Potassium depletion improves myocardial potassium uptake in vivo

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Bundgaard, Henning. Potassium depletion improves myocardial potassium uptake in vivo. Am J Physiol Cell Physiol 287: C135–C141, 2004. First published March 3, 2004; 10.1152/ajpcell.00580.2003.—Potassium depletion (KD) is a very common clinical entity often associated with adverse cardiac effects. KD is generally considered to reduce muscular Na-K-ATPase density and secondarily reduce K uptake capacity. In KD rats we evaluated myocardial Na-K-ATPase density, ion content, and myocardial K reuptake. KD for 2 wk reduced plasma K to 1.8 ± 0.1 vs. 3.5 ± 0.2 mM in controls (P < 0.01, n = 7), myocardial K to 80 ± 1 vs. 86 ± 1 μmol/g wet wt (P < 0.05, n = 7), increased Mg, and induced a tendency to increased Na. Myocardial Na-K-ATPase α2-subunit abundance was reduced by ~30%, whereas increases in α1- and K-dependent pNPase activity of 24% (n = 6) and 13% (n = 6), respectively, were seen. This indicates an overall upregulation of the myocardial Na-K pump pool. KD rats tolerated a higher intravenous KCl dose. KCl infusion until animals died increased myocardial K by 34% in KD rats reduce K uptake capacity. In KD rats we evaluated myocardial Na-K-ATPase regulation in response to K depletion and maximum K uptake capacity (7). However, we recently reported (3) that, in contrary to findings in vitro (23), a markedly increased myocardial K uptake capacity (7). However, we recently reported (3) that, in contrary to findings in vitro (23), a markedly increased myocardial Na-K pump density and in vivo increased K tolerance and myocardial K uptake rate during K repletion. Thus the heart is protected from major K losses and accumulates considerable amounts of K during exposure to high plasma K. This is of clinical interest, because a therapeutically induced rise in myocardial K may affect contractility and impulse generation-propagation and may attenuate increased myocardial Na, the hallmark of heart failure.

Na-K-ATPase; ion homeostasis; heart failure; iatrogenic potassium depletion

POTASSIUM (K) uptake in the myocardium depends on Na-K-ATPase transport of Na outward and K inward across the cell membrane in a 3:2 relationship. Factors affecting density or activity of the Na-K pump may alter the myocardial K homeostasis and secondarily the intracellular homeostasis of other ions. Such changes may affect secondary active transport processes (9) and membrane potential and impulse generation and propagation and under certain circumstances cause arrhythmia (13, 29) and affect myocardial systolic (27) as well as diastolic (30) properties. In some tissues primary disturbances may not only normalize myocardial K but also reduce myocardial Na, which may improve cardiac performance. This study was designed to evaluate the relation between myocardial Na-K-ATPase regulation in response to K depletion and myocardial K uptake in vivo.

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MATERIALS AND METHODS

Female Wistar rats bought at the age of 8 wk (~125 g) (Møllegaard Breeding Centre, Lille Skensved, Denmark) were used in the study. The study was conducted in agreement with legislation for experimental animals given by the Danish Ministry of Justice. The animals were kept in animal housing facilities at 22°C with a 12:12-h light-dark cycle (light 8 AM to 8 PM). Animals assigned to K depletion were housed in cages without access to urine and feces, were fed a low-K content diet containing (in mmol/100 g chow; n = measurements on 4 chow samples) 0.11 ± 0.01 K (mean ± SE), 11.52 ± 2.00 Na, and 3.30 ± 0.23 Mg, and had free access to distilled water. Control animals had reduced access to standard chow containing (in mmol/100 g chow; n = measurements on 4 chow samples) 22.87 ± 0.55 K, 9.09 ± 1.83 Na, and 7.37 ± 0.49 Mg to keep body weights comparable between the two groups (17). Animals were taken for experiments after 2 wk of treatment. After the animals were euthanized without any other instrumentation, myocardial ion and Na-K-ATPase measurements were also performed after 1, 3, and 7 days, and after 2 wk.

