Parathyroid Hormone Secretion Is Controlled by Both Ionized Calcium and Phosphate During Exercise and Recovery in Men

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Context: The mechanism by which PTH is controlled during and after exercise is poorly understood due to insufficient temporal frequency of measurements.

Objective: The objective of the study was to examine the temporal pattern of PTH, PO4, albumin-adjusted calcium, and Ca2+ during and after exercise.

Design and Setting: This was a laboratory-based study with a crossover design, comparing 30 minutes of running at 55%, 65%, and 75% maximal oxygen consumption, followed by 2.5 hours of recovery. Blood was obtained at baseline, after 2.5, 5, 7.5, 10, 15, 20, 25, and 30 minutes of exercise, and after 2.5, 5, 7.5, 10, 15, 20, 25, 30, 60, 90, and 150 minutes of recovery.

Participants: Ten men (aged 23 ± 1 y, height 1.82 ± 0.07 m, body mass 77.0 ± 7.5 kg) participated.

Main Outcome Measures: PTH, PO4, albumin-adjusted calcium, and Ca2+ were measured.

Results: Independent of intensity, PTH concentrations decreased with the onset of exercise (−21% to −33%; \( P \leq 0.001 \)), increased thereafter, and were higher than baseline by the end of exercise at 75% maximal oxygen consumption ( 52% to 110% ; \( P \leq 0.001 \)). PTH peaked transiently after 5–7.5 minutes of recovery (73% to 110% ; \( P \leq 0.001 \)). PO4 followed a similar temporal pattern to PTH, and Ca2+ followed a similar but inverse pattern to PTH. PTH was negatively correlated with Ca2+ across all intensities ( \( r = -0.739 \) to −0.790 ; \( P \leq 0.001 \)). When PTH was increasing, the strongest cross-correlation was with Ca2+ at 0 lags ( 3.5 min ) ( \( r = -0.902 \) to −0.950 ); during recovery, the strongest cross-correlation was with PO4 at 0 lags ( 8 min ) ( \( r = 0.987\)–0.995 ).

Conclusions: PTH secretion during exercise and recovery is controlled by a combination of changes in Ca2+ and PO4 in men. (J Clin Endocrinol Metab 101: 3231–3239, 2016)
At rest, PTH secretory activity is regulated by serum ionized calcium (Ca\(^{2+}\)), which is detected by the calcium-sensing receptor on the chief cells of the parathyroid gland (1). When Ca\(^{2+}\) decreases from the homeostatic set point, PTH is synthesized and secreted, increasing serum calcium (Ca) through mobilization of the bone reservoir via bone resorption and by increasing renal tubular reabsorption and intestinal Ca absorption (2–4). PTH has a dual effect on bone that appears to be dependent on the signaling mechanism and the length of time that concentrations remain elevated for (5). Prolonged elevations in PTH, which are seen with endurance type exercise and which can also result in the loss of the circadian rhythm of PTH, might cause an increase in bone resorption, whereas transient spikes in PTH, which are seen with high-intensity interval-type training, might cause an increase in bone formation (6), provided that the magnitude of the increase is sufficient. Chronic elevations in PTH concentrations have been associated with an increased fracture risk (7, 8). Complete fractures and stress fractures are debilitating injuries for elite athletes (9); therefore, understanding how PTH is regulated during exercise and recovery may have implications for both the general population and athletes who are at risk of chronically elevated PTH concentrations, because a positive calcium balance is necessary for bone adaptation to mechanical loading (10).

Exercise increases PTH concentrations (11–20), although studies have used different exercise modes, durations, and intensities. Exercise intensity is important, given that Scott et al (17) have shown that 60 minutes of running at 55%, 65%, and 75% of maximal oxygen consumption (VO\(_{2\text{max}}\)) results in different PTH responses during and after exercise. Therefore, any study investigating the underlying mechanisms responsible for the changes in PTH during exercise and recovery should examine the effects of exercise intensity.

