially cardiac hypertrophy) that have so far limited their clinical applicability (5, 10, 20).

We have demonstrated that the cardiac hypertrophy associated with β₂-agonist administration in rats and mice can be minimized through use of micromolar doses of highly selective β₂-adrenoceptor compounds, such as formoterol (28). In the present study, our purpose was to further limit potential systemic effects through single or multiple intramuscular injections of formoterol while maintaining the beneficial effects on skeletal muscle regeneration. We tested the hypothesis that direct intramuscular delivery of the β₂-agonist would improve muscle structure and function after injury. Furthermore, we hypothesized that a single intramuscular injection of formoterol would not be associated with cardiac hypertrophy.
parameters and contractile parameters were controlled and measured (0.2-ms duration) that were amplified (40 V, Ebony, dual-channel EDL muscles were stimulated by supramaximal square-wave pulses. nH11005

Adult male SD rats (420 – 480 g; injury. experiments. (Po) were determined as described previously (1, 26, 27). Briefly, twitch relaxation time (1/2RT), and maximum force of contraction

Muscle regeneration was assessed at 7, 10, and 14 days after injury.

In vitro muscle contractile properties. At the completion of the treatment period, rats were anesthetized via intraperitoneal injection of pentobarbital sodium, with supplemental doses administered as required. The muscles were surgically exposed and injected to holding capacity with 0.5% bupivacaine hydrochloride [1-butyl-N-(2, 6-dimethylpyridine)-2-piperidinobenzoxamide] as described previously (1). The left EDL muscles from control rats served as the uninjured control, and the right EDL muscle served as the injured control and was designated as the injured muscle. Following the surgical procedure, the right EDL muscle of treated rats was injected with formoterol (100 μg im in 0.1 ml saline) 5 days after myotoxic injury and was designated as the injured + formoterol muscle. This time point was chosen because bupivacaine causes extensive muscle fiber degeneration within the first two days after administration and myofiber regeneration commences thereafter (24, 25). We have also shown previously that at this time during regeneration, β2-adrenergocentor concentration is elevated significantly (1). Muscle regeneration was assessed at 7, 10, and 14 days after injury.

To determine if there were any crossover effects of intramuscular formoterol administration, the left untreated EDL muscles from formoterol-treated rats were weighed and their muscle mass compared with that of the left untreated EDL muscles from control rats.

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INTRAMUSCULAR FORMOTEROL ENHANCES EARLY MUSCLE REGENERATION

Fig. 1. Dose response for extensor digitorum longus (EDL) muscle mass as %contralateral control muscle following intramuscular formoterol administration. Formoterol was administered via a single intramuscular injection at doses of 0.01, 0.1, 1.0, or 100 μg in 0.1 ml of saline, with muscle mass determined 7 days later. Values are means ± SE.*P < 0.05 vs. control.

Table 1. Contractile properties of EDL muscles from control, injured, and injured + formoterol groups at 7, 10, and 14 days after injury

<table>
<thead>
<tr>
<th>Days Postinjury</th>
<th>Control</th>
<th>Injured</th>
<th>Injured + Formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Muscle mass, mg</td>
<td>7 Days</td>
<td>10 Days</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Muscle mass, mg</td>
<td>207±8</td>
<td>141±7*</td>
<td>165±8*#</td>
</tr>
<tr>
<td>Fiber CSA, μm²</td>
<td>2124±148</td>
<td>699±59*</td>
<td>1056±71#</td>
</tr>
<tr>
<td>Pt, mN</td>
<td>914±44</td>
<td>284±34*</td>
<td>636±45*#</td>
</tr>
<tr>
<td>TPT, ms</td>
<td>29±1</td>
<td>28±2</td>
<td>33±1</td>
</tr>
<tr>
<td>1/RRT, ms</td>
<td>33±1</td>
<td>42±5*</td>
<td>31±2#</td>
</tr>
<tr>
<td>Pm, mN</td>
<td>3204±113</td>
<td>977±73*</td>
<td>1867±161*#</td>
</tr>
<tr>
<td>sPm, mN</td>
<td>270±15</td>
<td>129±10*</td>
<td>205±10*#</td>
</tr>
<tr>
<td>Heart mass, mg</td>
<td>838±18</td>
<td>810±17</td>
<td>832±16</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = number of animals. EDL, extensor digitorum longus; CSA, cross sectional area; Pt, peak twitch force; TPT, time to peak twitch force; 1/RRT, one-half relaxation time during twitch; Pm, maximal tetanic force; sPm, force per CSA. *P < 0.05 vs. same-day control. #P < 0.05 vs. same-day injured.

blotting, PVDF membranes were stained with Ponceau stain to confirm equal protein loading (data not shown).