Instrumentation. The instrumentation of the animals was previously described in detail (4). In brief, animals were anesthetized by intraperitoneal injection of 0.05 mg/g body wt pentobarbital sodium (Mebumal, 50 mg/ml; Nycomed DAK) before catheterization of the jugular vein for infusion and the carotid artery for blood sampling. Fifteen minutes after completion of surgical procedures, the first blood sample (t = 0 min) was taken and continuous intravenous infusion of 1.5 ml·100 g body wt⁻¹·h⁻¹, or as indicated, of a solution of 0.5 mol/l KCl (i.e., 0.75 mmol KCl·100 g body wt⁻¹·h⁻¹) was initiated. During the infusion arterial blood samples of 0.2 ml were drawn at t = 5, 15, and 30 min and thereafter at 30-min intervals, or as indicated. After each sampling, blood that was drawn before sampling to avoid dilution was reinfused in addition to 0.2 ml of heparinized isotonic NaCl for intravascular volume compensation. During infusions a reduction in hemoglobin level was observed. Thus, after 60 min of infusion, reductions in hemoglobin of 0.3 ± 0.03 mmol/l in control rats and 0.4 ± 0.3 mmol/l in K-depleted rats were observed (n = 5–6, P > 0.8). During infusions animals were well oxygenated. Thus, after, e.g., 60 min, arterial oxygen saturations of 99 ± 2% (n = 6) in controls and 100 ± 3% (n = 6) in K-depleted rats were measured with an OSM3 (Radiometer, Copenhagen, Denmark). KCl infusions were continued until the animals died or as otherwise indicated. KCl infusions were then immediately stopped, the animals were decapitated, and the heart and in some instances, to verify the level of K depletion, the hind leg gastrocnemius muscles were excised and immediately taken for measurements. In some animals ouabain (12.5 mmol/g body wt) was administered intraperitoneally to block the ouabain-sensitive Na-K-ATPase subunits.

K, Na, and Mg. Arterial blood samples were immediately analyzed for plasma K and Na concentrations by ion-sensitive electrodes with an ABL 605 (Radiometer). Heart ventricular myocardium, gastrocnemius muscle, and chow K and Na contents were measured by flame photometry with an FL3M (Radiometer) with lithium as an internal standard. A sample of ~25 mg wet wt was dissolved in 1 ml of 30% H2O2, and the suspension was placed at 90°C for 12 h to allow complete evaporation. After addition of 2 ml of trichloroacetic acid (TCA; 5% wt/vol), 0.5 ml of the solution was used for flame photometry after final addition of a further 0.5 ml of 5% TCA and 1.5 ml of 5 mmol/l LiCl. Myocardial, skeletal muscle, and chow Mg contents were measured by atomic absorption (Perkin Elmer AAnalyst 100; Norwalk, CT) at a wavelength of 285.2 nm with a solution as used for flame photometry except that LiCl was replaced by 1.5 ml of redistilled water. Measurements were performed in duplicate.

