Renal vascular responses to static handgrip: role of muscle mechanoreflex

Afsana Momen,1 Urs A. Leuenberger,1 Chester A. Ray,1 Susan Cha,1 Brian Handly,1 and Lawrence I. Sinoway1,2

Renal vascular responses to static handgrip: role of muscle mechanoreflex. Am J Physiol Heart Circ Physiol 285: H1247–H1253, 2003. First published May 15, 2003; 10.1152/ajpheart.00214.2003.—During exercise, the sympathetic nervous system is activated, which causes vasoconstriction. The autonomic mechanisms responsible for this vasoconstriction vary based on the particular tissue being studied. Attempts to examine reflex control of the human renal circulation have been difficult because of technical limitations. In this report, the Doppler technique was used to examine renal flow velocity during four muscle contraction paradigms in conscious humans. Flow velocity was divided by mean arterial blood pressure to yield an index of renal vascular resistance (RVR). Fatiguing static handgrip (40% of maximal voluntary contraction) increased RVR by 76%. During posthandgrip circulatory arrest, RVR remained above baseline (2.1 ± 0.2 vs. 2.8 ± 0.2 arbitrary units; P < 0.017) but was only 40% of the end-grip RVR value. Voluntary biceps contraction increased RVR within 10 s of initiation of contraction. This effect was not associated with an increase in blood pressure. Finally, involuntary biceps contraction also raised RVR. We conclude that muscle contraction evokes renal vasoconstriction in conscious humans. The characteristic of this response is consistent with a primary role for mechanically sensitive afferents. This statement is based on the small posthandgrip circulatory arrest response and the vasoconstriction that was observed with involuntary biceps contraction.

Momen, Afsana, Urs A. Leuenberger, Chester A. Ray, Susan Cha, Brian Handly, and Lawrence I. Sinoway.

Address for reprint requests and other correspondence: L. Sinoway, Div. of Cardiology, H047, Penn State College of Medicine, PO Box 850, Hershey, PA 17033 (E-mail: lsinoway@psu.edu).

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renal vasoconstriction with an onset latency of 6–10 s and an MVC threshold of 50% for handgrip exercise and 30% for biceps contraction. This increase in RVR during biceps contraction was not due to central command. Finally, during fatiguing handgrip exercise, metaboreceptors contribute ~40% of the increase in RVR that is seen at the end of exercise. These findings suggest that in humans, muscle mechanoreflex engagement is the primary determinant of RVR during muscle contraction.

METHODS

Healthy volunteers (13 total: 7 men and 6 women, 18–37 yr of age) were studied. Average heights and weights were 171 ± 12 cm and 64 ± 11 kg, respectively, and average body mass index was 22 kg/m². All were normotensive nonsmokers, and none were taking medication. Each subject provided informed written consent to participate. The Institutional Review Board of the Milton S. Hershey Medical Center approved all procedures.

Recent advances in duplex ultrasonography provide the opportunity to visualize and simultaneously assess blood flow dynamics within intra-abdominal blood vessels such as the renal artery (4, 18). Accordingly, duplex ultrasound (HDI 5000, ATL Ultrasound; Bothell, WA) was used to examine renal hemodynamics as subjects performed four arm and forearm exercise paradigms.

Subjects were studied in the postabsorptive state and were supine as the renal artery was scanned (via an anterior abdominal approach). A curved-array C5-2 Doppler probe with a 2.5-MHz pulsed Doppler frequency was used. The focal zone was at the depth of the renal arteries. The probe insonation angle to the skin was ~60°. To obtain the highest quality Doppler tracings possible, the Doppler transducer had to be maintained in a constant position on the subject’s abdominal wall. During our pilot experiments, we noted that the renal artery moved with respect to the abdominal wall during the various phases of respiration, and thus we could not maintain high-quality velocity tracings during both phases of the respiratory cycle. Nevertheless, for each subject, we obtained velocity data during the same phase of the respiratory cycle for all portions of the respective paradigms. Accordingly, for each person, the data were obtained in the same phase of the respiratory cycle. No subjects performed the Valsalva maneuver during the protocols.

