Renal vascular response to static handgrip exercise: sympathetic vs. autoregulatory control

Afsana Momen,1 Douglas Bower,1 Urs A. Leuenberger,1 John Boehmer,1 Susan Lerner,2 Edward J. Alfrey,3 Brian Handly,1 and Lawrence I. Sinoway1,3

1Division of Cardiology, Department of Medicine, and 2Department of Surgery, College of Medicine, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey; and 3Lebanon Veterans Affairs Medical Center, Lebanon, Pennsylvania

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Momen, Afsana, Douglas Bower, Urs A. Leuenberger, John Boehmer, Susan Lerner, Edward J. Alfrey, Brian Handly, and Lawrence I. Sinoway. Renal vascular response to static handgrip exercise: sympathetic vs. autoregulatory control. Am J Physiol Heart Circ Physiol 289: H1770–H1776, 2005. First published June 10, 2005; doi:10.1152/ajpheart.01213.2004.—Static exercise causes activation of the sympathetic nervous system, which results in increased blood pressure (BP) and renal vascular resistance (RVR). The question arises as to whether renal vasoconstriction that occurs during static exercise is due to sympathetic activation and/or related to a pressure-dependent renal autoregulatory mechanism. To address this issue, we monitored renal blood flow velocity (RBV) responses to two different handgrip (HG) exercise paradigms in 7 kidney transplant recipients (RTX) and 11 age-matched healthy control subjects. Transplanted kidneys are functionally denervated. Beat-by-beat analyses of changes in RBV (observed via duplex ultrasound), BP, and heart rate were performed during HG exercise in all subjects. An index of RVR was calculated as BP/RBV. In protocol 1, fatiguing HG exercise (40% of maximum voluntary contraction) led to significant increases in RBV in both groups. However, at the end of exercise, RVR was more than fourfold higher in control subjects than in the RTX group (88 vs. 20% increase over baseline; interaction, P < 0.001). In protocol 2, short bouts of HG exercise (15 s) led to significant increases in RVR at higher workloads (50 and 70% of maximum voluntary contraction) in the control subjects (P < 0.001). RVR did not increase in the RTX group. In conclusion, we observed grossly attenuated renal vasoconstrictor responses to exercise in RTX subjects, in whom transplanted kidneys were considered functionally denervated. Our results suggest that renal vasoconstrictor responses to exercise in conscious humans are mainly dependent on activation of a neural mechanism.

DURING EXERCISE, THE SYMPATHETIC NERVOUS SYSTEM IS ACTIVATED, AND THIS RESULTS IN INCREASES IN HEART RATE (HR), BLOOD PRESSURE (BP), AND PERIPHERAL VASOCONSTRICTION. AS PART OF THIS PROCESS, RENAL VASOCONSTRICTION OCCURS AND SERVES TO MAINTAIN BP AS WELL AS TO REDISTRIBUTE BLOOD FLOW TO THE CONTRACTING SKELETAL MUSCLE BED.