3H-labeled ouabain binding. Measurements of 3Houabain binding were performed as previously described in detail for intact tissue samples (16). In brief, all procedures were performed by using freshly made vanadate (Merck, Darmstadt, Germany) buffer containing (in mmol/l) 10 Tris·HCl, 250 sucrose, 3 MgSO4, and 1 vanadate. pH was adjusted to 7.3 with Tris·HCl. Samples of ~4 mg wet wt were cut from the ventricular myocardium or gastrocnemius muscles and prewashed in unlabeled buffer at 0°C for 20 min (2 × 10 min). Incubations took place at 37°C in buffer containing [3H]ouabain (2.1 μCi/ml; Amersham International, Little Chalfont, UK) and ouabain (Sigma, St. Louis, MO) added to a final concentration of 1 × 10⁻⁶ mol/l for 2 h (2 × 1 h). Thereafter, a washout at 0°C in unlabeled buffer for 2 h (4 × 30 min) was performed to reduce the amount of [3H]ouabain in the extracellular space, thereby enhancing the precision of the method. After washout, samples were blotted, weighed, and soaked overnight in vials containing 0.5 ml of 5% (wt/vol) TCA. Thereafter, 2.5 ml of Opti-fluor scintillation mixture (Packard Instruments, Darmstadt, Germany) was added and [3H]activity in samples and incubation medium was assayed by liquid scintillation counting (Tri-Carb, 1600TR; Packard Instruments). On the basis of sample wet weight, 3H activity in the incubation medium, and 3H activity retained in the samples, the concentration of [3H]ouabain binding sites in the sample was calculated and expressed as picomoles per gram of wet weight. Na-K pumps internalized to endosomal pools or the ouabain-resistant α1-isomorph of the rat myocardium Na-K pump are not detected by [3H]ouabain binding. Myocardial water and protein contents were determined as previously described in detail (4). Heart weight and protein content were determined immediately after the heart was dissected out.

Immunoblotting. Immunoblotting was performed with crude homogenates (10 mg tissue/ml in His buffer; Ref. 20) as previously described in detail (2). Isoform-specific antibodies McKI and McB2 against the α1 and α2 Na-K-ATPase subtypes, respectively, were kindly provided by K. Sweadner (Harvard University). After protein concentrations were measured, equal amounts of protein were dissolved in Laemmli buffer (Bio-Rad), and loaded on a 7.5% Tris-HCl gel together with molecular weight standards (Precision Protein Standards, Bio-Rad), and run on Mini-Protean 3 cell electrophoresis system (Bio-Rad). Gels were blotted onto Immobilon 0.45-μm polyvinylidene difluoride (PVDF) membranes (Bio-Rad) with a Trans-Blot Semi-Dry transfer system (Bio-Rad) according to the manufacturer’s instructions. Membranes were blocked in PBS, 0.2% Tween 20, and 5% bovine albumin fraction V (AppIChem, Darmstadt, Germany) overnight at 4°C. Membranes were incubated with isotype-specific antibodies diluted 1:2,500 in blocking buffer overnight at 4°C, washed in PBS and 0.2% Tween 20, and incubated with antimouse IgG horseradish peroxidase-linked whole antibody (Amersham Life Science) diluted 1:2,500 in PBS and 0.2% Tween.Membranes were then washed in PBS and 0.2% Tween, followed by a wash in PBS only. The signal was detected with an enhanced chemiluminescence (ECL) kit and Hybond ECL film (Amersham Life Science). Multiple exposures were made to ensure that signals were within the linear range of the film. Immunoblots were quantified by scanning densitometry with Kodak Digital Science 1D Image Analysis Software (Rochester, NY). Changes in isoform abundances in K-depleted animals were expressed relative to values obtained in controls.

Calculations and statistics. Myocardial net K uptake rate during KCl infusions was calculated as the difference between mean myocardial K content without KCl infusion and K content in each heart after KCl infusion. Results are expressed relative to duration of KCl infusion (mol K/g wet wt⁻¹·min⁻¹). Results are given as means ± SE. Statistical significance among groups was ascertained by Student’s two-tailed t-test for unpaired observations. Linear regression analysis was performed by the method of least squares. Bonferroni’s correction was applied to correct for multiple comparisons. P < 0.05 is regarded as significant in all comparisons.

RESULTS

K depletion caused a 7% weight loss (P < 0.05, n = 6), but otherwise the dietary regiments were well tolerated and animals were clinically unaffected. Between K-depleted and control

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rats, i.e., rats with limited access to standard chow, no significant differences in body weight [118 ± 2 vs. 125 ± 4 g; \( P = \text{not significant (NS, } n = 6) \) or heart weight (0.39 ± 0.02 vs. 0.38 ± 0.02 g; \( P = \text{NS, } n = 6) \) were observed.

