Red blood cells do not contribute to removal of $K^+$ released from exhaustively working forearm muscle

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Maassen, N., M. Foerster, and H. Mairbäurl. Red blood cells do not contribute to removal of $K^+$ released from exhaustively working forearm muscle. J. Appl. Physiol. 85(1): 326-332, 1998.—$K^+$ released from exercising muscle via $K^+$ channels needs to be removed from the interstitium into the blood to maintain high muscle cell membrane potential and allow normal muscle contractility. Uptake by red blood cells has been discussed as one mechanism that would also serve to regulate red blood cell volume, which was found to be constant despite increased plasma osmolality and $K^+$ concentration ([K]$_{pl}$). We evaluated exercise-related changes in [K]$_{pl}$, pH, osmolality, mean cellular Hb concentration, cell water, and red blood cell $K^+$ concentration during exhaustive handgrip exercise. Unidirectional $^{86}$Rb$^+$ ($K^+$) uptake by red blood cells was measured in media with elevated extracellular $K^+$, osmolality, and catecholamines to simulate particularly those exercise-related changes in plasma composition that are known to stimulate $K^+$ uptake. During exercise [K]$_{pl}$ increased from 4.4 ± 0.7 to 7.1 ± 0.5 mmol/l plasma water and red blood cell $K^+$ concentration increased from 137.2 ± 6.0 to 144.6 ± 4.6 mmol/l cell water (P < 0.05), but the intracellular $K^+$-to-mean cellular Hb concentration ratio did not change. $^{86}$Rb$^+$ uptake by red blood cells was increased by ~20% on stimulation, caused by activation of the Na$^+$-K$^+$ pump and Na$^+$-K$^+$-2Cl$^-$ cotransport. Results indicate the $K^+$ content of red blood cells did not change as cells passed the exhaustively exercising forearm muscle despite the elevated [K]$_{pl}$. The tendency for an increase in intracellular $K^+$ concentration was due to a slight, although statistically not significant, decrease in red blood cell volume. $K^+$ uptake, although elevated, was too small to move significant amounts of $K^+$ into red blood cells. Our results suggest that red blood cells do not contribute to the removal of $K^+$ released from muscle and do not regulate their volume by $K^+$ uptake during exhaustive forearm exercise.

potassium; muscle; red blood cell volume; potassium uptake; sodium-potassium pump; sodium-potassium-2-chloride cotransport

IT IS WELL ESTABLISHED THAT extracellular $K^+$ ([K]$_e$) increases during high-intensity exercise, reaching values even higher than 10 mm in the interstitial space (12, 14) and ~8 mm in plasma ([K]$_{pl}$) (22, 25). $K^+$ decreases within minutes after exercise is terminated. The increase in [K]$_{pl}$ is caused by $K^+$ release from working muscles, probably through $K^+$ channels during action potentials, inadequate reuptake via the Na$^+$-K$^+$ pump in between action potentials (6), and/or release of cellular $K^+$ through ATP- and/or Ca$^{2+}$-sensitive $K^+$ channels (27).

An excessive increase in [K]$_e$ reduces the excitability of muscle cells (27). Therefore, if the reuptake into the muscle cells is inadequate, additional means of $K^+$ removal are required to keep the [K]$_e$ concentration low to warrant a normal muscle cell membrane potential and excitability. One mechanism suggested is diffusion of the released $K^+$ into the plasma to be transported to inactive tissues, where it is taken up, e.g., by nonworking muscle (15, 16, 18, 21, 25, 29). However, data suggesting an involvement of red blood cells in this process are conflicting: Böning et al. (3), Bodemann et al. (2), and Juel et al. (15) found no change in red blood cell $K^+$ in venous blood during incremental, exhaustive bicycle exercise. Hespel et al. (11) reported a decrease in red blood cell $K^+$ concentration ([K]$_{rb}$) in cubital venous blood during bicycle ergometry at 80% of maximal oxygen uptake and argued for a stress release of $K^+$ from red blood cells during exercise. McKelvie et al. (20) also show a slight decrease in femoral venous blood [K]$_{rb}$ but an increase in that in arterial blood (20) during repeated 30-s bouts of maximal bicycle ergometry.