OF NOTE, THE OBSERVED INCREASE IN RENAL VASCULAR RESISTANCE (RVR) IS ASSOCIATED WITH AN INCREASE IN ARTERIAL PRESSURE. THUS THE QUESTION ARISES AS TO WHETHER RENAL VASOCONSTRICTION THAT OCCURS DURING STATIC EXERCISE IS DUE TO SYMPATHETIC ACTIVATION AND/OR RELATED TO A PRESSURE-DEPENDENT RENAL AUTOREGULATORY MECHANISM. TO ADDRESS THIS ISSUE, WE MONITORED RENAL HEMODYNAMIC RESPONSES DURING TWO DIFFERENT HANDGRIFF EXERCISE PARADIGMS IN A GROUP OF KIDNEY TRANSPLANT RECIPIENTS (RTX) AND IN AGE-MATCHED HEALTHY CONTROL SUBJECTS. PREVIOUS REPORTS (7, 8, 16) SUGGEST THAT TRANSPLANTED KIDNEYS REMAIN FUNCTIONALLY DENERVATED FOR SEVERAL MONTHS AFTER TRANSPLANTATION. IN STUDIES MEASURING TISSUE NOREPINEPHRINE IN RAT KIDNEY GRAFTS (7), RESEARCHERS FOUND GROSSLY DIMINISHED NOREPINEPHRINE LEVELS COMPARED WITH NATIVE KIDNEYS 9 MO AFTER TRANSPLANTATION. SIMILARLY, NERCYPSMS FROM HUMAN RENAL ALLOGRAFTS DEMONSTRATE A REDUCTION IN SYMPATHETIC GANGLIA SYNAPTIC DENSITY 3 YR AFTER TRANSPLANTATION (16). IN ADDITION, THE RESEARCHERS IN THIS REPORT ALSO DEMONSTRATED THAT MOST OF THE SYMPATHETIC GANGLIA THAT SUPPLY THE KIDNEY ARE NOT TRANSPLANTED. PREVIOUS STUDIES OF HUMANS (8) FOUND THAT SYMPTHEOXITATION EVOKED BY LOW LEVELS OF LOWER BODY NEGATIVE PRESSURE LED TO AN ATTENUATED REDUCTION IN RENAL PLASMA FLOW IN RENAL TRANSPLANT RECIPIENTS. THESE PATIENTS WERE STUDIED 2–27 MO AFTER RENAL TRANSPLANTATION. BASED ON THIS EVIDENCE, TRANSPLANTED KIDNEYS ARE CONSIDERED TO REMAIN FUNCTIONALLY DENERVATED SEVERAL MONTHS AFTER TRANSPLANTATION. IN THIS CONTEXT, WE POSTULATED THAT RENAL VASOCONSTRICITOR RESPONSES TO HANDGRIFF EXERCISE WOULD BE ATTENUATED IN RTX COMPARED WITH AGE-MATCHED HEALTHY SUBJECTS. OUR STUDIES SUPPORT THIS POSTULATE AND SUGGEST THAT SYMPATHETIC ACTIVATION IS NECESSARY FOR THE FULL EXPRESSION OF THE RENAL VASOCONSTRICITOR RESPONSE TO HANDGRIFF EXERCISE.

METHODS

Study Population

A group of 11 healthy volunteers [7 males and 4 females, 44 ± 4 yr of age, 26 ± 1 kg/m² mean body mass index (BMI)]; and 7 RTX subjects (3 males and 4 females, 50 ± 5 yr of age, 31 ± 1 kg/m² mean BMI) participated in the study. Each subject signed a written informed consent and had his or her physical examination done before the study protocols were conducted. These protocols were approved by the Institutional Review Board at the Milton S. Hershey Medical Center. All healthy volunteers were nonsmoking, normotensive, and on no medication. Of the 11 healthy volunteers, 5 individuals were also studied in a prior report (12).

Seven RTX patients with preserved native kidneys were recruited from the renal transplantation clinic at the Hershey Medical Center. Transplant surgeries were performed 7–14 mo before the study. One subject had two kidney transplants, and one was transplanted ~12 yr before the study was performed. All transplant subjects had stable allograft function with serum creatinine levels of <2.0 mg/dl. Each of seven patients was receiving a calcineurin inhibitor to prevent allo-
evidence of acute graft rejection were excluded from the study. We also examined three heart transplant recipient patients (HTX; 2 male and 1 female, 40 ± 2 yr of age) with normal renal function (serum creatinine ≤ 1.0 mg/dl). These HTX patients were all on immunosuppressive and calcium channel blocker (CCB) therapy. Of note, all RTX subjects were on immunosuppressive therapy and four of seven subjects were on CCB therapy. The HTX patients performed the same handgrip protocols as the RTX subjects. The HTX patients had innervated kidneys and similar medications as the RTX subjects. If renal responses were present in HTX and not RTX patients, then a role for the sympathetic nervous system in renal response to exercise would be suggested.