**Plasma K.** Plasma K was reduced to 1.8 ± 0.1 mmol/l in the K-depleted group compared with 3.5 ± 0.2 mmol/l in the control group, i.e., by 51% (\( P < 0.01, n = 7 \)). No significant difference in plasma K was observed between normal control rats (3.6 ± 0.1 mmol/l) and weight-matched control rats. No difference in plasma Na was observed between the two groups. Plasma K changes in response to KCl infusions are described below.

**Myocardial K, Na, and Mg content.** K depletion induced a gradual decrease in myocardial K content, reaching 80 ± 1 \( \mu \text{mol/g wet wt} \) after 2 wk compared with 86 ± 1 \( \mu \text{mol/g wet wt} \) in control rats (\( P < 0.05, n = 7 \)). This decrease (~6%) was considerably less than the decrease observed in gastrocnemius muscle K, to 84 ± 2 \( \mu \text{mol/g wet wt} \) compared with 111 ± 2 \( \mu \text{mol/g wet wt} \) in controls, i.e., by 23% (\( P < 0.01, n = 6 \)). This reduction is in agreement with previous findings (3). Only a tendency to an increase in myocardial Na was seen in K-depleted animals compared with controls (40 ± 2 vs. 38 ± 2 \( \mu \text{mol/g wet wt} \); \( P > 0.4, n = 7 \)), whereas a significant increase in gastrocnemius muscle Na to 36 ± 1 compared with 22 ± 1 \( \mu \text{mol/g wet wt} \), i.e., by 60% (\( P < 0.01, n = 6 \)), was seen. K depletion was associated with an increase in myocardial Mg content to 11.0 ± 0.4 vs. 9.6 ± 0.2 \( \mu \text{mol/g wet wt} \) in controls, i.e., by 14% (\( P < 0.05, n = 6 \)), and an increase in gastrocnemius muscle Mg to 12.9 ± 0.1 vs. 12.0 ± 0.3 \( \mu \text{mol/g wet wt} \) in controls, i.e., by 8% (\( P < 0.05, n = 6 \)).

**Myocardial Na-K-ATPase.** In the K-depleted rats myocardial K-dependent pNPPase activity showed a tendency to increase after K depletion for 3 days, reaching the level of significance after 2 wk at 2.7 ± 0.1 vs. 2.4 ± 0.1 \( \mu \text{mol·min}^{-1}·\text{g}·\text{wet wt}^{-1} \) in controls, i.e., an increase of 13% (\( P < 0.05, n = 6 \); Fig. 1). This indicates that the total myocardial Na-K pump pool was upregulated. Linear regression analysis of data from K-depleted and control rats obtained from the start of the dietary regimens until day 14 showed a negative linear relationship between mean myocardial K-dependent pNPPase activities and mean myocardial K (\( y = -0.05x + 6.44, r^2 = 0.8, P < 0.01, n = 7 \); Fig. 2). Thus K-dependent pNPPase activity was higher in the samples with lower K content.

To quantify putative K depletion-induced changes in the abundance of the ouabain-sensitive \( \alpha_2 \)-isoform of myocardial Na-K-ATPase, \( ^3 \text{H} \)ouabain binding measurements were performed. \( ^3 \text{H} \)ouabain binding site concentration was reduced to 106 ± 11 pmol/g wet wt compared with 149 ± 9 pmol/g wet wt in control rats, i.e., by 29% (\( P < 0.05, n = 6 \)). In gastrocnemius muscle a significant \( ^3 \text{H} \)ouabain binding site concentration decrease of 67% was seen. Further assessment was obtained by immunoblotting. Thus, in accordance with the decline in myocardial \( ^3 \text{H} \)ouabain binding site concentration of 29%, a decrease in \( \alpha_2 \)-isoform abundance of 28% (\( P < 0.05, n = 6 \)) was observed. The by far most abundant \( \alpha_1 \)-isoform of the rat myocardial Na-K-ATPase was increased by 24% (\( P < 0.05, n = 6 \); Fig. 1). It should be noted that no significant differences were observed between hearts from K-depleted rats and control rats concerning water content (76.1 ± 0.1% vs. 76.8 ± 0.3%; \( P = \text{NS, } n = 5 \) or 6) or protein content (233 ± 2 vs. 228 ± 4 mg/g wet wt; \( P = 0.2, n = 6 \)).