During exercise, reductions in circulating Ca do not explain the increase in PTH because the concentration of albumin-adjusted calcium (ACa), a surrogate for Ca\(^{2+}\), is either increased (12, 15, 17) or unchanged (14, 18, 19) concomitantly with PTH. Barry et al (16) showed that Ca ingestion before exercise attenuated but did not abolish the increase in PTH, suggesting that some other mechanism contributed to the increase. This could involve phosphate (PO\(_4\)), because an increase in PO\(_4\) increases PTH in rested individuals (21). After exercise, PO\(_4\) concentrations decrease and the timing and magnitude of these decreases reflect those in PTH (17, 18, 20), also suggesting that PO\(_4\) may be involved in PTH regulation with exercise.

The hypothesis that decreased Ca\(^{2+}\) triggers increased PTH during exercise has not yet been proven (16). PTH is secreted within seconds of a decrease in Ca\(^{2+}\), and subsequent increases in Ca\(^{2+}\) take only minutes to occur in response to increased PTH, highlighting a dynamic relationship (1, 22). Despite this, no studies have measured PTH and other markers of Ca metabolism until 20 minutes of exercise has been completed, by which time PTH is elevated. Most studies have started taking measurements at 30 minutes after exercise, by which time PTH has returned to near pre-exercise levels (15–19, 23). Single or infrequent measurements of PTH, ACa, and PO\(_4\) during and after exercise might fail to capture the dynamic nature of Ca regulation with exercise (16). Using repeated measurements with a high frequency, we examined the temporal pattern of PTH, PO\(_4\), ACa, and Ca\(^{2+}\) during and after 30 minutes of treadmill running at three exercise intensities.

## Materials and Methods

### Participants

Ten healthy, physically active men ([mean ± 1 SD] age 23 ± 1 y, height 1.82 ± 0.07 m, body mass 77.0 ± 7.5 kg) volunteered for the study, which was approved by the Institutional Ethics Committee. Participants were nonsmokers, had not suffered a fracture in the past 12 months, were free from musculoskeletal injury, and were not taking any medication or experiencing any problems known to affect Ca or bone metabolism. Eligibility was confirmed during the initial session, when participants provided written informed consent.

### Experimental design

Participants completed a preliminary visit for health screening, habituation, and measurement of VO\(_{2\text{max}}\). Participants then completed three randomized (Latin square design), 3-day experimental trials, each separated by 1 week. On days 1–2, participants refrained from exercise, caffeine, and alcohol. On day 2, participants consumed a self-selected diet that was repeated for each trial. On day 3, participants performed a 30-minute bout of running at 55%, 65%, or 75% VO\(_{2\text{max}}\), followed by 2.5 hours of recovery.

### Trial procedures

#### Maximal oxygen consumption

Participants performed an incremental treadmill test to determine lactate threshold, followed by a ramp test to determine VO\(_{2\text{max}}\), as per Jones and Doust (24). The level running velocities corresponding to 55% (8.7 ± 0.6 km/h\(^{-1}\)), 65% (10.1 ± 0.8 km/h\(^{-1}\)), and 75% VO\(_{2\text{max}}\) (11.9 ± 0.9 km/h\(^{-1}\)) were calculated based on the regression of VO\(_{2}\) and velocity.

### Main trials

Participants arrived (9:00 AM) after an overnight fast and after consuming 500 mL of water upon awakening. After voiding, participants had their body mass measured before adopting a semirecumbent position and having a cannula inserted into a forearm vein. After 10 minutes of rest, a baseline blood sample (5 mL) was collected for measurement of PTH, PO\(_4\), ACa, and