Renal Blood Flow Velocity

All subjects were studied in the postabsorptive state. Duplex ultrasound (HDI 5000; ATL Ultrasound; Bothell, WA) was used to determine renal blood flow dynamics. The renal artery was scanned using the anterior abdominal approach while the subject was lying supine. A curved-array transducer (2–5 MHz) with a 2.5-MHz pulsed Doppler frequency was used. The probe inclination angle to the renal artery was <60°. The focal zone was set at the depth of the renal artery. In the RTX group, transplanted kidneys were situated in the iliac fossa and the renal artery was more superficial than in control subjects. To obtain optimum velocity tracings, the transducer was held in a constant position. Therefore, the data were obtained in the same phase of the respiratory cycle of each respective subject. Care was taken to ensure that the subjects did not perform Valsalva maneuvers during the handgrip exercise protocols. Each cardiac cycle Doppler tracing was analyzed using the software of the ATL machine to obtain mean renal blood flow velocity (RBV) measurements. Each velocity measurement was normalized to a time constant of 1 s. Subsequently, RVR was calculated by dividing mean arterial pressure (MAP) by RBV (in cm/s). RVR is expressed in arbitrary units.

Beat-by-beat recordings of RBV were obtained during two handgrip exercise paradigms. Continuous recordings of HR (via electrocardiogram) and BP (Finapres; Ohmeda; Madison, WI) were also obtained throughout the protocols. An automated sphygmomanometer (Dinamap; Critikon; Tampa, FL) was used to determine resting BP values. A force transducer was used to measure the force of muscle contraction.

Study Protocols

Protocol 1: Fatiguing static exercise followed by posthandgrip circulatory arrest. Maximum voluntary contraction (MVC) of the nondominant arm was determined in each subject before the study began. Baseline HR, MAP, and RBV values were obtained over 5 min. Each subject performed handgrip exercise at 40% MVC and continued until fatigue. At the end of exercise, each subject graded his/her perceived level of exertion as 20 (maximum effort) on the Borg scale (2). Immediately before exercise was stopped, posthandgrip circulatory arrest (PHG-CA) was initiated by inflation of a previously placed BP cuff around the arm at ~250 mmHg, which was kept inflated for 2 min. Vascular resistance responses during PHG-CA are thought to be due to 1) engagement of the muscle metaboreflex; and/or 2) myogenic vasoconstriction, if BP remains above baseline (13).

Protocol 2: Static handgrip exercise at graded intensity. This protocol was designed to examine the effects of short bouts of handgrip exercise at different tension levels on RVR. The temporal relationship between renal vascular response and arterial BP was also determined.

Baseline data of HR, MAP, and RBV were collected for 5 min. Each subject completed 15-s bouts of static handgrip exercise at 10, 30, 50, and 70% of his own MVC. The same sequence was maintained for all subjects. Each bout of exercise was preceded by a 1-min rest period.

Data Analysis and Statistics

Beat-by-beat sequential analyses of HR, MAP, RBV, and RVR were performed for all subjects. Baseline values for each parameter were considered as the average data values obtained during a 5-min rest period before each paradigm.

In the fatiguing static handgrip protocol, each variable was measured around the time that represented 10, 20, 40, 60, 80, and 100% (peak) of the respective subject’s time to exhaustion. Data from the last 15-s time period during circulatory arrest were used in the statistical analysis. In protocol 2, data were analyzed in 5-s time periods. Statistical analyses were performed separately on each 5-s period (i.e., 1–5, 6–10, and 11–15 s).

Resting values between RTX and healthy control subjects were compared using unpaired t-tests. Paired t-tests were used to compare baseline and PHG-CA values. Repeated-measures one-way ANOVAs and post hoc analyses (Dunnett’s test) were performed to compare variables to baseline in individual groups. Repeated-measures two-way ANOVAs were applied for each variable to test for two main effects, namely, the group effect (between RTX and healthy subjects) and the handgrip paradigms effect. To compare the RTX and control groups, tests of simple effects were performed at respective time periods during the exercise paradigms. P < 0.05 was considered significant. Data are presented as means ± SE. Owing to the small number of subjects in the HTX group (n = 3), we did not perform statistical analysis on the data obtained from these subjects.

RESULTS

Baseline hemodynamic variables for the RTX and healthy control subjects are presented in Table 2. No significant group differences were found with respect to age, MVC, and MAP. However, HR and BMI were higher in the RTX group than in the control subjects.
Table 2. Resting data for RTX and control groups

<table>
<thead>
<tr>
<th></th>
<th>RTX</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum voluntary contraction, kg</td>
<td>28±4</td>
<td>36±3</td>
</tr>
<tr>
<td>Age, yr</td>
<td>50±5</td>
<td>43±4</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67±3</td>
<td>58±2†</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>92±9</td>
<td>94±4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31±1</td>
<td>26±1‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. †P < 0.045; ‡P < 0.013, RTX vs. control subjects (unpaired t-test).