In a different study, McKelvie et al. (21) show an increase in [K]$_{rb}$ from the brachial artery and antecubital veins during supramaximal bicycle ergometry. Their explanation is that $K^+$ is taken up by red blood cells via active transport systems, to be transported to inactive tissues (20, 21). Similar results were reported by Lindinger et al. (17). However, in none of the studies reporting an increased [K]$_{rb}$ has the activity of cation transport by red blood cells been measured. Because cation transport activity is very low in human red blood cells compared with other tissues (e.g., Refs. 4, 8, 13, 19, 24), their role as a sink for $K^+$ released from working muscles appears unlikely.

The present study was undertaken to clarify the role of red blood cells in $K^+$ removal from working muscle. In contrast to the studies mentioned above, only small-muscle groups were exercised in an exhaustive forearm exercise test. Blood was sampled to quantify plasma and red blood cell $K^+$ content and parameters to determine water shifts and changes in red blood cell volume. To obtain an estimate of the capacity of red blood cells to take up $K^+$, the unidirectional $^{86}$Rb$^+$ ($K^+$) uptake was measured in vitro under conditions simulating those changes in plasma composition found during exercise, which are known to activate $K^+$ uptake by red blood cells. The results of both tests indicate that red blood cells do not take up $K^+$ released from muscle into the interstitium and plasma during exhaustive forearm exercise. Preliminary results have been reported previously (6).

MATERIALS AND METHODS

Forearm exercise. Ten male subjects not specifically trained in arm exercise participated in this study after giving in-
removal during exercise

K⁺ removal during exercise was performed with the arm fixed in a horizontal, stretched position. In control experiments, the workload (adjusted with springs of different elasticity) was determined that caused exhaustion within ~2 min at a contraction frequency of 30 contractions/min. The tests were then performed at this exercise intensity.

To minimize the blood flow to the skin, the forearm was cooled by immersing the skin and cooling it with a fan. Under these conditions the blood drawn from antecubital veins has been shown to originate mainly from working muscle (30). Immediately before the test and about every 30 s during exercise, blood was drawn into heparinized syringes (1 U/ml). The blood was processed immediately for further measurements except for the samples, which were kept on ice for up to 2 h, taken to determine the acid-base status. Control experiments revealed that pH values were stable under these conditions. Blood pH was measured with the BMS 3 Blood Micro System (Radiometer), and the plasma osmolality was determined with an osmometer (Roebeling) from the freezing-point depression.

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[K'_{\text{ery}}] = \frac{(\text{milliliters water per milliliter plasma})}{1,000}
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To obtain a value for the red blood cell K⁺ content that is independent of possible changes in red blood cell volume, the \([K'_{\text{ery}}]\)-to-MCHC ratio was calculated, where \([K'_{\text{ery}}]\) is in millimoles per liter of packed blood cells and MCHC is in grams Hb per liter of packed red blood cells.

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\text{K⁺}^{86} \text{uptake into red blood cells. Heparinized blood (1 U/ml) was drawn from antecubital veins of six healthy male volunteers. The red blood cells were washed twice with washing solution (150 mM NaCl, 2 mM HEPES, pH 7.3, at room temperature). Contaminating leukocytes and platelets were removed by aspiration of the buffy coat. Because leukocytes have a high transport activity that might be modified by various stimuli, it was important to ensure that the results of flux measurements were not affected by leukocyte and platelet contamination. Therefore, in control experiments, fluxes were also measured in red blood cells after removal of platelets together with the plasma after spinning of whole blood at 50 g at room temperature for 10 min. The remaining cells were filtered through a cellulose column to remove leukocytes (1). The comparison of both methods revealed that careful removal of the buffy coat was sufficient to avoid obscuring of results by leukocyte and platelet contamination of the red blood cell population.}