Cardiac cycle Doppler signals were analyzed to determine the mean blood flow velocity (MBV). Each velocity measurement was normalized with a time constant of 1 s for the RVR calculations. For each data point, we averaged two or three cardiac cycles. Data smoothing was not used to obtain mean velocity data. Software developed for the HDI 5000 was used to analyze Doppler signals. In each cardiac cycle, the peak-velocity envelope was traced manually to determine the MBV. The RVR represents the quotient of mean arterial pressure (MAP) and the respective MBV value. RVR is expressed in arbitrary units (au).

HR (obtained by electrocardiogram), BP (measured with Finapres, Ohmeda; Madison, WI), and beat-by-beat renal artery blood flow velocity (RBV) measurements were obtained continuously throughout all protocols. Resting BP was determined using an automated sphygmomanometer (Dinamap, Critikon; Tampa, FL). A force transducer was used to measure the force of muscle contractions.

Study Protocols

Fatiguing static handgrip exercise followed by PHG-CA. In this protocol, the time course of renal vasoconstriction during sustained, fatiguing static handgrip was characterized. A second goal was to determine the role played by metabolitesensitive muscle afferents in evoking renal vasoconstriction. This was done by examining RVR during PHG-CA (20).

Baseline HR, MAP, and RBV measurements were collected for 5 min. Static handgrip exercise at 40% of MVC was then performed until the subjects (n = 9) were unable to maintain the prescribed tension. At the end of contraction, all subjects graded their perceived level of effort as 20 on the Borg scale (3). Immediately before the handgrip exercise was ended, PHG-CA was initiated by inflating a previously placed arm cuff to 250 mmHg.

Graded intensity of static handgrip exercise. The aim of this protocol was to examine RVR within the first few seconds of handgrip exercise. A second aim was to determine the temporal relationship between renal vasoconstriction and BP. A final goal was to examine the effects of MVC (by percent) on RVR.

After baseline data were collected, subjects (n = 9) performed 15-s bouts of static handgrip at 10, 30, 50, and 70% of MVC using the nondominant forearm. This sequence was the same for all subjects. Subjects rested for ~1 min between each handgrip exercise bout.

Graded intensity of biceps contraction. The biceps MVC level was determined in each subject at the beginning of the protocol. In determining the MVC values, care was taken to ensure that subjects (n = 6) used only the biceps muscle. After baseline data were collected, the subjects performed voluntary biceps contractions at 7, 15, 30, and 60% of MVC.

Voluntary versus involuntary biceps contractions. The aim of this protocol was to determine whether involuntary biceps contraction evokes renal vasoconstriction. Involuntary contraction eliminates central command (20, 23).

In each subject (n = 6), involuntary biceps contraction was induced by percutaneous electrical stimulation. Electrical pads (5 × 5 cm²) were placed ~3 cm apart. The biceps muscle was then electrically stimulated (200 V; phase duration, 0.3 ms; phase interval, 0.1 ms). Electrical biceps contraction evoked ~15–30% of MVC without causing pain. Once tension reached a steady state, it had to be sustained for 5–7 s. The subjects then performed 15 s of voluntary biceps contractions at the same tension that had been generated during involuntary contraction.

Data Analysis and Statistics

Beat-by-beat sequential analyses of HR, MAP, RBV, and RVR were performed for all subjects in each protocol.

In the fatiguing static handgrip protocol, the time to fatigue for each subject was noted, and the HR, BP, flow velocity, and RVR values at 10, 20, 40, 60, 80, and 100% were determined (35). To ensure that RVR measurements obtained during PHG-CA represented steady-state values, data from the last 30-s time period are presented and used in the statistical analysis. PHG-CA values were compared with baseline data using a paired t-test.

