The assessment of potassium (K) effects in hypertension involves a history of complex research in cell K function and body K homeostasis. These studies provide evidence for the role of K ions in vascular and renal function, insulin resistance, glucose uptake, and the renin–angiotensin–aldosterone system; and there have been an impressive number of clinical and epidemiologic research relating dietary intake K and regulation of blood pressure. However, the usual technique by which K metabolism is assessed in clinical practice (plasma or serum K) provides no useful data for estimating disorders in cell K transport that occurs in hypertensive patients or that may follow the administration of diuretics, β-blockers, or nonsteroidal anti-inflammatory drugs. This fact becomes more crucial if associated with the physiologic decline in body K stores occurring after the age of 30 years, which may impair the long-term treatment of hypertensive individuals. In this context, this article presents a review of the clinical and research methods that can be used to assess more accurately K metabolism and cell K physiology in hypertensive patients, including a heritable defect in red blood cell K transport. Am J Hypertens 2006;19:432–436 © 2006 American Journal of Hypertension, Ltd.

**Key Words:** Essential hypertension, bioelectrical impedance analysis, cell K transport, red blood cell potassium, total body potassium, trans-tubular K gradient.
studies by McDonough et al.\(^9\) using “K Clamp” in rats, provide the best evidence for this integrated function of muscle mass and kidney, independently of plasma K.

However, a large number of hormonal and nonhormonal factors also intervene, which have important clinical implications. For example insulin and epinephrine are both capable of inducing a rapid inward shift of K into the cells, whereas extracellular acidosis rapidly decreases cell K content, in most cases without appreciable changes in the extracellular fraction,\(^10\) suggesting that sampling of serum or plasma K may not be a reliable index of cell K homeostasis. In fact, the relationship between decreased K intake and hypertension or stroke has not been sustained by the presence of hypokalemia,\(^11–13\) whereas the improvement of blood pressure (BP) by the DASH diet, spironolactone, or K tablets occurs with little or no changes in the extracellular K.\(^2,14–15\) The experimental relationship is also true: impaired cell K uptake in skeletal muscle, kidney, or RBC has been reported in hypertension and stroke despite normal K in plasma.\(^16,17\)

In addition to these observations, it is interesting to note that a number of prescribed treatments in hypertensive individuals may also induce cell K abnormalities, modify K distribution, or even improve cell K homeostasis. Particularly important are the diuretics (thiazide, furosemide), the K-sparing drug amiloride, angiotensin-converting enzyme inhibitors, β-blockers, calcium-channel-blockers, digitalis, and nonsteroidal anti-inflammatory drugs.\(^2–5\) For instance, a significant reduction in serum and TBK by diuretics has been related to an increased risk of cardiac arrhythmias, glucose intolerance, and abnormal lipid metabolism, whereas replacement of this ion has been shown to decrease the risk of arrhythmias and thiazide-induced hyperglycemicas.\(^18\) Unfortunately only a measure of serum or plasma K is usually obtained in these patients.

A more reliable index of cell K transport involves the measurement of ATPase activity and intracellular ions in RBC, an “organ system” affecting not only plasma K but kidney K excretion. In this context the relative changes in RBC K permeability have been found to be increased in patients with compensated renal insufficiency compared to a control group and diabetic patients,\(^19\) suggesting a role of RBC in plasma K regulation; whereas the strong correlation between changes in RBC K content and renal K excretion after intravenous furosemide in normal subjects (\(r = -0.94\))\(^20\) suggests a signaling mechanism for tubular K excretion. This role of RBC is further supported by the rapid stimulation of unidirectional K and net K transport in RBC, just 120 sec after suspension of these cells obtained from rested subjects into exercise-stimulated plasma, which implies a feedback K mechanism between RBC and skeletal muscle during intensive exercise.\(^21\) Interestingly, in K-depleted Sprague-Dawley rats and spontaneously hypertensive rats, RBC and plasma K are rapidly reduced,\(^16\) along with a decreased aortic and skeletal muscle K,\(^17\) suggesting that intracellular K deficit extends to tissues beyond RBC.