Successive intramuscular injections of formoterol to injured muscles. A second group of adult male SD rats (300–380 g, n = 11) were randomly assigned to either an untreated group (n = 5) or a 2× formoterol-treated group (n = 6) to determine the effect of successive intramuscular injections. The right EDL muscles were injured with bupivacaine hydrochloride as described previously (see Intramuscular administration of formoterol following myotonic injury), with the left EDL muscles of the untreated group serving as uninjured controls. Following the surgical procedure, treated rats received two intramuscular formoterol injections (100 μg in 0.1 ml saline) at 5 and 7 days after myotonic injury. Muscle structure and function were assessed at 10 days after injury. While under deep anesthesia, the rats were killed by cardiac excision. The hearts were trimmed of atria and any adhering nonmuscle tissue, blotted, and weighed.

Examination of systemic effects of intramuscular formoterol administration. To determine whether intramuscular administration was associated with any deleterious effects on cardiovascular function, a group of SD rats (~270 g; n = 4), were instrumented with a surgically inserted radio telemeter (TA11PA-C40 telemeter; Data Sciences International, St. Paul, MN). Rats were anesthetized with pentobarbital sodium, with supplemental doses administered to maintain an adequate depth of anesthesia such that there was no response to tactile stimulation. Before surgery, each rat received a subcutaneous injection of the analgesic meloxicam (Metacam, 0.2 ml/kg; Boehringer Ingelheim, Ingelheim, Germany). The descending abdominal aorta was exposed by a midline abdominal incision and was cannulated rostral to the femoral bifurcation with the arterial pressure cannula of a radio telemeter. The telemeter body was placed in the abdominal cavity and was secured to the abdominal musculature. The rats were allowed to recover from the surgical procedure for 14 days before taking any readings.

To examine cardiovascular responses after intramuscular formoterol administration, we measured heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) following a single intramuscular injection of formoterol (100 μg in 0.1 ml saline) while the rat was anesthetized. Cardiovascular parameters were obtained by using four receiver pads (Data Sciences International) connected to a receiver multiplexer (RMM10; Data Sciences International) and one channel on the consolidation matrix (BCM100; Data Sciences International). Data were analyzed using the Dataquest A.R.T. program (v. 2.2, Data Sciences International). SBP, DBP, and HR parameters were recorded at a sampling rate of 64 Hz for a period of 20 s every 5 min. Recordings were obtained while the rats were anesthetized and were grouped into a 15-min preinjection (baseline) period, 0–30 min immediately after formoterol administration, and 30–90 min after formoterol administration. Telemetry recording continued for ~12 h.

Statistical analyses. All values in the text and tables are reported as means ± SE. Data for groups of muscles were compared between treatments by using either two-factor ANOVA with Fisher’s least significant difference post hoc multiple-comparison procedure to identify the differences between groups. For the telemetry experiments, a single ANOVA was performed. In all cases, differences between groups were considered significant when P < 0.05.

RESULTS

Optimal dose of formoterol for intramuscular injection. The results of the dose-response experiment are presented in Fig. 1. EDL muscle mass was increased at all doses of formoterol tested (P < 0.05). The maximal hypertrophic response of the EDL to a single intramuscular injection of formoterol occurred at a dose of 100 μg, and this dose was chosen for the remaining experiments.

Morphometric properties of regenerating EDL following a single intramuscular injection of formoterol. Injured EDL muscle mass was reduced by 32 and 15% compared with...
control values at 7 and 10 days after injury, respectively ($P < 0.05$). However, by 14 days after injury, there was no difference in muscle mass between injured and control muscles (Table 1). The decrease in muscle mass observed at 7 and 10 days after injury was associated with a 67 and 52% decrease in muscle fiber CSA compared with control values, respectively ($P < 0.05$). Muscle mass of injured muscles was restored to control values by 14 days, but muscle fiber CSA remained 40% below control values ($P < 0.05$).