In the graded static tension paradigms, data were analyzed in 5-s time periods. Statistical analyses were performed separately on each 5-s period (i.e., 0–5, 6–10, and 11–15 s, respectively). For the involuntary contraction paradigm, data obtained during the first 5 s after steady-state involuntary tension were compared with the same tension that had been generated by voluntary contraction and to baseline values.
The voluntary contraction data used in these analyses were the 11- to 15-s data. Data are presented as means ± SE. Repeated-measures one-way ANOVA and Dunnett’s test were applied to compare variables to baseline data. The level of significance was set at \( P < 0.05 \).

**RESULTS**

**Fatiguing Static Handgrip Protocol**

The time to fatigue at 40\% MVC was 112 ± 14 s. At 10\% of the time to fatigue, HR and BP values were higher than the baseline measurements. Renal flow was ~7\% lower and RVR was ~16\% higher than baseline values (Fig. 1). RVR at 100\% of the time to fatigue was 76\% greater than the baseline value. Of note, the reduction in RBV paralleled the increase in BP (Table 1).

During PHG-CA, RVR was greater than the baseline measurement (2.1 ± 0.2 vs. 2.8 ± 0.2 au; \( P < 0.017 \); \( n = 8 \)). However, the RVR value during PHG-CA represented only 40\% of the RVR value seen at end grip. PHG-CA values for the other measured variables are shown in Table 2.

**Graded Handgrip Contraction Protocol**

The data for HR, MAP, RVR, and RBV are shown in Fig. 2 and Table 3. No increase in vascular resistance was found in the 0- to 5-s time frame (i.e., the \( P \) value for 0- to 5-s RVR was not significant). Vascular resistance measurements for the 6- to 10-s \( (P < 0.016) \) and 11- to 15-s \( (P < 0.026) \) time periods were higher than baseline values. Post hoc analyses demonstrated that vascular resistance values during handgrip exercise were different from baseline measurements at 50 and 70% MVC for the 6- to 10- and 11- to 15-s time periods.

**Biceps Contraction Protocol**

Static biceps contraction increased RVR early (one-way ANOVA main effect, \( P < 0.042 \); Fig. 3). Post hoc analyses demonstrated a trend toward a significant effect at the 7\% and 30\% workloads (comparisons to baseline, \( P < 0.092 \) at 7\% and \( P < 0.073 \) at 30\%; Fig. 3). The effects of biceps contractions were more pronounced at the 6- to 10- and 11- to 15-s time periods. Comparisons to baseline values demonstrated that the 30% workload (6–10 s and 11–15 s) and the 60% workload (6–10 s and 11–15 s) were different from baseline measurements.

<table>
<thead>
<tr>
<th>Time to Fatigue, %</th>
<th>Baseline</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>63 ± 3</td>
<td>70 ± 4*</td>
<td>77 ± 7*</td>
<td>77 ± 5*</td>
<td>76 ± 6*</td>
<td>83 ± 6*</td>
<td>83 ± 5*</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>97 ± 5</td>
<td>105 ± 8*</td>
<td>107 ± 10</td>
<td>112 ± 9*</td>
<td>114 ± 4*</td>
<td>122 ± 9*</td>
<td>129 ± 8*</td>
</tr>
<tr>
<td>Mean blood velocity, cm/s</td>
<td>49 ± 4</td>
<td>45 ± 4*</td>
<td>43 ± 7*</td>
<td>44 ± 4*</td>
<td>42 ± 7*</td>
<td>42 ± 5*</td>
<td>37 ± 5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Statistics for values reflect one-way ANOVA (\( P < 0.001 \)). *\( P < 0.05 \), Dunnett’s test comparing values with baseline.

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**Table 1. Fatiguing static handgrip protocol data**

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**Fig. 1.** A: renal vascular resistance (RVR) index as a function of the percent time to fatigue during static handgrip exercise (40\% maximal voluntary contraction (MVC)). Data are means ± SE. \( P \) value for one-way ANOVA: *\( P < 0.05 \), significant difference from baseline (Base). Resistance data are presented in arbitrary units. B: comparison of baseline and posthandgrip circulatory arrest (PHG-CA) vascular resistance. *\( P < 0.05 \). C: resistance data are presented from baseline (0\%) to end-grip (100\%) measurements. Metaboreceptor contribution is calculated as (PHG-CA – end grip) \( \times 100 \).
workload values were different from baseline measurements. Notably, BP did not increase during biceps contraction (Table 4).

