An integrated view of potassium homeostasis

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was a similar trend favoring patency in patients who received statins. Also, treatment with a drug-coated balloon was associated with improved patency over a conventional balloon in both patients receiving statins and those not receiving statins. The beneficial effects of statins may be additive to those of drug-coated balloons.

In summary, our trial showed that angioplasty with a drug-coated balloon maintained vessel patency that was superior to that of angioplasty with a standard balloon, and it showed superiority for a functional end point on the Walking Impairment Questionnaire. We agree that all patients should receive maximum tolerated doses of statins and that data from larger studies are lacking to confirm the beneficial effects on quality of life and physical functioning conferred by angioplasty with a drug-coated balloon over conventional angioplasty with a standard balloon.

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An Integrated View of Potassium Homeostasis

TO THE EDITOR: The review article by Gumz et al. (July 2 issue) on renal potassium handling focuses on the cortical collecting duct. We would emphasize the emerging recognition of the role of the distal convoluted tubule in potassium homeostasis. Dietary potassium was recently shown to rapidly (within minutes) inactivate the sodium–chloride cotransporter in the distal convoluted tubule. This induced natriuresis and kaliuresis, probably by increasing sodium delivery to potassium secretory segments. Because aldosterone does not mediate this process, it is part of the feed-forward kaliuretic reflex. In another study, potassium-induced natriuresis was preserved in a model of depletion of extracellular fluid volume (which normally results in avid sodium reabsorption); this indicates the physiologic importance of this process. The opposite is also true — a low-potassium diet activates the sodium–chloride cotransporter. With such a diet, activity of the sodium–chloride cotransporter increases through changes in cell-membrane voltage, intracellular chloride, and kinases that regulate the sodium–chloride cotransporter. Clinically, the activation of the sodium–chloride cotransporter by a low intake of dietary potassium may explain the well-known link with salt-sensitive hypertension. In summary, the distal convoluted tubule acts as a potassium sensor and affects downstream potassium secretion by regulating sodium delivery.

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TO THE EDITOR: As Gumz et al. correctly state, “the healthy kidney has a robust capacity to excrete potassium,” and most people can ingest very large quantities of potassium without clinically significant hyperkalemia. However, it is not
widely known that excessive ingestion of potassium-rich foods or drinks because of a psychiatric disorder can cause clinically significant hyperkalemia in people with healthy kidneys and adrenal glands who do not have precipitating factors such as diabetes or the use of potassium-sparing medications. For example, in an adolescent with anorexia nervosa, recurrent hyperkalemia occurred with obsessive eating of up to 20 bananas per day. Hyperkalemia developed in another patient who had schizophrenia and psychogenic polydipsia when she replaced the water in her diet with orange juice. Finally, recurrent hyperkalemia due to excessive ingestion of dried fruits developed in a healthy person, possibly because of an undiagnosed eating disorder.

Excessive consumption of potassium-rich foods or drinks because of a mental disorder should be considered in the differential diagnosis of unexplained hyperkalemia in otherwise healthy people. A careful history regarding the patient’s dietary habits should be obtained.3

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TO THE EDITOR: Gumz et al. propose that circadian clocks within renal tubular cells are accountable for the kaliuretic effect of aldosterone. Yet, another paradoxical phenomenon also contributes to the kaliuretic effects of aldosterone: during volume depletion, aldosterone increases sodium reabsorption without increasing potassium secretion. Conversely, in hyperkalemic states, aldosterone leads to potassium secretion without increasing sodium reabsorption. This effect is mediated through angiotensin II, which activates the sodium–chloride cotransporter and epithelial sodium channel (ENaC) and inhibits the potassium channel (ROMK); this happens with no signaling of lysine-deficient protein kinase 4, so there is no increase in potassium excretion. Furthermore, hyperkalemia without volume depletion also occurs because of low angiotensin II levels and aldosterone-activated sodium reabsorption through the ENaC and potassium secretion through ROMK.1

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THE AUTHORS REPLY: We agree with Hoorn and colleagues that the late distal convoluted nephron participates in potassium homeostasis. This is shown in Figure 2 of our article.

Hoorn et al. cited a study by Sorensen et al.1 that examined the effect of the administration of a large potassium load by means of gastric lavage that increased the plasma level to approximately 9 to 11 mmol per liter in sodium–chloride cotransporter–null and control mice. Sorensen and colleagues proposed that this maneuver inhibited activity of the sodium–chloride cotransporter in the early distal convoluted tubule and enhanced delivery of sodium to the late distal convoluted tubule, the connecting tubule, and collecting duct. According to this model, potassium secretion in these latter segments is limited by sodium delivery, and the shift of sodium absorption from the early distal convoluted tubule to these downstream segments explains the observed kaliuresis. However, even modest increases in the plasma potassium level that are less than the values observed by Sorensen et al. have been shown in in vivo microperfusion studies to directly increase potassium secretion by cells in the distal nephron when the luminal perfusion rate and sodium delivery are held constant; thus, an alternative explanation of the results of Sorensen et al. merits consideration. In addition, because the kaliuretic response occurred before a change in plasma aldosterone,
Hoorn et al. propose that this hypothesized kaliuretic mechanism is a component of the feed-forward kaliuretic reflex. According to our current understanding, however, a feed-forward system requires neither a change in the plasma aldosterone level nor a change in the plasma potassium level.

Pavletic calls attention to an uncommon cause of hyperkalemia. The clinician should be able to identify it from a careful history.

Ardalan and Golzari interpret our article to mean that the circadian clock is responsible for a kaliuretic effect of aldosterone. To clarify this point, the primary and consistent effect of aldosterone on external sodium and potassium balance is to promote sodium retention, which is observed regardless of the time of day when aldosterone is administered. Aldosterone has important effects on internal potassium homeostasis by stimulating plasma membrane pump–leak kinetics and by its action to preserve sodium balance and blood pressure. Long-term mineralocorticoid stimulation reduces the level of plasma potassium in the absence of discernible changes in the level of total-body potassium. Conversely, the study of Todkar and coworkers involving aldosterone synthase–null mice shows that appropriate excretion of potassium occurred in the complete absence of aldosterone. These mice excreted a high physiologic, but not supraphysiologic, level of potassium as long as other compensatory systems were preserved.

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Nitroglycerin and Nitric Oxide — A Rondo of Themes in Cardiovascular Therapeutics

TO THE EDITOR: Steinhorn et al. (July 16 issue) note “anecdotal evidence” of “Sunday heart attacks” caused by withdrawal from nitroglycerin in an occupational setting. In reality, since 1882, considerable research involving people who worked with dynamite has validated such withdrawal syndromes (e.g., headaches, angina, and heart attacks). The authors further note that sildenafil was originally designed as an antiangiinal drug and then was shown to be an effective treatment for erectile dysfunction. However, they did not voice any concerns about similar effects of withdrawal associated with the use of phosphodiesterase type 5 inhibitors.

The exponential worldwide sales of longer-acting cyclic guanosine monophosphate phosphodiesterase inhibitors for daily use and the obvious marketing to younger populations suggest that a large proportion of the male population may be at risk for withdrawal syndromes that were previously noted only in workers with long-term exposure to nitroglycerin. Perhaps a more appropriate theme for this drug discovery may be “bench to bedside to bedroom to grave.”

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