For flux measurements, red blood cells were washed once with flux medium and incubated in flux medium for 15 min at 37°C to allow equilibration. \(\text{K⁺}^{86} \text{uptake was measured as described previously (19). Briefly, after equilibration the flux was started by suspending the red blood cells in the respective flux medium that contained 2 µCi/ml of \(\text{K⁺}^{86}\). The final Hct was 2%. To obtain two time points, in separate sets of samples the uptake was stopped after 3 min and 63 min of incubation at 37°C, respectively, by addition of five volumes of ice-cold, tracer-free flux medium followed by 10-s centrifugation in a Microfuge (Fisher Scientific). After removal of the supernatant, the cells were washed four times with ice-cold tracer-free flux medium to remove contaminating \(\text{K⁺}^{86}\). The cells were lysed with 0.1% Triton X-100 in water, and protein was then precipitated with 0.6 N perchloric acid and removed by 3-min microcentrifugation. The radioactivity was measured in the clear supernatant. Fluxes were calculated according to Canessa et al. (5). In control experiments, the flux medium contained (in mM) 135 NaCl, 5 KCl, 10 Na-lactate, and 5 glucose, 10 sucrose to simulate those changes in plasma composition that occur during exercise, which are known to stimulate \(\text{K⁺} \) uptake. The pH was kept at 7.4 because acidosis is known to inhibit cation transport by red blood cells in vitro (8). When indicated, epinephrine and norepinephrine were added at a concentration of 0.1 μM bumetanide. The leak flux was taken as the86Rb current that occurred in the absence of inhibitors. Separate experiments indicated that the total \(\text{K⁺}^{86} \) uptake was similar in plasma and the flux medium, when the medium’s K⁺ concentration (\([K’]\)) and osmolality were the same. To stimulate \(\text{K⁺} \) uptake by red blood cells, the composition of the flux medium was modified to contain the following: (in mM) 10 KCl, 10 Na-lactate, and 10 NaCl, 1 MgSO₄, 1 Na₂HPO₄, and 20 HEPES-Tris, pH 7.4, at 37°C. Protein was omitted to avoid obscuring of flux measurements by protein binding of inhibitors. Separate experiments indicated that the total \(\text{K⁺}^{86} \) uptake was similar in plasma and the flux medium, when the medium’s K⁺ concentration (\([K’]\)) and osmolality were the same. 

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Reagents were of analytical grade. Epinephrine, norepinephrine, HEPES, Tris (2-amino-2-hydroxymethyl-1,3-propanediol), sucrose, and ouabain were from Sigma Chemical. Bumetanide was a gift from Hoffman-LaRoche, and $^{86}$Rb was from Amersham.

Statistical evaluation. Results are presented as means ± SD. When the time course of changes of parameters during forearm exercise was evaluated, analysis of variance for repeated measures was performed. Scheffé’s tests were used for post hoc testing. Control values and values after termination of exercise as well as $^{86}$Rb fluxes under control and simulated exercise conditions were compared by using paired t-tests, respectively. The level of significance was P < 0.05.

RESULTS

Forearm exercise. Forearm exercise was performed to avoid an increase in $K_+^+$ in the systemic circulation and to test whether the red blood cells collected in the venous outflow had taken up $K_+^+$ as they passed the maximally working muscles and thus would participate in $K_+^+$ removal from working muscles.

Hematologic parameters and plasma composition measured in blood collected from antecubital veins before and during forearm exercise are summarized in Table 1. Table 1 shows a significant increase in Hb and Hct during exercise, but the slight increase in MCHC (3%) was statistically not significant. During exercise plasma osmolality increased by 28 mosmol/kg H$_2$O (12%), and plasma protein concentration increased by ~10%. Plasma pH decreased by ~0.16 pH units. The $[K_+^+]$ measured with ion-selective electrodes increased by ~8 mmol/l.

Figure 1 shows an increase in $[K_+^+]$ of ~2.7 mmol/l. The peak values of plasma $K_+^+$ were reached within 1 min of exercise. The $[K_+^+]$ per liter of cell water was ~137 mmol/kg cell water under control conditions and tended to increase during exercise. The slight decrease in the cell water content (~2%), calculated from MCHC, was statistically not significant (Fig. 2). $[K_+^+]$-to-MCHC ratio, used as a cell volume-independent measurement of red blood cell $K_+^+$ content, remained practically constant during the test, indicating that red blood cell $K_+^+$ content did not change during forearm exercise. In six additional measurements, only control values and values at the termination of exercise were determined to measure the cell water content from the wet weight-to-dry weight ratio. The results (not shown) support the original finding of tendencies for an increase in MCHC, a decrease in the cell water content (P < 0.06), and a slight increase in $[K_+^+]$ (P < 0.1; P values shown for the pooled data).