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Ca\(^{2+}\). Thirty minutes of treadmill running at 55%, 65%, or 75% VO\(_{2}\max\) commenced thereafter. Additional blood was collected after 2.5, 5, 7.5, 10, 15, 20, 25, and 30 minutes of exercise. After exercise, participants adopted a semirecumbent position, and blood was collected at 32.5, 35, 37.5, 40, 45, 50, 55, 60, 90, 120, and 180 minutes. Ca\(^{2+}\) was measured immediately, but due to equipment availability, Ca\(^{2+}\) was measured only in participants 5–10. Blood samples were transferred to precooled standard serum tubes (Becton Dickinson Vacutainer System) to clot at room temperature for 60 minutes. Samples were centrifuged at 2000 revolutions/min \(^{-1}\) and 5°C for 10 minutes, and the resulting serum was transferred into Eppendorf tubes and frozen at \(-80\)°C. After the last blood sample, the cannula was removed and body mass measured. Participants were given 3 mL/kg body mass \(^{-1}\)/h \(^{-1}\) of water to consume throughout the trials. The timings of blood samples and exercise were identical in each trial to ensure that circadian rhythms of the metabolites were controlled for.

Biochemical analysis

PTH was measured using electrochemiluminescence immunoassay on a Modular Analytics E170 analyzer (Roche Diagnostics). Interassay coefficient of variation (CV) for PTH was less than 4% between 1 and 30 pmol/L \(^{-1}\) and sensitivity of 0.8 pmol/L \(^{-1}\). PO\(_4\), total Ca, and albumin were measured using standard colorimetric assays and spectrophotometric methods, performed on an ABX Pentra 400 (Horiba ABX). Interassay CVs were 3.6% or less between 0.09 and 7.80 mmol/L \(^{-1}\) for PO\(_4\), 1.7% or less between 0.04 and 5.00 mmol/L \(^{-1}\) for total Ca, and 1.9% or less between 0.02 and 5.99 g/dL \(^{-1}\) for albumin. Because fluctuations in protein, particularly albumin, may cause total Ca levels to change independently of the Ca\(^{2+}\) concentrations, total Ca concentrations were corrected to give Ca\(^{2+}\) values: 0.8 mg/dL \(^{-1}\) was subtracted from total Ca concentrations for every 1.0 g/dL \(^{-1}\) that albumin concentrations were less than 4 g/dL \(^{-1}\) or 0.8 mg/dL \(^{-1}\) was added to total Ca concentrations for every 1.0 mg/dL \(^{-1}\) that albumin concentration was greater than 4 mg/dL \(^{-1}\). Ca\(^{2+}\), glucose, and lactate were measured in whole blood using a blood gas analyzer (Radiometer ABL90 FLEX). Ca\(^{2+}\) is estimated directly between pH 7.2–7.6 with no pH correction applied. The inter- and intraassay CV for Ca\(^{2+}\) was 3% or less between 0.2 and 9.99 mmol/L \(^{-1}\), for glucose was 5% or less between 0 and 60 mmol/L \(^{-1}\), and for lactate was 26.7% or less between 0.1 and 31 mmol/L \(^{-1}\).

Statistical analysis

Statistical significance was accepted at \(P \leq 0.05\). Baseline concentrations were compared using a one-way ANOVA. All data were analyzed using a repeated-measures ANOVA, with intensity (55% vs 65% vs 75% VO\(_{2}\max\)) and time (of sampling) as within-subject factors. Parametric assumptions of normality and sphericity were confirmed using Shapiro-Wilks and Mauchly’s tests. A Tukey’s honestly significant difference post hoc test was used to compare time points against baseline and to compare exercise intensities at each time point, where appropriate. Pearson’s correlation coefficients were calculated for PO\(_4\), ACa, and Ca\(^{2+}\) with PTH.

Cross-correlational analyses were performed to determine the temporal relationships between PTH and PO\(_4\), ACa, and Ca\(^{2+}\). Cubic interpolation was performed to adjust for unevenly spaced data points, and cross-correlational analyses were subsequently performed using R (version 3.2.2). To determine whether one time series led another, cross-correlation functions were computed at seven lag time points for PEAK (data points between baseline and peak PTH concentrations [5 min of recovery]), in which each lag represented 3.5 minutes, and six lag time points for DEC (all data points during the decrease in PTH concentrations [5–90 min of recovery]), in which each lag represented 8 minutes.