Involuntary Contraction Paradigm

Involuntary biceps contraction led to renal vasoconstriction (one-way ANOVA; \( P < 0.037 \)), whereas voluntary contraction at the same workload did not evoke renal vasoconstriction (Fig. 4). The increase in RVR was 9% with voluntary contraction and 29% with involuntary contraction.

DISCUSSION

We performed four separate protocols that together suggest that the renal vasoconstriction of exercise is due predominantly to stimulation of mechanically sensitive muscle afferents. We first discuss the study findings and then prior literature that is germane to this topic.

Study Findings

Fatiguing static handgrip exercise led to a progressive increase in RVR measurements. This effect was seen at the 10% endurance time (∼11 s). Thus this effect was not due to metaboreflex engagement, because the onset latency for this response in humans is ∼1 min for static handgrip (20). Of note, the increase in RVR was also associated with a rise in MAP. This elevation in RVR could either have been due to mechanoreflex-mediated sympathetic vasoconstriction or renal myogenic vasoconstriction of the renal artery. Myogenic constriction occurs when transmural pressure increases within a blood vessel (7). Thus the increase in BP alone conceivably could have evoked renal vasoconstriction. Prior work suggests that myogenic constriction can be seen in the renal vasculature (29).

Although RVR values were greater than baseline measurements, during PHG-CA, this value was only ∼40% of the end-grip level. This is different from the response observed in skeletal muscle, where end-grip MSNA values are similar to those observed during PHG-CA. This finding has been widely interpreted to suggest that muscle metaboreceptor engagement is almost entirely responsible for the increase in MSNA that is seen at end grip (9, 20, 27, 31, 33, 34, 40). Because the renal effect was observed early (i.e., at the 10% fatigue time), and the PHG-CA response represented less than one-half of the end-grip RVR value, it is unlikely that the renal vasoconstriction observed was due predominantly to metaboreflex engagement.

In the graded handgrip contraction protocol, subjects performed 15-s bouts of handgrip exercise at workloads of 10, 30, 50, and 70%. An increase in RVR was noted during the 6- to 10- and 11- to 15-s time periods, and renal vasoconstriction was seen at the two highest workloads. BP was elevated at the time that renal vasoconstriction was noted. Thus the vasoconstrictor response observed had an MVC threshold, and the observed vasoconstrictor response had an onset latency of between 6 and 10 s. These findings also suggest that the vasoconstrictor response is not likely due to engagement of the muscle metaboreflex and is likely due to an increase in central command, engagement of the mechanoreflex, or myogenic vasoconstriction.

Biceps contraction also led to a renal vasoconstrictor response. This effect was seen clearly during the 6- to 10- and 11- to 15-s time periods. We did observe a main effect for constriction during the first 5 s, although none of the individual workload values were different from baseline measurements. The increase in RVR was seen at a lower MVC workload than was observed during handgrip exercise, which suggests an inverse relationship between muscle mass and the tension necessary to evoke the reflex (15, 30). Importantly, in this protocol, we observed increases in RVR without changes in BP. These results suggest that a myogenic reflex did not cause the observed vasoconstriction. Thus the results of this paradigm are consistent with engagement of either central command or the muscle mechanoreflex.
Involuntary biceps contraction evoked an increase in RVR values. This finding suggests that central command was not needed to evoke renal vasoconstriction. The increase in RVR was therefore due to either the muscle metaboreflex or the muscle mechanoreflex. The results of the present study are consistent with prior literature by Mueller et al. (26), which suggests that the increase in RVR early in exercise is due to a sympathetic vasoconstrictor response. Work by Victor et al. (37) suggests that hindlimb contractions induced by electrical stimulation of the tibial nerve in chloralose-anesthetized cats evokes an increase in renal sympathetic nerve activity that is due to stimulation of mechanically sensitive muscle afferents. Our findings are also consistent with earlier work that suggests there is a relationship between the tension developed and the magnitude of the increase in renal sympathetic nerve activity (21). An additional area of agreement of this report with prior work is that we observed that the metaboreceptors contribute to the reflex increase in RVR (22).