$^{86}$Rb uptake by red blood cells. Unidirectional Rb$^+$ ($K^-$) uptake measurements were performed under control conditions and after stimulation in a medium that was composed to simulate those exercise-related changes in plasma composition that cause an increase in unidirectional $K^+$ uptake by activating ion-specific transport systems. Under these conditions, MCHC was 335 ± 7 and 356 ± 6 g/l, respectively. Figure 3 summarizes the results of the unidirectional $^{86}$Rb ($K^-$) uptake measurements. Figure 3 shows that, under

![Figure 1. $K^+$ concentration in red blood cells (■) and plasma (●) before and during dynamic, exhaustive forearm exercise. Plasma $K^+$ concentration was corrected for volume of plasma proteins. Red blood cell $K^+$ concentration was calculated, as indicated in text, after correction for volume of Hb and red blood cell stroma. Values are means ± SD. ow, Cell water; pw, plasma water. *Significant differences between control and exercise, P < 0.05.](http://jap.physiology.org/)

![Figure 2.](http://jap.physiology.org/)
Under stimulated conditions, the total 86Rb uptake was increased significantly by 0.42 mmol·l cells⁻¹·h⁻¹. In vitro experiments show that the unidirectional 86Rb cotransport contributed ~15%. Under stimulated conditions, the total 86Rb uptake was increased significantly by ~15%. Most of this increase can be attributed to a stimulation of Na⁺-K⁺-2Cl⁻ cotransport. Catecholamines activated Na⁺-K⁺ pump activity significantly but only under the stimulated conditions, whereas Na⁺-K⁺-2Cl⁻ cotransport and leaks were not affected by these hormones. The increase in the total unidirectional 86Rb uptake achieved on stimulation with increased K⁺, osmolarity, and catecholamines was ~20% of the flux under control conditions, or 0.42 mmol·l cells⁻¹·h⁻¹.

**DISCUSSION**

The results show that, despite an exercise-induced increase in [K⁺] and [K⁺], the amount of K⁺ in red blood cells does not change significantly as they pass through the maximally working forearm muscle. In vitro experiments show that the unidirectional 86Rb (K⁺) uptake by red blood cells is significantly increased when fluxes were measured in an artificial medium that simulates some changes in plasma that occur during exercise, changes known to activate transport. However, under both control and stimulated conditions, the magnitude of even the unidirectional Rb⁺ (K⁺) uptake is far too small to explain any significant increase in red blood cell K⁺ content within short time periods. This indicates that red blood cells are unable to take up significant amounts of K⁺ as they pass through the exercising forearm muscle and seem therefore not to be involved in the removal of K⁺ released from there for delivery to nonworking muscles.

K⁺ release from working small-muscle groups. In contrast to other experiments on the issue of K⁺ removal from working muscle (3, 11, 20), our in vivo experiments were performed on a small-muscle group. In this experimental setup, the amount of K⁺ released from the maximally exercising forearm muscles was high enough to cause a significant increase in the [K⁺] of the venous outflow (Table 1); it was about as high as, or even higher than, values reported from bicycle ergometry (e.g., Refs. 3, 17, 22, 26, 29). In contrast to whole body exercise, in this setup the amount of released K⁺ was too small to increase the [K⁺] in the entire circulating blood. Therefore, the gradient for the diffusion of K⁺ from the interstitium to the blood in the exercising muscle remains high throughout the experiment. When large-muscle groups were exercised, the [K⁺] is increased not only in the venous effluent of working muscles but also systemically. In this case, the diffusion of K⁺ from the interstitium into plasma might be impaired because of a decrease in the concentration gradient. It is important to distinguish between these two different experimental setups to answer the question of whether red blood cells play any significant role...
as a sink for K$^+$ and as a K$^+$-transport vehicle. If red blood cells are involved in the redistribution of K$^+$, they should take up K$^+$ where its concentration is highest, i.e., during the passage through the exercising muscle and in venous drainage.