Results

Baseline biochemistry

Baseline PTH, PO\(_4\), ACa, and albumin were not significantly different between trials (\(P = 0.339\)-982). Baseline Ca\(^{2+}\) at 55% VO\(_{2}\max\) was significantly (\(P \leq 0.05\)) higher than at 65% VO\(_{2}\max\) and 75% VO\(_{2}\max\) (Table 1).

Parathyroid hormone

There was no main effect of intensity, but there was a main effect of time (\(P \leq 0.001\)) and an intensity \(\times\) time interaction (\(P \leq 0.001\)). PTH concentrations decreased with the onset of exercise and were significantly lower than baseline after 5 minutes of exercise at 55% VO\(_{2}\max\) (−23%; \(P \leq 0.05\)) and 75% VO\(_{2}\max\) (−33%; \(P \leq 0.001\)) but not at 65% VO\(_{2}\max\) (−21%; \(P = 0.305\)) (Figure 1A, all participants, and Figure 2A, participants 5–10). Thereafter, PTH increased, becoming significantly greater than baseline at the end of exercise (30 min) at 75% VO\(_{2}\max\) (+52%; \(P \leq 0.001\)) and after 2.5 minutes of recovery at 55% VO\(_{2}\max\) (+43%; \(P \leq 0.001\)) and 65% VO\(_{2}\max\) (+52%; \(P \leq 0.001\)). PTH concentrations peaked after 5 minutes of recovery at 55% VO\(_{2}\max\) (+73%; \(P \leq 0.001\)) and 75% VO\(_{2}\max\) (+110%; \(P \leq 0.001\)) and after 7.5 minutes of recovery at 65% VO\(_{2}\max\) (+76%; \(P \leq 0.001\)). PTH concentrations then decreased but remained significantly higher than baseline until 15 minutes into recovery at 55% VO\(_{2}\max\) and until 25 minutes at 65% VO\(_{2}\max\) and 75% VO\(_{2}\max\). PTH concentrations decreased below baseline after 60 minutes of recovery in all trials (−8% to −17%).

PTH concentrations were not significantly different at any time point between 55% and 65% VO\(_{2}\max\) trials. Ex-

<table>
<thead>
<tr>
<th>Measure</th>
<th>55% VO(_{2}\max)</th>
<th>65% VO(_{2}\max)</th>
<th>75% VO(_{2}\max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH, pmol/L (^{-1})</td>
<td>2.62 ± 0.88</td>
<td>2.51 ± 0.50</td>
<td>2.63 ± 0.60</td>
</tr>
<tr>
<td>PO(_4), mmol/L (^{-1})</td>
<td>1.14 ± 0.12</td>
<td>1.17 ± 0.25</td>
<td>1.12 ± 0.16</td>
</tr>
<tr>
<td>ACa, mmol/L (^{-1})</td>
<td>2.83 ± 0.21</td>
<td>2.83 ± 0.23</td>
<td>2.78 ± 0.22</td>
</tr>
<tr>
<td>Albumin, g/dL (^{-1})</td>
<td>4.60 ± 0.14</td>
<td>4.63 ± 0.19</td>
<td>4.57 ± 0.22</td>
</tr>
<tr>
<td>Ca(^{2+}), mmol/L (^{-1})</td>
<td>1.27 ± 0.03 (^{a})</td>
<td>1.25 ± 0.02</td>
<td>1.24 ± 0.01</td>
</tr>
</tbody>
</table>

Data are mean ± 1 SD.

\(^{a}\) Baseline Ca\(^{2+}\) at 55% VO\(_{2}\max\) was significantly (\(P \leq 0.05\)) higher than at 65% and 75% VO\(_{2}\max\).
and higher than exercise at 65% VO\textsubscript{2max} at the end of exercise (P ≤ .001) and at 2.5 (P ≤ .05) and 5 (P ≤ .001) minutes into recovery.