**K clearance capacity: Plasma K.** During intravenous KCl infusion, plasma K increased rapidly and almost linearly in the control group whereas a lower increase rate was observed in the K-depleted group. Thus after the first 15 min of infusion plasma K had increased by 3.3 ± 0.3 mmol/l in K-depleted rats compared with 4.3 ± 0.2 mmol/l in control rats (\( P < 0.05, n = 6 \)). After ~30-min infusion the plasma K increase rate leveled off in the K-depleted group. K-depleted rats died after 118 ± 16 min of KCl infusion, whereas control rats died after 53 ± 4 min (\( P < 0.01, n = 6 \)). The last plasma K value measured before the animals died was 11.8 ± 0.8 mmol/l in K-depleted rats and 11.9 ± 0.9 mmol/l in control rats (\( P > 0.9, n = 6 \)), indicating that a similar level of hyperkalemia was tolerated in the two groups.

**Myocardial K content after maximum KCl infusion.** From KCl infusion until the animals died (see above) myocardial K increased to 108 ± 2 \( \mu \text{mol/g wet wt} \), i.e., by 34% (\( P < 0.05, n = 6 \)), in the K-depleted group and to 101 ± 2 \( \mu \text{mol/g wet wt} \), i.e., by 18% (\( P < 0.05, n = 6 \)), in control rats (Fig. 3). The rates of net myocardial K uptake during KCl infusions were 0.26 ± 0.03 \( \mu \text{mol·g wet wt}^{-1}·\text{min}^{-1} \) in K-depleted animals vs. 0.30 ± 0.05 \( \mu \text{mol·g wet wt}^{-1}·\text{min}^{-1} \) in controls (\( P > 0.4, n = 6 \)). It should be noted that before (see above) as well as after infusions no significant differences in myocardial water content were observed between K-depleted and control rats (73.5 ± 0.6% vs. 73.9 ± 0.7%; \( P = 0.7, n = 6 \)).

**Myocardial K after equal KCl dosages.** The higher increase in myocardial K in K-depleted rats after maximum KCl infusion may have been due to the more than twice as long KCl infusion period in the K-depleted rats compared with control rats. Therefore, further assessment of myocardial K uptake was performed by infusing KCl for equal periods of time in the two groups.
uptake rates of 0.18/1006 respectively, in the two groups (Fig. 3), corresponding to net K uptake of K-depleted rats and weight-matched controls before and after intravenous infusion of different KCl doses (0.75 mmol KCl weight-matched controls before and after intravenous infusion of different KCl doses (0.75 mmol KCl weight-matched controls). Each point represents measurements in 5–7 animals. The equation for the linear regression line and the $r^2$ value are shown. The linear correlation was significant ($P < 0.01$).

Myocardial K after clamping of plasma K by KCl infusion. KCl infusions were not associated with changes in myocardial Mg, whereas a general tendency to a reduction in myocardial Na was seen. Thus, comparing values before and after KCl infusions in both groups were adjusted to obtain similar plasma K levels in the upper normal range, i.e., 5.5 mmol/l. Plasma K was maintained at this level for ~15 min before infusions were stopped and the heart was immediately excised for ion measurements. After infusion for 39 ± 3 and 43 ± 6 min ($P > 0.4, n = 8$) in K-depleted and control rats, respectively, final plasma K values of 5.5 ± 0.2 mmol/l in K-depleted rats and 5.5 ± 0.1 mmol/l in control rats ($P < 0.01, n = 8$) were obtained. Infused KCl dosages were 0.37 ± 0.03 and 0.13 ± 0.02 mmol ($P < 0.01, n = 8$), respectively. After infusions myocardial K contents reached 89 ± 2 μmol/l wet wt in K-depleted rats vs. 90 ± 1 μmol/l wet wt in control rats ($P > 0.3, n = 8$; Fig. 3). This corresponds to net myocardial K uptake rates of 0.22 ± 0.04 vs. 0.10 ± 0.03 μmol/g wet wt $^{-1}$ min$^{-1}$ ($P < 0.05, n = 8$; see Calculations and statistics). Thus, with plasma K clamped within the upper normal range at equal levels in the two groups, a higher net K uptake was observed in the K-depleted rats compared with control rats.