Mechanisms of K$^+$ removal. An elevated K$^+_o$ concentration disturbs the muscle cell membrane potential and might impair muscle contractility. Because the elevation of K$^+_o$ was discussed as one mechanism that causes muscular fatigue (25, 27), it is important to remove any K$^+$ released from the interstitial space surrounding working muscles.

K$^+$ accumulated in the interstitial space between exercising muscle cells diffuses into plasma and is then distributed to nonworking tissues, where it is taken up, thus keeping the [K$^+$] lower in arterial plasma that enters exercising muscles (18, 20, 21, 25) than in the venous effluent. Because red blood cells occupy a large proportion of the total blood volume, it has been suggested that they might act as a vehicle for K$^+$ removal (18, 20). If this mechanism acts in vivo, it would lead to an improved clearance of K$^+$ from the interstitial space. This holds partially true for lactate, which is taken up by red blood cells via a specific transport protein, causing the red blood cell lactate content to increase as the extracellular lactate concentration increases (7, 18).

However, the situation for K$^+$ uptake into red blood cells is different from that of lactate because the [K$^+_o$]-to-[K$^+_e$] ratio is ~30 times higher than the [K$^+_o$]. Therefore, the concentration gradient for K$^+$ is directed out of the red blood cells, which counteracts K$^+$ uptake. Even in plasma contained in the vasculature draining the exercising muscle in which plasma K$^+$ is increased, the [K$^+_o$]-to-[K$^+_p$] ratio is still ~15. Any admixture of plasma with a normal [K$^+_p$] would again increase the concentration gradient and again increase the force opposing K$^+$ uptake. To force K$^+$ into the red blood cells against this concentration gradient, it has to be postulated that during exercise specific K$^+$ uptake mechanisms were activated. However, our results show that despite the increase in [K$^+_p$] by ~3 mM (Table 1), the K$^+$ content of the red blood cells leaving the exercising muscles was not altered significantly. This is indicated by the unchanged [K$^+_e$] expressed per liter of cell water and the [K$^+_e$]-to-MCHC ratio used as a cell volume-independent measurement of the red blood cell K$^+$ content.

Cation fluxes in red blood cells. Unidirectional $^{86}$Rb$^+$ uptake measurements were performed to obtain a measure of the capacity for K$^+$ uptake by red blood cells and to see whether this flux would be high enough to mediate the uptake of amounts of K$^+$ from plasma large enough to contribute significantly to the removal of K$^+$ from the interstitium of exercising muscle. These fluxes represent unidirectional K$^+$ uptake but are no measure of the net K$^+$ flux into or out of the red blood cells, the magnitude of which is determined by the net electrochemical driving force, the state of activation of the respective transport pathways, as well as by outward K$^+$ leaks. To achieve an estimate of transport capacity, unidirectional $^{86}$Rb$^+$ (K$^+$) uptake was measured in a medium with an increased [K$^+$] and osmolality similar to what is found in plasma during exercise. Fluxes were deliberately measured at normal pH because acidosis is known to inhibit red blood cell Na$^+$-K$^+$.2Cl$^-$ cotransport (8), which would reduce $^{86}$Rb$^+$ uptake. Catecholamines were added because they increase during exercise, although their effects on red blood cell ion transport are unclear. The results shown in Fig. 3 indicate an increase in unidirectional $^{86}$Rb$^+$ (K$^+$) uptake from 2.1 mmol·l$^{-1}$.h$^{-1}$ under control conditions to ~2.5 mmol·l$^{-1}$.h$^{-1}$ under stimulated conditions. Even if these fluxes represented the net K$^+$ uptake by red blood cells, this increased flux is too small to account for a millimolar increase in the K$^+$ content of red blood cells even during prolonged exposure to this environment.