In human beings, RBC accounts for 7% of TBK (~250 mmol) and has a complex machinery for ion transports (K, Na, Mg, HCO\(_3\), and H\(^+\)) and a physiologic role in arterial pH balance (Bohr’s effect). Such physiologic functions and the relative ease of the methodologic approach have made the RBC the most suitable model for the study of biochemical and genetic abnormalities of ion transport systems in essential hypertension.\(^4,7,16,19–25\)

### Assessment of Renal Potassium Excretion

Usually, the renal function of K handling in hypertensive patients is evaluated by measurement of K in urinary samples (spot or 24-h), K clearance, or Na/K and creatinine/K molar ratio. However, the exact mechanism by which dietary K stimulates or suppresses the in vivo renal K excretion remains unresolved.\(^26\) For instance, urinary K is usually increased in diuretic-treated hypertensive patients, but also has been observed in healthy normotensive athletes on prolonged hypokinesia. In both groups, negative K balances occurred despite normal plasma K (3.5 mmol/L to 5.0 mmol/L), whereas in all of them the urinary K excretion became greater with the addition of supplements of K.\(^27,28\) How and why this occurs is a matter of debate. In this context, transtubular K gradient (TTKG) may improve such evaluation.\(^29,30\) A recent 2-year follow-up trial in more than 300 hypertensive patients from our laboratory\(^31\) found that the lower TBK and RBC K were the key findings explaining the lower TTKG, suggesting that the tubular cells were responding to the cell K content rather than to plasma K. In fact, one half of these subjects had nocturnal polyuria (>1.15 mL/min),\(^32,33\) a renal functional disorder in K depletion.\(^3,8\) Although no other laboratory has conducted this evaluation, our findings might be important in hypertensive patients on DASH diet or K supplements, as an increased dietary K would be of little value without correcting the defective mechanisms in cell K transport.\(^2–6,13–16,27,28\)

### Assessment of Body Potassium Stores

Since the first measurement of TBK in the 1960s, whole-body K has been an important study in assessing body K homeostasis, leading to predictive equations of TBK in normal individuals. In healthy persons, TBK amounts to 53 to 55 mmol/kg of body weight (3700 to 3800 mmol of K for a 70-kg man), an average of 150 mmol/L of cell water, or 109 ± 6 mmol/kg of cell. These values allow an estimation of body cell mass (BCM[kg] = TBK mmol/108.6), with differences in age, sex, and ethnicity, which should be considered in longitudinal studies in essential hypertension.\(^34\) For example, African Americans were found to have a greater TBK decline with age (95 to 112 mmol/decade in men), and also a decreased tolerance for an intravenous K load, despite unchanged serum and uri-
nary K compared with their white counterparts, suggesting a functional disorder in cell K transport or uptake.

Unfortunately, TBK has been “the missing tool” in the physiologic assessment of K in hypertensive patients, with only a few studies conducted two decades ago. Ericsson reported lower TBK (87%), and decreased erythrocyte and muscle K in hypertensive patients, whereas Beretta-Piccoli et al suggested that lower TBK was an important finding in the early stages of hypertension. Other findings included the TBK depletion by diuretic thiazide, as well as its increase with the use of amiloride, but with little information on the effects of angiotensin-converting enzyme inhibitors, β-blockers, or angiotensin type II receptor blockers. More recently, a reassessment of TBK has been suggested in hemodialysis patients because of the decline of TBK with age (0.23 to 0.26 mmol/kg per year) and on those affecting TBK in hypertension, the gold standard measurement of TBK is still complex, impractical, and expensive for clinical use.

A more available technique for estimating TBK is the bioelectrical impedance analysis (BIA). Although the predictive equation for TBK, TBK-derived BCM and FFM bioelectrical impedance analysis (BIA). Although the predictive equation for TBK, TBK-derived BCM and FFM have been accurately validated by body 40K counting, dual X-ray absorptiometry, or deuterium dilution in healthy individuals and in renal and surgical patients, only two studies have considered the usefulness of BIA in estimating TBK in hypertension. We reported first that hypertensive patients had lower TBK and TBK/FFM ratios compared with normal subjects in the presence of increased arterial stiffness and pulse wave velocity, suggesting a critical role of body K homeostasis in the regulation of BP and vascular compliance. However, the GenNet investigators reported a gender difference in TBK and vascular compliance in healthy subjects independent of age, height, and weight, providing a good explanation for the unexpected higher arterial stiffness in female than male subjects. In general these findings strongly support the inclusion of BIA research in hypertension and cardiovascular disease.