KCl infusions were not associated with changes in myocardial Na (or K-homeostasis) in vivo. After intraperitoneal injection of 12.5 mmol ouabain/g body wt, plasma K increased from 1.8 ± 0.1 mmol/l to a maximum of 3.4 ± 0.3 mmol/l after 15 min in K-depleted rats ($n = 6$ at $t = 0$ min, $P < 0.01$) and from 3.3 ± 0.1 mmol/l to a maximum of 7.6 ± 0.3 mmol/l after 90 min in control rats ($n = 7$ at $t = 0$ min, $P < 0.01$) (Fig. 4). The plasma K rise is most likely due to...
inhibition of the α2-isoform of the Na-K pump in skeletal muscles. The plasma K increases were associated with increases in myocardial K content to $87 \pm 2 \text{ mmol/g wet wt}$ in K-depleted rats ($P < 0.05, n = 6$) and to $92 \pm 2 \text{ mmol/g wet wt}$ in control rats ($P < 0.05, n = 6$) (Fig. 3). In gastrocnemius muscle no significant changes were seen in K-depleted rats ($86 \pm 2 \text{ mmol/g wet wt}; P > 0.5, n = 6$) or in control rats ($110 \pm 2 \text{ mmol/g wet wt}; P > 0.9, n = 6$).

**DISCUSSION**

The present study demonstrates an increase in rat myocardial Na-K-ATPase concentration in response to a minor decrease in myocardial K after 2 wk of K depletion. This K depletion-induced upregulation was shown for the first time to be associated with an increase in net myocardial K uptake during intravenous K repletion in vivo.

*Na-K pump regulation in K depletion.* Na-K pump regulations in response to K depletion were measured longitudinally, i.e., during the course of gradually developing K depletion. The overall upregulation of myocardial Na-K pump density of 13%, as measured by K-dependent pNPPase activity, after 2 wk of K depletion was the differentiated outcome of a 30% reduction in α2-isoform abundance—composing ~10% of the myocardial Na-K pump pool (31)—and a 24% upregulation of the vast majority of rat myocardial Na-K pumps, i.e., α1. The downregulation of α2 was of same order of magnitude as previously seen (1). In that study K depletion of rats for 2 wk reduced plasma K to $3.1 \pm 0.3 \text{ mmol/l} (n = 4–7)$ and reduced body weight by 12%. The presently observed increase in α1 is in acceptable agreement with results obtained in the former study (1) of no significant changes in α1, considering the less pronounced hypokalemia achieved and that the weight loss may have influenced the results. Extreme K depletion may cause generalized catabolism, including reductions in Na-K pump density. Furthermore, in the two former studies (1, 24) no longitudinal measurements were reported. The presently seen α1 upregulation is in agreement with observations in K-depleted rabbits of a ~15% upregulation of α1-isoform as assessed by [3H]ouabain binding (34) and a 13% increase as assessed by patch clamping with patch pipette Na concentrations at a near-saturating level (28).