A single intramuscular injection of formoterol (at day 5 after injury) increased muscle mass by 17% ($P < 0.05$) at day 7, but at 10 and 14 days after injury there was no difference in muscle mass between injured and injured + formoterol groups. The increase in muscle mass at 7 days after injury in the injured + formoterol group was associated with a 51% increase in muscle fiber CSA ($P < 0.05$). There was no difference in muscle fiber CSA between injured and injured + formoterol groups at days 10 and 14.

EDL muscle mass in the untreated contralateral limb from formoterol-treated rats was not different from control EDL muscle mass at 7, 10, or 14 days (data not shown), indicating that there were no crossover effects of a single intramuscular injection of formoterol.

A single intramuscular injection of formoterol did not alter heart mass at any of the time points examined (Table 1).

**Contractile properties after a single intramuscular injection of formoterol.** Injured EDL muscles exhibited a reduction in maximum isometric $P_t$ at 7, 10, and 14 days ($P < 0.05$, Table 1). At day 7, injured muscles had a prolonged $1/2RT$ compared with uninjured control muscles, but this was restored to control values by day 10. $P_o$ of injured muscles was 31, 53, and 72% that of uninjured muscles at 7, 10, and 14 days after injury,
respectively ($P < 0.05$). When $P_o$ was corrected for changes in muscle CSA (s$P_o$), injured muscles were 48, 59, and 71% of uninjured values at 7, 10, and 14 days after injury, respectively ($P < 0.05$).

At 7 days after injury, a single intramuscular injection of formoterol administered to injured muscles at 5 days after injury increased $P_t$ by 124% compared with untreated injured muscles ($P < 0.05$), but $P_t$ of formoterol-treated injured muscles remained below that of uninjured controls. This effect did not persist beyond day 7. In addition, formoterol treatment decreased 1/2RT of injured muscles such that there was no difference compared with uninjured values. Formoterol treatment increased $P_o$ and s$P_o$ at 7 days after injury by 91 and 59% compared with untreated injured muscles, but no effect was observed at 7 days after injury.

Fatigability and recovery of EDL muscles after intramuscular formoterol administration. Compared with uninjured control muscles, injured EDL muscles were less susceptible to fatigue and had a greater recovery of function at 7, 10, and 14 days ($P < 0.05$, Fig. 2). Interestingly, a single intramuscular formoterol injection increased the rate of fatigue and impaired recovery at day 7 compared with untreated injured muscles. By day 10, fatigability and recovery had returned to injured control levels (Fig. 2). Similar to untreated injured EDL muscles, formoterol-treated injured muscles were less susceptible to fatigue and were better able to recover than control muscles at 7, 10, and 14 days.

MyHC isoforms and EYA1 mRNA and protein levels at day 7 after injury. Control uninjured EDL muscles had a higher proportion of slow/intermediate type Ila and IId/x MyHC isoforms than fast type IIb isoforms (58 vs. 42%, respectively; $P < 0.05$; Fig. 3). At 7 days after injury, EDL muscles contained a 24% greater proportion of type Ila and IId/x MyHCs than control uninjured muscles, with a concomitant decrease in the proportion of type IIb MyHCs. Importantly, 2 days after a single intramuscular injection of formoterol, there was no difference in MyHC isoform composition compared with control EDL muscles at 7 days after injury. Hence intramuscular injection of formoterol resulted in 24% increase in the MyHC IIb isoform at 7 days after injury ($P < 0.05$, Fig. 3).

At 7 days after injury, both treated and untreated EDL muscles exhibited a trend toward a reduced EYA1 mRNA expression, but this was not significant (Fig. 3). At the protein level, injured EDL muscles exhibited a 37% decrease in the level of EYA1 compared with control muscles ($P < 0.05$). Conversely, there was no significant difference in EYA1 protein levels at 7 days after injury after a single intramuscular formoterol injection.