### Low RBC K as an Intermediate Phenotype in Hypertension

For years, a decreased RBC K measured by emission spectrophotometry (<92 mmol/L of cell), or nuclear magnetic resonance (<148 mmol/L) has been found in hypertensive individuals and their normotensive offspring, despite normal K-diet and serum K fraction. These observations, initially related to Na/K ATPase disorder, have recently been challenged by the reports of a non–sodium-dependent low RBC K in hypertensive subjects with normal plasma K and dietary K intake. This finding was characterized as a new intermediate phenotype in essential hypertension because of its bimodal distribution in normotensive young offspring of hypertensive patients, and its correlation with systolic BP in these adolescents and with diastolic BP in untreated hypertensive patients.

Furthermore the recent observation that reversal of this abnormal RBC K content was associated with a decline and better control of BP, fasting plasma glucose, and regression of the ST-T alterations in hypertensive patients with LVH or CAD, supports a more thorough evaluation of cell K transport in clinical and experimental models of essential hypertension (Table 1). In effect the progressive improvement of the ST-T changes as well as symptoms of heart failure or angina observed in our patients in a trial of low-dose amiloride and calcium gluconolate was supported by the reports of an increased TBK with amiloride, and the experimental evidence that this drug, loop diuretics, and digitalis have identical effects on the myocardium, nephron, and RBC. Unfortunately, the beneficial effects of other K-sparing drugs such as spironolactone or eplerenone on cell K transport have not been evaluated.

<table>
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<th>Table 1. Proposed clinical and research methods of evaluation of cell K physiology in essential hypertension</th>
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<tr>
<td><strong>Primary Attending Center</strong></td>
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<tr>
<td>Plasma K(*)3,9,11 12-h urine K (night)31-33 TTKG29-31 TBK/BIA31,38,39,41,42 TBK/FFM39,40 FPG10,18 ECC51-54</td>
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TTKG = (trans-tubular K gradient); TBK/BIA = total body K by bioelectrical impedance analysis; FFM = fat-free mass; FPG = fasting plasma glucose; ECC = electrocardiogram; RBC = red blood cells; TBW = total body water; ECW = extracellular water space; ICW = intracellular water space.

Superscript numbers are references except in 40K.

* Serum K ≥0.3–0.5 mmol than plasma K.
Although this approach opens new insights in the management of CAD, it is surprising that these ST-T alterations have received such little attention by most investigators, even when the improved ventricular repolarization abnormalities result in lower morbidity and mortality for all cardiovascular events in hypertensive persons with LVH or CAD.\textsuperscript{54–56} Finally it should be noted that comparable ST-T changes may be induced by diuretics, $\beta$-blockers, or calcium channel blockers, implying a role for body or cell K homeostasis on the normal repolarization of the ventricles.

**Conclusion**

In summary, to assess cell K physiology in hypertensive patients, clinicians should recognize the following. First, some of the K alterations observed in clinical practice are the consequences of inappropriate K diet, drugs affecting the cell K transport, and the genetic control of the individual’s cell K transport. Second, the usual measurement of serum K does not reflect cell K homeostasis. Third, it is more likely that the patients would present with clinical alterations related to K deficiency, such as loss of BP control, nocturnal polyuria, ventricular repolarization changes or cardiac arrhythmias, despite a normal serum K. Therefore, under ideal conditions, several methods would be available to estimate extracellular K regulation, including the following: 1) determination of plasma K and blood pH, with insulin and aldosterone levels; 2) profile of cell K uptake through the measurement of RBC K values, Na and water contents, and Na/K ATPase activity in these cells; 3) assessment of renal K handling by the measurement of TTKG, Na/K ratio; 4) evaluation of the circadian rhythm of water and electrolyte excretion in timed urinary samples; and 5) the estimation of body K content from the measurements of body $^{40}$K counting and the BIA-derived TBK values, as compared with their predictive values for sex, age and ethnicity in normal individuals. In this context, a more accurate evaluation of K metabolism and cell K physiology would aid in explaining how dietary K, cell K transport or a coding genetic defect are involved in the pathogenesis and management of essential hypertension.

**Acknowledgment**

The author thanks Lillian Gleiberman for her valuable assistance in editing this article.

**References**