**Phosphate**

There was no main effect of intensity, but there was a main effect of time (P ≤ .001) and an intensity \times time interaction (P ≤ .05). PO\textsubscript{4} concentrations increased with the onset of exercise at all intensities, being significantly higher than baseline from 7.5 minutes to the end of exercise at 55% VO\textsubscript{2max} (+16%; P ≤ .001) and between 5 minutes and the end of exercise at 65% VO\textsubscript{2max} (+22%) and 75% VO\textsubscript{2max} (+26%) (P ≤ .05 to P ≤ .001) (Figure 1B). PO\textsubscript{4} concentrations peaked at the end of exercise and decreased thereafter but remained significantly higher than baseline until 5 minutes into recovery at 55% VO\textsubscript{2max} 10 minutes at 65% VO\textsubscript{2max}, and 15 minutes at 75% VO\textsubscript{2max}. PO\textsubscript{4} concentrations decreased below baseline at 60 minutes of recovery and remained so until 150 minutes of recovery at 65% VO\textsubscript{2max} (5% to 10%) and 75% VO\textsubscript{2max} (7% to 12%) (P ≤ .05 to P ≤ .001). Concentrations did not decrease significantly below baseline at 55% VO\textsubscript{2max}.

Exercise at 65% VO\textsubscript{2max} resulted in significantly higher PO\textsubscript{4} concentrations than exercise at 55% VO\textsubscript{2max} at 10 (P ≤ .05), 20 (P ≤ .001), and 25 (P ≤ .05) minutes of exercise.

**Albumin-adjusted calcium**

There was no main effect of intensity, but there was a main effect of time (P ≤ .001) and an intensity \times time interaction (P ≤ .001). AC\textsubscript{a} concentrations increased with the onset of exercise and were significantly higher than baseline between 7.5 minutes and the end of exercise at 65% VO\textsubscript{2max} (9%; P ≤ .001) and between 2.5 minutes and the end of exercise at 75% VO\textsubscript{2max} (14%; P ≤ .001) (Figure 1C). AC\textsubscript{a} concentrations peaked after 20 minutes of exercise and decreased thereafter but remained significantly higher than baseline until 5 minutes into recovery at 65% VO\textsubscript{2max} and 7.5 minutes at 75% VO\textsubscript{2max}. AC\textsubscript{a} concentrations decreased below baseline 15 minutes into recovery and remained so until 30 minutes of recovery at 55% VO\textsubscript{2max} (7% to 9%; P ≤ .05 to P ≤ .001) and 25 minutes into recovery at 65% VO\textsubscript{2max} (6% to 8%; P ≤ .05 to P ≤ .001). AC\textsubscript{a} concentrations did...
not decrease significantly below baseline at 75% VO$_{2\text{max}}$

Exercise at 75% VO$_{2\text{max}}$ resulted in significantly higher ACA concentrations than exercise at 55% VO$_{2\text{max}}$ after 20 minutes of exercise ($P \leq .05$), 25 minutes ($P \leq .001$), and 30 minutes of exercise ($P \leq .001$) and after 25 minutes of recovery ($P \leq .01$).

**Albumin**

There was no main effect of intensity, but there was a main effect of time ($P \leq .001$) and an intensity x time interaction ($P \leq .001$). At 55% VO$_{2\text{max}}$, Ca$^{2+}$ concentrations decreased after 10 minutes of exercise, being significantly below baseline between 25 minutes and the end of exercise (Figure 2B) ($-2\%$; $P \leq .001$). Ca$^{2+}$ concentrations continued to decrease into recovery, remaining significantly below baseline until 90 minutes of recovery ($-2\%$ to $-6\%$; $P \leq .001$). At 65% VO$_{2\text{max}}$ and 75% VO$_{2\text{max}}$, Ca$^{2+}$ concentrations increased with the onset of exercise and were significantly higher than baseline between 2.5 and 10 minutes of exercise at 65% VO$_{2\text{max}}$ ($+2\%$ to $+3\%$; $P \leq .001$) and between 2.5 and 7.5 minutes at 75% VO$_{2\text{max}}$ ($+2\%$ to $+3\%$; $P \leq .001$). Thereafter, Ca$^{2+}$ concentrations decreased and were significantly below baseline between 2.5 and 30 minutes of recovery at 65% VO$_{2\text{max}}$ ($-3\%$ to $-4\%$; $P \leq .001$) and 75% VO$_{2\text{max}}$ ($-3\%$ to $-4\%$; $P \leq .001$).