Protocol 1: Fatiguing Static Exercise and Subsequent PHG-CA

The time to fatigue was shorter in the RTX group than in the control subjects (62 ± 6 s vs. 118 ± 12 s; P < 0.0001). During fatiguing handgrip exercise, the increase in RVR was greater in control than in RTX subjects (interaction, P < 0.001). Simple effects demonstrated that compared with the control subjects, RVR increases in RTX subjects were grossly attenuated at the 40, 60, 80, and 100% time periods (percent change in RVR, interaction; P = 0.001; Fig. 1A). At the end of the exercise, RVR responses were more than fourfold higher in the control subjects compared with the RTX group. A paradigm main effect was noted, which suggests that handgrip exercise increased RVR above baseline levels in both groups (Fig. 1A). The increase in MAP was greater in control than RTX subjects (Table 3; group main effect, P < 0.009). Simple effects demonstrated that increases in MAP at the 80 and 100% time periods were twofold higher in the control group compared with the RTX group (percent change in MAP, interaction; P = 0.02; Table 3). RBV decreased by 24% in the control group at the end of exercise. In contrast, there was no reduction in RBV in the RTX group at the end of exercise (Table 3). No significant interaction was noted for increases in HR (Table 3) during handgrip exercise.

Hemodynamic responses to fatiguing HG exercise were also examined in the HTX subjects (Fig. 2). Interestingly, the RVR increased by 20–30% in the HTX group; this is similar to the changes seen in the RTX group and much less than the increase in RVR seen in control subjects (see Fig. 1).

RVR values in RTX and control subjects were significantly higher during PHG-CA than during baseline measurements (Fig. 1B). The PHG-CA value represented 50% of the end grip value in each group. Other variables during PHG-CA are shown in Table 4.

Protocol 2: Static Handgrip Exercise at Graded Intensities

RVR, MAP, and RBV data are shown in Fig. 3 and Table 5. Significant increases in RVR were found in the control subjects during 15-s bouts of handgrip exercise at 50 and 70% of MVC (Fig. 3). In the RTX group, RVR did not increase with handgrip exercise, although there was a trend for RVR to increase during the 11–15-s time period at high workloads (Fig. 3). Significant increases in MAP were noted in both subject groups (Table 5). Significant reduction in RBV was also noted in the control subjects at 70% MVC (11–15 s; Table 5). In contrast, RBV increased in the RTX group at 70% MVC (11–15 s; Table 5). HR data are also shown in Table 5.

Data from the RTX, control, and HTX (n = 3) subjects are shown in Fig. 4. RVR values in the HTX group tended to be higher than in the RTX group. In general, RVR values in HTX subjects appeared to be similar to the values seen in control subjects.

Discussion

Studies of different animal species have documented that renal sympathetic nerve activation plays an important role in evoking renal vasoconstrictor responses during muscle contraction. In many of these reports, renal sympathetic vasoconstriction has been determined by comparing renal vasoconstrictor responses in innervated and denervated kidneys (4, 5, 9, 11, 14). In our study, we compared renal vasoconstrictor responses in RTX patients and age-matched healthy controls. Transplanted kidneys are functionally denervated (7, 8, 16).

Protocol 1: Static Fatiguing Exercise and Subsequent PHG-CA

There was no difference in baseline MAP between RTX and healthy control subjects. Because the position of the renal arteries was so different in the two study groups, we thought that attempts to compare indexes of RVR in the two groups would be problematic. Thus relative changes in RVR during exercise were compared in the two groups.

During fatiguing handgrip exercise, resistance increased in both groups (paradigm main effect, P < 0.001). However, the
 increase in RVR in the RTX group was only about one-fourth of that observed in the control group (see Fig. 1A). Interestingly, at the end of exercise, the percent increase in RVR in RTX and HTX patients was similar and much less than in control subjects. This suggests that factors aside from sympathetic constriction contribute to the RVR response that is seen with fatiguing handgrip exercise. Both the RTX and HTX subjects were on immunosuppressive drugs, and an effect of these drugs on RVR must be seriously considered.