The increase in $^{86}$Rb$^+$ uptake found in red blood cells under stimulated conditions is caused by an activation of the Na$^+$-K$^+$ pump and of Na$^+$-K$^+$.2Cl$^-$ cotransport. The latter is activated both by the elevated K$^+_o$ (5) and by cell shrinkage (4, 8, 19). The Na$^+$-K$^+$ pump is activated by elevated K$^+_o$ (13) and catecholamines. Interestingly, pump activation by catecholamines was only seen when flux was measured in the experimental flux medium but not under control conditions. The mechanisms are not clear.

Red blood cell volume during exercise. Results on red blood cell volume changes during exercise are conflicting. On the basis of the increase in plasma osmolality during forearm exercise shown in Table 1, a decrease in cell volume in the range of ~10% might be expected. However, we found the cell water content to be practically unaltered (Fig. 2). The lack of shrinkage of the red blood cells in this environment indicates that cell volume perturbations must have been balanced. Because the K$^+$ content of the cells did not change, the cell volume has to be kept stable by means other than K$^+$ uptake. One possible explanation is the exercise-induced acidosis (Table 1) that causes red blood cells to swell because of shifts in Donnan equilibrium (3, 9). This indicates that, in this situation, there is actually no need for the red blood cells to regulate their cell volume by K$^+$ uptake via specific cation-transport systems.

Discrepancies with other studies. The question arises, Why do different studies report different results on changes in red blood cell K$^+$ during exercise that lead to different conclusions on the role of red blood cells in K$^+$ removal from working muscle? Hespel et al. (11) reported a decrease in [K$^+_e$] during submaximal bicycle exercise and explained it by K$^+$ leakage because they found no exercise-related change in the activity of cation-transport systems. To measure [K$^+_e$], they washed the cells with a medium containing 140 mM choline chloride. This medium is slightly hypotonic relative to plasma osmolality under control conditions but significantly hypotonic relative to exercise conditions, when plasma osmolality is elevated (see Table 1). Therefore, when washed with this medium, red blood
cells can be expected to swell, which will dilute red blood cell K\(^+\). In this case, [K\(_\text{ery}\)] (but not the cells’ K\(^+\) content) will be lower than reported normal values (e.g., Ref. 25). On the contrary, McKelvie et al. (20, 21) reported increased red blood cell K\(^+\) during exercise and argued for a role of red blood cells in removing K\(^+\) released from the exercising muscle. In the work of McKelvie et al., [K\(_\text{ery}\)] was calculated from [K\(_p\)] and [K\(_w\)] measured with ion-selective electrodes on the basis of Hct. McKelvie et al. appear not to have considered that the ratio of the volume of water in both compartments differs from Hct because of the specific volume of proteins in plasma and red blood cells. This explains the underestimation of the [K\(_\text{ery}\)] per liter of cell water, which they found to be in the range of 110 to 120 mmol/l cell water (20, 21), whereas these values are typically ~130 mmol/l cell water (e.g., Ref. 31). Also, considering these specific volumes of red blood cell and plasma constituents, correcting Hct reduces the increase in [K\(_\text{ery}\)] reported (21) during exercise to ~2 mmol/l cell water, which is within the experimental error of the measurements. The results of other studies cannot be reevaluated because Hb and plasma protein concentrations are not available. It appears, therefore, that the main reason for the diverging results reported on changes in red blood cell K\(^+\) comes from differences in the methods used to evaluate the red blood cell K\(^+\) content. The results of the studies noted above (11, 20, 21) agree very well with ours, when a cell volume-independent measurement of [K\(_{\text{cell}}\)] (i.e., red blood cell K\(^+\) content) is introduced. This supports our notion of no increased red blood cell K\(^+\) content during exercise. Red blood cells seem, therefore, not to serve as transport vehicles to remove K\(^+\) released from the working muscle to inactive tissues. This transport appears to be mediated solely by plasma. They also do not use muscle K\(^+\) to restore their cell volume when they are exposed to increased plasma osmolality during exercise. For both actions, K\(^+\) uptake for removal and for cell volume regulation, even the unidirectional uptake rates for K\(^+\) into red blood cells, is far too slow (24).

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