There were no significant differences between the three trials at any time point other than at baseline (Table 1), which created the significant intensity x time interaction.

**Correlation analyses**

Changes in PTH were not correlated with changes in PO$_4$ or ACA in any trial. Across all data points, PTH was significantly ($P \leq .001$) negatively correlated with Ca$^{2+}$ at all intensities (Table 2).

Across PEAK data points, PO$_4$ was correlated with PTH at all exercise intensities ($r = 0.661$ to 0.772) (Table 3) when the PTH series was lagged by 1 time point (3.5 min) behind the PO$_4$ series, suggesting that increases in...
PO₄ precede increases in PTH by 3.5 minutes. Ca²⁺ was most strongly correlated with PTH at all exercise intensities (\(r = -0.902\) to \(-0.950\)) when there was no time lag, suggesting that increases in PTH occur within 3.5 minutes of a decrease in Ca²⁺. Across DEC data points, PO₄, ACa, and Ca²⁺ were correlated with PTH at all exercise intensities. PO₄ was most strongly correlated with PTH at all exercise intensities (\(r = -0.987\) to 0.995) (Table 3) when there was no time lag, suggesting that decreases in PTH occur within 8 minutes of a decrease in PO₄.

### Discussion

The novel findings from this study are the following: 1) changes in PTH, PO₄, ACa, and Ca²⁺ occur within 2.5 minutes of the onset of exercise; 2) there is an initial decrease in PTH concentrations at the start of exercise that coincides with a significant increase in Ca²⁺ concentrations at the two higher exercise intensities; 3) peak PTH concentrations occur within 5–7.5 minutes of recovery; 4) increases in PO₄ precede increases in PTH; 5) decreases in Ca²⁺ precede increases in PTH; and 6) postexercise decreases in PTH concentrations are preceded by decreases in PO₄.

The pattern of change in PTH in this study is comparable with previous studies, with PTH concentrations increasing during exercise (15, 17–20) and peaking in the first minutes of recovery (12). The pattern of change in PTH was similar across the three exercise intensities, with an initial decrease from baseline to 5 minutes of exercise. We are the first to observe this initial response in PTH, due to the higher temporal frequency of blood sampling at the start of exercise compared with previous studies. This response requires verification from further studies and the use of even more frequent sampling. The lack of a resting control group in the present study means that we cannot confirm whether this is a characteristic physiological response to the onset of exercise or whether this reflects the circadian rhythm of PTH at the time of sampling. The nadir in PTH occurs between 8:00 and 10:00 AM (25–28), and our baseline blood was taken at 8:55 AM with exercise commencing at 9:02 AM. If the initial decrease in PTH were due to the circadian rhythm, however, it would be expected that the decrease would have lasted longer than 5 minutes into exercise. Additionally, a decrease of 33% from baseline, followed by a rapid reversal in the direction of change, as shown here, has not been reported in circadian studies. Peak PTH concentrations have previously been shown to occur 15 minutes after exercise (12) due to a lower sampling frequency, but the results of the present study show that the peak in PTH after exercise occurs within 5–7.5 minutes of recovery (+73% to +110% from baseline). This peak is also transient; PTH concentrations start to decrease immediately after reaching peak concentrations. Transient spikes in PTH have been shown to be anabolic for bone (5), resulting in net bone gain (29). As such, our identification of peak PTH concentrations 5–7.5 minutes after exercise could be used as a tool for improving bone health among individuals at risk of fractures, stress fractures, or poor bone health, including the development of an exercise regimen involving bouts of running sufficient to cause a spike in PTH concentrations, followed by rest periods to ensure that the spike is transitory. Further work is required to determine whether the response of PTH to this type of exercise is consistent and whether the