...
Cardiovascular function, there was no cardiac hypertrophy. Muscular administration was associated with acute changes in operating EDL muscles at 7 days after injury. Although intra-
not increase Po of injured/regenerating EDL muscles after the 

Table 2. Contractile properties of EDL muscles from control, injured, and injured +2× formoterol groups at 10 days after injury

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Injured</th>
<th>Injured +2× Formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>MM, mg</td>
<td>194±1</td>
<td>185±8</td>
<td>184±7</td>
</tr>
<tr>
<td>P0, mN</td>
<td>3402±76</td>
<td>1839±101*</td>
<td>2368±149*#</td>
</tr>
<tr>
<td>sP0, mN</td>
<td>262±8</td>
<td>158±14*</td>
<td>211±13*#</td>
</tr>
</tbody>
</table>

Values are mean ± SE; n = number of animals. MM, muscle mass. *P < 0.05 vs. same-day control. #P < 0.05 versus same-day injured.

Successive intramuscular formoterol injections extend the hypertrophic response. Similar to a single intramuscular formoterol injection, two successive intramuscular formoterol injections did not alter EDL muscle mass at 10 days after injury (Table 2). In contrast to the single intramuscular results, at 10 days after injury, two intramuscular formoterol injections increased P0 and sP0 by 29 and 34% compared with untreated injured muscles (P < 0.05). As with a single intramuscular injection of formoterol, two intramuscular injections also did not affect heart mass (data not shown).

Systemic cardiovascular effects of a single intramuscular formoterol injection. Using radio telemetry, an 18% increase in HR was observed within 30 min of the single intramuscular formoterol injection, which was associated with a 31 and 44% decrease in SBP and DBP compared with baseline values, respectively (P < 0.05; Table 3 and Fig. 4). Both SBP and DBP decreased by a further 8 and 7%, respectively, over the next 60 min (P < 0.05). These cardiovascular parameters returned to baseline levels within 10–12 h (Table 3).

DISCUSSION

The most important finding of this study was that a single intramuscular injection of the β2-agonist formoterol increased regenerating EDL muscle mass and force-producing capacity at 7 days after injury. In addition, we have demonstrated that formoterol can elicit a dramatic shift in the MyHC isoform phenotype of regenerating EDL muscles within 2 days of intramuscular administration. It should be noted that in a previous study we showed that daily systemic (intraperitoneal) administration of a β2-agonist (fenoterol) to rats for 7 days did not increase P0 of injured/regenerating EDL muscles after the same myotoxic injury (1). In contrast, the findings of the present study reveal that even a single intramuscular injection of formoterol can increase muscle fiber size and P0 of regenerating EDL muscles at 7 days after injury. Although intramuscular administration was associated with acute changes in cardiovascular function, there was no cardiac hypertrophy.

Table 3. Selected cardiovascular parameters 30 min, 90 min, and 12 h after a single intramuscular injection of 100 μg formoterol

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0–30 min</th>
<th>30–90 min</th>
<th>12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>339±7</td>
<td>399±11*</td>
<td>398±6*</td>
<td>349±6</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>111±1</td>
<td>77±4*</td>
<td>68±1*#</td>
<td>111±3</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>82±5</td>
<td>46±2*</td>
<td>40±1*#</td>
<td>77±3</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. *P < 0.05 vs. control. #P < 0.05 vs. 0–30 min.

These findings highlight the efficacy of intramuscular formoterol administration to increase functional recovery after injury and support the hypothesis that an intramuscular injection of formoterol can enhance early skeletal muscle regeneration after injury without deleteriously affecting heart mass.

Although intramuscular injection of β2-agonists represents a novel mode of administration for these agents, the results do support previous findings where systemic administration of β2-agonists is associated with increased fiber CSA, muscle mass, and force-producing capacity (8, 26). The skeletal muscle hypertrophy in response to β2-adrenoceptor stimulation is thought to result from an increase in protein synthesis and a decrease in protein degradation (18, 22). β2-agonist-induced hypertrophy has been linked previously to cAMP-dependent signaling pathways (7, 22), but recent evidence suggests that the phosphatidylinositol 3-kinase-Akt signaling pathway also plays a significant role in the hypertrophic response (15, 17).