Additionally, in this report we did not examine the effects of hormone production on RVR during fatiguing handgrip exercise. Changes in plasma epinephrine concentration during isometric exercise are reflective of exercise-induced sympathoadrenal stimulation (17). As part of another report, we have recently measured plasma renin activity (PRA; n = 10) and plasma epinephrine (n = 9) levels in healthy subjects during isometric handgrip exercise (unpublished observations). Plasma samples were drawn during baseline conditions and at the time of fatiguing handgrip exercise at 40% of MVC. No significant differences were found in PRA. However, epinephrine concentration was increased during fatiguing handgrip exercise.

Previous animal (1) and human (6) studies have revealed that epinephrine infusions evoke renal vasoconstriction. Thus we cannot rule out the possibility that handgrip exercise led to adrenal epinephrine release, which in turn contributed to the increase in RVR noted at the end of fatiguing handgrip exercise.

RVR values during PHG-CA represented ~50 and 60% of the respective end-grip RVR values in RTX and control subjects. Because of the small number of HTX subjects, statistical analyses were not performed.

### Table 3. Protocol 1: Heart rate, mean arterial pressure, and renal blood flow velocity values

<table>
<thead>
<tr>
<th>Variable Change</th>
<th>10% RTX</th>
<th>20% RTX</th>
<th>40% RTX</th>
<th>60% RTX</th>
<th>80% RTX</th>
<th>100% RTX</th>
<th>10% Control</th>
<th>20% Control</th>
<th>40% Control</th>
<th>60% Control</th>
<th>80% Control</th>
<th>100% Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHeart rate, %</td>
<td>3.9±2.7</td>
<td>12.8±2.9</td>
<td>5.2±2.6</td>
<td>8.0±2.9</td>
<td>11.9±4.3</td>
<td>26.4±5.0*</td>
<td>13.5±3.7</td>
<td>29.3±5.7*</td>
<td>15.8±2.9</td>
<td>33.2±5.4*</td>
<td>Group, P &lt; 0.015</td>
<td></td>
</tr>
<tr>
<td>ΔMean arterial pressure, %</td>
<td>6.3±1.1</td>
<td>6.8±2.0</td>
<td>7.3±1.4</td>
<td>10.9±1.8</td>
<td>12.4±2.7</td>
<td>26.2±4.0*</td>
<td>15.8±3.4</td>
<td>33.2±4.7*</td>
<td>18.8±4.0</td>
<td>37.5±4.2*</td>
<td>Group, P &lt; 0.009</td>
<td></td>
</tr>
<tr>
<td>ΔRenal blood flow velocity, %</td>
<td>-1.0±4.0</td>
<td>-6.0±2.4</td>
<td>0.0±4.1</td>
<td>-10.4±2.3</td>
<td>-4.7±2.6</td>
<td>-10.3±3.6*</td>
<td>2.9±4.1</td>
<td>-15.6±4.5*</td>
<td>1.4±4.2</td>
<td>-22.6±4.8*</td>
<td>-1.1±2.8</td>
<td>-23.7±5.2*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Fatiguing static handgrip exercise protocol was performed. Statistics reflect two-way ANOVA comparing RTX and control subjects; *P < 0.05 (from post hoc analysis).

### Table 4. Minute 2 of posthandgrip circulatory arrest during protocol 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>RTX Baseline</th>
<th>PHG-CA</th>
<th>Control Baseline</th>
<th>PHG-CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>66.6±3.4</td>
<td>70.6±3.3</td>
<td>57.5±2.0</td>
<td>59.7±2.7</td>
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<td>Blood pressure, mmHg</td>
<td>91.9±9.3</td>
<td>106.1±11.4†</td>
<td>93.5±3.5</td>
<td>121.9±2.8‡</td>
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<tr>
<td>Renal blood flow velocity, cm/s</td>
<td>31.3±3.7</td>
<td>32.8±3.7</td>
<td>53.4±3.8</td>
<td>47.7±4.2</td>
</tr>
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</table>