In prior work by Middlekauff et al. (24), PET scanning techniques were used to examine renal cortical blood flow during a variety of handgrip exercise interventions in human subjects. PET scanning is a reliable and regionally sensitive method. With the use of this methodology, this research team demonstrated that handgrip exercise evokes renal vasoconstriction. The authors' report suggests that the metaboreflex as well as either the mechanoreflex and/or the central command contribute to the reflex engagement. Our report adds to this study by demonstrating the beat-by-beat time course of the vasoconstriction in humans, the effects of tension and mass on the reflex, as well as the relative contributions of the muscle reflex and central command to the renal vasoconstrictor response. Our report disagrees with the findings of Middlekauff et al. in that they found that the increases in RVR were similar with handgrip exercise at 30% MVC and during PHG-CA. Thus this earlier report could be interpreted to suggest that muscle metaboreflex engagement is a crucial determinant of renal vasoconstriction during static handgrip exercise. In addition, the prior report demonstrated similar renal vascular responses “early” in 10% MVC (first 2 min of a 2.5-min contraction) and “late” in 30% MVC (last 2 min of a 3.5-min contraction). The reasons for these differences between the earlier

Table 3. Graded handgrip contraction protocol data

<table>
<thead>
<tr>
<th>Time Frame for Measurement</th>
<th>Baseline</th>
<th>10</th>
<th>30</th>
<th>50</th>
<th>70</th>
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<tr>
<td>Heart rate, beats/min</td>
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<td>65 ± 4</td>
<td>64 ± 3</td>
<td>67 ± 4</td>
<td>70 ± 5</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>98 ± 5</td>
<td>105 ± 7*</td>
<td>102 ± 8</td>
<td>104 ± 6*</td>
<td>105 ± 7*</td>
</tr>
<tr>
<td>Mean blood velocity, cm/s</td>
<td>51 ± 4</td>
<td>52 ± 5</td>
<td>52 ± 6</td>
<td>53 ± 6</td>
<td>55 ± 6</td>
</tr>
<tr>
<td>6–10 s</td>
<td>61 ± 3</td>
<td>64 ± 4*</td>
<td>65 ± 4*</td>
<td>68 ± 3*</td>
<td>70 ± 4*</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>98 ± 5</td>
<td>101 ± 6</td>
<td>100 ± 8</td>
<td>105 ± 6*</td>
<td>106 ± 6*</td>
</tr>
<tr>
<td>Mean blood velocity, cm/s</td>
<td>51 ± 4</td>
<td>50 ± 4</td>
<td>51 ± 6</td>
<td>50 ± 5</td>
<td>52 ± 5</td>
</tr>
<tr>
<td>11–15 s</td>
<td>61 ± 3</td>
<td>64 ± 3*</td>
<td>65 ± 3*</td>
<td>69 ± 4*</td>
<td>75 ± 5*</td>
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<td>Blood pressure, mmHg</td>
<td>98 ± 5</td>
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<td>100 ± 8</td>
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<tr>
<td>Mean blood velocity, cm/s</td>
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<td>50 ± 5</td>
<td>52 ± 6</td>
<td>51 ± 5</td>
<td>52 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SE. Statistics reflect a one-way ANOVA. *P < 0.05, Dunnett's test comparing values with baseline.