During early regeneration, skeletal muscle predominantly expresses the embryonic and neonatal MyHC isoforms of and a high oxidative capacity, which confer a high degree of fatigue resistance (32, 34). In the rat EDL muscle, as regeneration progresses these embryonic and neonatal MyHC isoforms are replaced by mature fast-twitch type II fibers, which renders the EDL muscle more susceptible to fatigue (9). It is interesting to note that two days after a single intramuscular injection of formoterol, the fatigue profile of regenerating EDL muscles closely resembled that of control uninjured muscles. This result was associated with a shift in MyHC isoform composition from slow/intermediate isoforms to the fast glycolytic type IIb MyHC isoforms, such that there was no difference in MyHC composition between injured treated muscles and control muscles. Although differences in muscle-fatigue characteristics among groups may be due to variety of adaptive changes, the results highlight the rapid plastic response of skeletal muscle following β2-agonist administration.

Although numerous studies have focused on the mechanisms leading to a shift in MyHC isoform composition toward a slow-twitch phenotype (16, 30), very few have examined the underlying mechanisms responsible for a shift toward a fast-twitch phenotype. Grifone and colleagues (11) showed that a...
member of the Six/sine oculis family of homeoproteins (SIX1) and the associated cotranscription factor EYA1 can act synergistically to drive the transformation of slow fibers to a fast-fiber phenotype. Although the results of the present study do not support a role for EYA1 in the formoterol-induced shift in the MyHC phenotype, it must be noted that we examined EYA1 mRNA and protein levels 2 days after formoterol injection. Thus it remains possible that EYA1 (and/or SIX1) is elevated acutely by formoterol administration. In addition, EYA1 (and SIX1) is known to be regulated posttranscriptionally, such that it is transported into the nucleus in fast type IIb fibers. Therefore it will be important in future studies to determine the cellular localization of these factors after β2-agonist administration. Interestingly, at 7 days after injury there was a significant decrease in EYA1 mRNA and protein levels, a time when the MyHC isoform composition is shifting from the slow type IIa and IIId/x isoforms to the faster type IIb isoforms. To our knowledge, this is the first study to implicate EYA1 in skeletal muscle regeneration, and, although beyond the scope of the present study, the findings highlight the need for future studies to examine the interaction between SIX1 and EYA1 in regenerating skeletal muscle.

The response of injured/regenerating muscles to a single intramuscular injection of formoterol indicates that this mode of administration could have therapeutic application for conditions where muscle wasting and weakness are indicated. However, because of the transient nature of the increases in muscle size and force-producing capacity, it was important to determine the effect of successive intramuscular injections. The results demonstrate that multiple intramuscular injections can prolong the hypertrophic response observed with a single intramuscular injection of formoterol and reinforce the therapeutic potential of this approach.

One of the major factors limiting the use of β2-agonists for treating muscle wasting and weakness relates to their cardiovascular effects. Chronic systemic β2-agonist administration has been associated with cardiac hypertrophy and altered cardiovascular function (10, 26–28). In the present study, neither a single nor successive intramuscular injections were associated with cardiac hypertrophy, but it must be noted that this route of administration did not obviate the acute cardiovascular effects. The in vivo radio telemetry data indicate that intramuscular formoterol administration is also associated with increased HR and decreased blood pressure, effects that might preclude this treatment for some patients. However, the dose used in the current study (100 μg) was chosen so as to maximize the effects on regenerating skeletal muscle. Because regenerating skeletal muscle appears more receptive to β2-agonist administration (2), further research into the optimal therapeutic dose of intramuscular formoterol injection in regenerating muscle may yield more promising results with respect to limiting unwanted cardiovascular side effects.

Importantly, this study has demonstrated for the first time that intramuscular administration of formoterol can enhance early muscle regeneration. Although the improvements in regenerating fiber size and muscle function associated with a single intramuscular formoterol injection were transient, these favorable responses could be prolonged with successive injections. Of particular importance was the finding that intramuscular administration of the β2-agonist did not cause the cardiac hypertrophy normally associated with intraperitoneal, subcuta-

neous, or oral administration of these compounds. However, intramuscular formoterol injection did have transient effects on some cardiovascular parameters, and these must be minimized before this form of treatment could be advocated for clinical application. The findings suggest that intramuscular administration has therapeutic potential for conditions where muscle wasting and weakness are indicated.

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