The effects of K depletion on myocardial Na-K-ATPase show similarities with changes in skeletal muscle Na-K-ATPase. Thus α2 in skeletal muscles is reduced, whereas α1 is unaltered (1, 3, 6). Because α2 composes the majority (75–85%) of the Na-K pumps in rat skeletal muscles (15), K depletion may cause a marked reduction in skeletal muscle Na-K-ATPase concentration—up to 70% in rats (23). In humans a K depletion-induced reduction of up to 19% has been reported (12). Taken together, whereas K depletion causes Na-K-ATPase downregulation in skeletal muscles, myocardial Na-K-ATPase seems to be upregulated. Furthermore, the present results illustrate how a quantitatively differentiated response to a stimulus between tissues can be achieved by differentiated Na-K-ATPase isoform distribution. Between species the myocardial response to K depletion may depend on which isoforms are expressed. For instance, rabbit myocardium only expresses the α1-isoform, which seems to protect from any K depletion-induced downregulation (28, 34). Interestingly, this phenotype also seems to protect from any myocardial K loss during K depletion (34). In humans, α1-, α2-, and α3-isoforms of the Na-K pump are expressed in myocardium (26). If regulations in humans in response to K depletion are similar to those seen in rats and rabbits, the balance between an upregulation of α1 and downregulation of α2 may be decisive for the clinically adverse cardiovascular effects of K depletion. However, a prediction of clinical effects is hampered by the lack of knowledge about regulation of α3 in K depletion.

*Myocardial ion homeostasis in K depletion-repletion.* The present results confirm that in response to hypokalemia there is
a marked difference in K loss between myocardium (6%) and skeletal muscles (23%) (23). On the other hand, the present results show that in response to increased extracellular K—during intravenous KCl infusion—there was a considerable myocardial net K uptake of ~34% after ~2 h of KCl infusion in K-depleted rats and 18% after ~1 h in control rats. It is important to assess how much of these increases can be accounted for by the increase in extracellular K. Thus during these ~2 h of KCl infusion in K-depleted rats an increase in myocardial K of ~28 μmol/g wet wt and a rise in plasma K from 1.8 to 11.8 mmol/l were seen. Assuming identical K concentrations in plasma and in the extracellular space and an extracellular volume (ECV) of 20% of tissue weight, it can be calculated that ~7.1% [(11.8 – 1.8 mmol/l) × 0.20 ml ECV/g wet wt ÷ 28 μmol/g wet wt × 100] of the increase in myocardial K content is accounted for by increased ECV K concentration. In controls the corresponding value is 11.2%. Thus the majority of the KCl infusion-induced increase in myocardial K content was due to increased intracellular K. We previously reported (3) an increase in skeletal muscle K of 41–56% in K-depleted rats and 10% in control rats after KCl infusions for ~3.5 and 1 h, respectively. Thus, during maximum KCl infusion, skeletal muscle and myocardial K rises are of the same order of magnitude in K-depleted rats, whereas in controls the K increase in the myocardium is about twice as high as in skeletal muscle (3). This indicates that in contrast to the differentiated tissue K losses developing during K depletion, the heart participates—in a weight basis—in buffering of increases in plasma K to an extent comparable to skeletal muscles, i.e., the heart is not only “passively” protected by K buffering in skeletal muscles. This high net K uptake in the heart is in agreement with a previously reported 10% increase in net myocardial K content only 2 days after commencement of oral K loading (2).

The maximum net myocardial K uptake rate of ~0.3 μmol·g wet wt−1·min−1 was similar to the previously observed gastrocnemius muscle K uptake rate of ~0.3 μmol·g wet wt−1·min−1 (3). These net K uptake rates in myocardium and skeletal muscles do not reflect that the Na-K-ATPase density in myocardium is approximately six times higher than in skeletal muscles (24). This indicates that differences in net K uptake rates between tissues are not determined by Na-K-ATPase densities, whereas differences in Na-K-ATPase densities within tissues affect maximum net K uptake rates. Differences in K uptake between tissues are likely to be due to differences in tissue function and differences in the extent of secondary active transport of other ions and nutrients and thus differences in magnitude of cellular loss of K and gain of Na.