Prior Reports on This Topic

These findings support a number of prior reports on animals that suggest a role for mechanically sensitive afferents in increasing renal sympathetic nerve activity and in causing renal vasoconstriction. Our report is consistent with prior literature by Mueller et al. (26), which suggests that the increase in RVR early in exercise is due to a sympathetic vasoconstrictor response. Work by Victor et al. (37) suggests that hindlimb contractions induced by electrical stimulation of the tibial nerve in chloralose-anesthetized cats evokes an increase in renal sympathetic nerve activity that is due to stimulation of mechanically sensitive muscle afferents. Our findings are also consistent with earlier work that suggests there is a relationship between the tension developed and the magnitude of the increase in renal sympathetic nerve activity (21). An additional area of agreement of this report with prior work is that we observed that the metaboreceptors contribute to the reflex increase in RVR (22).

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![Fig. 3. RVR values for voluntary biceps contraction. See Figs. 1 and 2 for additional information. *Values are different from baseline. P refers to one-way ANOVA.](http://ajpheart.physiology.org/)

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report and this study are not entirely clear but may relate to the differences in methodologies used to measure renal blood flow. For this reason, some mention of the comparative strengths and weaknesses of the PET and Doppler methods is necessary. PET is reliable and regionally sensitive. Its major limitation is the time necessary to obtain each data point. Doppler methods provide measures of flow velocity but not volume of flow. Moreover, it could be argued that this method does not have the regional sensitivity necessary to understand and interpret RBV responses to muscle contraction. However, it must be emphasized that renal cortical blood flow comprises ~90% of total renal blood flow. Cortical blood flow responses are more sensitive to sympathetic nerve stimulation than are medullary blood flow responses. Moreover, Leonard et al. (19) have shown that both cortical and medullary vasoconstriction occur with sympathoexcitation. Thus PET flow and Doppler velocity should yield similar directional responses to an intervention.

Table 4. Biceps contraction protocol data

<table>
<thead>
<tr>
<th>Time Frame for Measurement</th>
<th>Baseline 7</th>
<th>Baseline 15</th>
<th>Baseline 30</th>
<th>Baseline 60</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>54 ± 2</td>
<td>57 ± 3</td>
<td>56 ± 3</td>
<td>58 ± 3</td>
<td>NS (P = 0.074)</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>85 ± 3</td>
<td>87 ± 4</td>
<td>91 ± 5</td>
<td>94 ± 4</td>
<td>NS (P = 0.026)</td>
</tr>
<tr>
<td>Mean blood velocity, cm/s</td>
<td>61 ± 4</td>
<td>64 ± 4</td>
<td>61 ± 4</td>
<td>57 ± 3</td>
<td>NS (P = 0.015)</td>
</tr>
</tbody>
</table>

Values are means ± SE. Statistics reflect one-way ANOVA. *P < 0.05, Dunnett’s test comparing values with baseline.

Limitations

In these studies, we were not able to precisely measure renal artery diameter using ultrasound methodology. This is because spatial resolution decreases as the frequency of the ultrasound transducer decreases (17). To obtain an optimal velocity signal from the renal artery, a low-frequency (2.5-MHz) transducer was employed. At this frequency level, spatial resolution of the technique is not sufficient to precisely measure diameter changes that would be seen in the relatively small renal artery.

In conclusion, when all of the protocols are viewed collectively, they suggest that in intact conscious humans, muscle contraction evokes renal vasoconstriction. The voluntary biceps contraction protocol demonstrates that an increase in BP and engagement of the myogenic reflex are not necessary for renal vasoconstriction to occur with muscle contraction. The involuntary biceps contraction paradigm results suggest that central command is also not necessary to evoke renal vasoconstriction with muscle contraction. The primary stimulus for renal vasoconstriction is not likely to be chemical in nature, because the PHG-CA response represents only a small percentage of the total vasoconstrictor response (during the fatiguing static handgrip protocol); vasoconstriction was observed early in all contraction protocols. Thus each protocol can be explained by a variety of different mechanisms. However, muscle mechanoreflex engagement is the only mechanism that can explain each and every protocol presented.

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DISCLOSURES

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Fig. 4. RVR values for baseline, voluntary (VC), and involuntary (IVC) biceps contractions. Tension values for voluntary and involuntary contractions were the same. *Comparison of IVC with baseline using Dunnett’s test (P < 0.05 for this comparison). P value represents one-way ANOVA.

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