#### Table 2. Pearson’s Correlation Coefficient Values for Changes in PTH, With Changes in PO₄, ACa, and Ca²⁺

<table>
<thead>
<tr>
<th>Value</th>
<th>Time Lag</th>
<th>r Value</th>
<th>Time Lag</th>
<th>r Value</th>
<th>Time Lag</th>
<th>r Value</th>
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</thead>
<tbody>
<tr>
<td>PO₄</td>
<td></td>
<td></td>
<td>ACa</td>
<td></td>
<td></td>
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<tr>
<td>55% VO₂max</td>
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<tr>
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<td>-0.950</td>
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<tr>
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<td></td>
<td></td>
<td>Ca²⁺</td>
<td></td>
<td></td>
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<tr>
<td>75% VO₂max</td>
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<td>0.994</td>
<td>0</td>
<td>0.809</td>
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<td>-0.817</td>
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</tbody>
</table>

#### Table 3. Maximum Cross-Correlation Values and Corresponding Lag Times for PTH With PO₄, ACa, and Ca²⁺

### Exercise Intensity PO₄ ACa Ca²⁺

<table>
<thead>
<tr>
<th>PEAK data points (baseline to 5 min of recovery)</th>
<th>Time Lag</th>
<th>r Value</th>
<th>Time Lag</th>
<th>r Value</th>
<th>Time Lag</th>
<th>r Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>55% VO₂max</td>
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<td>-0.431</td>
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<td>-0.902</td>
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<tr>
<td>65% VO₂max</td>
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<tr>
<td>75% VO₂max</td>
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<td>0</td>
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<tr>
<td>DEC data points (5–90 min of recovery)</td>
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<td>-0.794</td>
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<tr>
<td>55% VO₂max</td>
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<td>-0.817</td>
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</table>
magnitude of the changes in PTH are sufficient to induce such an effect.

Cross-correlations suggested that PTH secretion during exercise and recovery is controlled by a combination of changes in Ca\(^{2+}\) and PO\(_4\). Ca\(^{2+}\) is not routinely measured due to analytical difficulties; consequently, ACa is estimated as a surrogate and has been shown clinically to be a reliable indicator of Ca metabolism at rest (30). We have shown different responses to exercise and recovery between ACa and Ca\(^{2+}\) and also different relationships with PTH; Ca\(^{2+}\) concentrations were correlated with PTH, whereas ACa was not. Albumin changes taking place during exercise will have a greater effect on the ACa estimation compared with the small effect that can occur on Ca\(^{2+}\) measurement; changes in pH were not sufficient to have a major effect on Ca\(^{2+}\) measurement by the blood gas analyzer. The results support previous data (14, 15, 17–20) suggesting that changes in ACa do not explain the changes in PTH or regulation of PTH during exercise because, as PTH is increasing, ACa either also increases (15, 17) or is unchanged (14, 18, 19). Scott et al (19) argued that because both PTH and ACa were increased after 20 minutes of exercise, a decrease in Ca\(^{2+}\) could have occurred in the first few minutes of exercise, stimulating the secretion of PTH and causing serum Ca\(^{2+}\) concentrations to increase as a result of PTH-stimulated bone resorption and Ca\(^{2+}\) liberation. However, through frequent sampling, we have shown that ACa and Ca\(^{2+}\), at 65% and 75% VO\(_{2}\)\(_{\text{max}}\) increase within 2.5 minutes of exercise, with ACa increasing and Ca\(^{2+}\) decreasing thereafter.

Although it is well established that PTH responds rapidly to a reduction in Ca\(^{2+}\) at rest (1, 22), this is the first study to show that this rapid response also occurs during exercise. The lack of an initial increase in Ca\(^{2+}\) at 55% VO\(_{2}\)\(_{\text{max}}\) is surprising and the reason for this is currently unknown. The strong negative correlation of PTH and Ca\(^{2+}\) during exercise at all three intensities with a 0 time lag (r = −0.902 to −0.950) suggests that as Ca\(^{2+}\) decreases, PTH increases within 3.5 minutes. This negative cross-correlation supports the findings of Bouassida et al (11), who showed that as Ca\(^{2+}\) decreased during 42 minutes of running, PTH increased.