The myocardial K uptake rate was significantly higher in K-depleted rats with increased Na-K-ATPase density compared with control rats when plasma K levels were kept equal by KCl infusion in the two groups. This confirms the concept of a positive correlation between Na-K-ATPase density and K uptake capacity (7), and the finding is also in agreement with K depletion-induced increases in Na-K pump affinity for extracellular K and for intracellular Na (28). Finally, the intracellular reduction in K and increase in Na reduce the K inhibition at the cytoplasmic Na sites of the Na-K ATPase (32). This mechanism favors preservation of cellular K during K depletion and increases K uptake during K repletion.

The ouabain-induced increases in plasma K and myocardial K without changes in skeletal muscle K content were most likely caused by near saturation of the skeletal muscle α2-isoform of the Na-K pump by ouabain. These findings give an indication of the magnitude of the ongoing skeletal muscle K leakage—K uptake at rest—even in the K-depleted animals. The ouabain-induced increase in myocardial K indicates that myocardial α1—composing 90% of the rat myocardial Na-K pump pool (31)—has a higher K affinity than skeletal muscle α1—composing 15–25% of the skeletal muscle Na-K pump pool—or reflects the difference in Na-K pump density between myocardium and muscle. Thus it is of major interest that differences between tissues in Na-K-ATPase isoform concentration, distribution, and K affinity may have marked effects on K homeostasis in vivo. Indeed, the changes in tissue K induced by ouabain injection illustrate how a functional inhibition of α2, mimicking K depletion-induced α2 downregulation, seems to favor protection of myocardial K at the expense of skeletal muscle K. The present results are not easily translatable into effects of digoxin in humans, because all three Na-K pump isoforms in human skeletal muscle and myocardium are ouabain sensitive (11, 26).

We previously reported (3) that Mg content in skeletal muscles increases in response to K depletion, and in this study we observed an increase in myocardial Mg as well. This increase was not caused by decreased myocardial water content or increased Mg content in the chow. Clinically, muscular K and Mg are generally considered positively correlated (10), and in patients with cardiac arrhythmias suspected to be associated with K/Mg depletion, K as well as Mg is generally acutely administered. However, whereas this positive correlation between K and Mg applies to K depletion induced by K-wasting diuretics (12), the present results suggest that this is not the case when a selective negative K balance induces K depletion.

Myocardial Na was not significantly affected by K depletion but only showed a tendency to be increased (by ~5%). A similar tendency has been observed by others (34). It cannot be ruled out that this tendency might be related to a higher Na content in the chow administered to the K-depleted animals, but it is more likely that an increase represents a compensatory mechanism for the decrease in cellular K. Such a compensation may be caused by a plasma K-induced reduction in Na-K pump activity, which, in turn, may not be fully compensated for by the increase in myocardial Na-K pump density. As previously reported for skeletal muscles (3), a tendency to a reduction in myocardial Na was seen after KCl infusion. Myocardial hypertrophy and heart failure are associated with increased intracellular myocyte Na in animals and in humans (for review, see Ref. 25). Because of the interplay between intracellular Na and Ca, changes in Na may have profound effects on myocardial contractility and arrhythmogenesis. Pogwizd et al. (25) suggested that increased myocardial Na in heart failure might be offset by a fall in myocardial K. It is of major interest that K depletion seems to induce a similar pattern of myocardial Na/K changes as seen in heart failure. However, it is not clear whether an increase in myocardial Na, e.g., caused by K depletion, may cause heart failure—or whether a myocardial Na increase in heart failure only develops as a homeostatic compensation to increase contractility. On the basis of the present results it is tempting to suggest that the intracellular Na and K changes seen in K depletion could in some instances
play a primary role in development of cardiomyopathy and that iatrogenic K depletion might worsen heart failure. In keeping with this it is of considerable clinical interest that drugs that have been shown to improve morbidity and mortality in patients with heart failure, i.e., angiotensin-converting enzyme inhibitors, aldosterone antagonists, and β-adrenoceptor antagonists (for recent review, see Ref. 18), all tend to increase plasma K, whereas K-wasting diuretics, which may cause significant skeletal muscle and myocardial K depletion, may be deleterious (8). Further attention to K homeostasis may prove to be of utmost clinical value in cardiovascular medicine.

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