Values are means ± SE. Data reflect the last 15 s of posthandgrip circulatory arrest (PHG-CA) of the fatiguing static handgrip exercise protocol. †P < 0.005; ‡P < 0.001, baseline vs. PHG-CA (paired t-test).
Table 5. Raw data from protocol 2

<table>
<thead>
<tr>
<th></th>
<th>RTX</th>
<th>P Value</th>
<th>Control</th>
<th>P Value</th>
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<tr>
<td>Maximum voluntary contraction</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67.0±3.5</td>
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<td>67.0±3.5</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>87.6±9.7</td>
<td>0.001</td>
<td>87.6±9.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal blood flow velocity, cm/s</td>
<td>30.7±3.4</td>
<td>0.004</td>
<td>30.7±3.4</td>
<td>0.004</td>
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Values are means ± SE. Graded handgrip contraction protocol raw data and one-way ANOVA results are shown. NS, not significant. *P < 0.05, comparing points to baseline within same group (Dunnett’s test).
groups. Because the renal vascular bed is functionally denervated in the RTX group, it is unlikely that the increases in RVR during PHG-CA were due to engagement of muscle metaboreflex. Thus renal vascular responses during PHG-CA are not an exclusive measure of muscle metaboreflex-mediated renal sympathoexcitation. It should be noted that elevated RVR values seen during PHG-CA were associated with significant increases in BP in both groups. Therefore, it can be argued that the increments in RVR seen during PHG-CA were due to myogenic constriction and/or some effect of hormones on the renal vascular bed.

Despite comparable MVC values in the two groups, the average time to fatigue during handgrip exercise was much less in the RTX group than in the control group (62 ± 6 vs. 118 ± 12 s; P < 0.0001). The exact cause of this finding is unclear. However, reports have documented that calcineurin is involved in regulating the expression of oxidative, fatigue-resistant muscle (3, 10, 19). Because all RTX patients were on calcineurin-inhibitor therapy, we speculate that the forearm muscles of RTX patients were less oxidative and were thus more rapidly fatigued during protocol 1.

Protocol 2: Static Handgrip Exercise at Graded Intensity

In the normal volunteers, we observed an increase in RVR at the higher workloads. In contrast, there was no significant increase in RVR in the RTX patients despite the fact that a significant rise in BP was noted. These findings support the concept that the increase in RVR with short bouts of handgrip exercise is due primarily to sympathetic vasoconstriction. Our results are consistent with the findings of a study by Mueller et al. (14). This study, which was performed on conscious rabbits, demonstrated that renal vasoconstriction was increased within 10 s of initiation of dynamic exercise in the innervated kidney, whereas no such response was seen in the denervated kidney. Other studies on cats and rabbits have also found that renal sympathetic nerve activity increases within seconds after the onset of muscle contraction (11, 15, 18).

To determine whether the reduced RVR responses seen in the RTX group were due to an inability to increase BP, we examined and compared RBV and BP values in the control and RTX patients (data not shown). We found that for a given BP level, RBV tended to be lower in the control subjects than in the RTX group. Thus the inability to vasoconstrict the kidney in the RTX group was not secondary to an inability to increase BP. Additionally, the HTX patients increased RVR during the 15-s bouts of handgrip exercise, whereas RTX patients did not. Yet both groups had similar BP responses (see Fig. 4). If the BP level were responsible for an increase in RVR, then RVR in HTX and RTX subjects should have been similar. These data support the concept that the sympathetic nervous system plays a crucial role in mediating RVR responses early in exercise.

In conclusion, we observed grossly attenuated renal vasoconstrictor responses to exercise in the RTX patient group, in whom kidneys were considered functionally denervated. Our results support the hypothesis that activation of sympathetic neural mechanisms plays an important role in evoking renal vasoconstriction during bouts of handgrip exercise.

Fig. 4. Percent changes in RVR index (top) and MAP (bottom) responses from baseline (B) during short bouts of handgrip exercise at 10, 30, 50, and 70% of MVC in HTX (n = 3) and RTX (n = 7) recipients and healthy control subjects (n = 11). Data are shown for each 5-s time period of 15-s contraction.
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