These findings suggest that Ca\(^{2+}\) may control PTH secretion during exercise. The reasons for the initial increase in Ca\(^{2+}\) at the start of exercise in the two higher exercise intensities are unknown, although this might be important in explaining the decreased PTH concentrations with the onset of exercise. It could have been related to exercise-induced acidosis occurring in the first few minutes of exercise, before aerobic metabolism stabilizes (31, 32), which can increase Ca\(^{2+}\) concentrations (33) but have minimal effects on ACa. Blood pH did not, however, decrease significantly during exercise, suggesting that exercise-induced acidosis was not the reason for the initial increase in Ca\(^{2+}\). Further mechanistic studies are needed to identify why this initial increase occurs, but it could be from calcium being released from other binding proteins such as transferrin (34) or calcium dissociating from PO\(_4\) (35, 36).

Changes in systemic PO\(_4\) can influence PTH secretion, with Ahmad et al (37) showing that circadian changes in PO\(_4\) precede changes in PTH. During the increase in PTH in the present study, PO\(_4\) and PTH were most strongly positively cross-correlated at −1 time lag, suggesting that increases in PO\(_4\) precede those in PTH by less than 3.5 minutes. This cross-correlation was not as strong, however, as the cross-correlation between Ca\(^{2+}\) and PTH, which might indicate that both PO\(_4\) and Ca\(^{2+}\) are influential during the increase in PTH. Our data do not fully support that the exercise-induced increases in PTH are driven solely by increased PO\(_4\) because PO\(_4\) increased with the onset of exercise despite the initial decrease in PTH. The increase in PO\(_4\) might reflect the release of PO\(_4\) from PTH-induced bone resorption (15, 37, 38) toward the end of exercise or that PO\(_4\) is being released from muscle tissue, although this is speculative (39, 40). Taken together, these results suggest that Ca\(^{2+}\) is the stronger driver of PTH secretion and synthesis at the onset of exercise; however, it is possible that the degree of association/dissociation between Ca\(^{2+}\) and PO\(_4\) varies during exercise, meaning that PTH regulation might change accordingly.

With the decrease in PTH during recovery, the strongest positive cross-correlation between PO\(_4\) and PTH occurred at a 0 time lag, suggesting that PTH decreased within 8 minutes of a decrease in PO\(_4\). These findings support Scott et al (15, 18–20), who showed that PO\(_4\) followed the same response as PTH after exercise. If the decrease in PTH during recovery is explained by renal clearance (11), the strong cross-correlation may suggest that PO\(_4\) is driving PTH clearance and overriding Ca\(^{2+}\) regulation in recovery. Alternatively, the elevated PTH concentrations could be enhancing renal PO\(_4\) excretion and causing a subsequent decrease in circulating PO\(_4\). (41).

Reductions in vitamin D concentrations can contribute to an increase in PTH because 1,25-dihydroxyvitamin D regulates the active transport of Ca and PO\(_4\) absorption in the small intestine (42). Vitamin D status was not measured, so we cannot confirm whether a change occurred during the study. The three trials were, however, completed within 1 month for each participant, and the order of trials was randomized, meaning that, although changes in vitamin D concentrations could have occurred, they are unlikely to have influenced the results.
In conclusion, at the onset of exercise PTH transiently decreases and then increases throughout exercise, peaking in the first minutes of recovery, before decreasing below the baseline concentration during ongoing recovery. Changes in Ca\(^2+\) and PO\(_4\) occur in close temporal relation to changes in PTH. A cross-correlational analysis suggests that PTH secretion during exercise and recovery is controlled by a combination of changes in Ca\(^2+\) and PO\(_4\) and that the mechanism might be different during exercise and recovery. ACa may not be a suitable surrogate for Ca\(^2+\) when investigating the rapid response to exercise because ACa concentrations do not reflect temporal PTH responses or correlate strongly with PTH.

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