Hypokalemic weakness in hyperaldosteronism: Activity-dependent conduction block

Abstract—The authors describe a 48-year-old man who presented with acute weakness. Serum K^+ was 1.7 mmol/L, and investigations established hyperaldosteronism. Nerve excitability studies during hypokalemia demonstrated that axons were of high threshold with a fanning out of threshold electrotonus, consistent with hyperpolarization. Activity-dependent conduction block was induced by voluntary contraction. Excitability abnormalities resolved with K^+ replacement. Activity-dependent conduction block induced by normal activity may contribute to weakness and paralysis developing with hypokalemia.

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Hypokalemic weakness and paralysis are potentially reversible emergencies that may develop secondary to inherited disorders (e.g., hypokalemic periodic paralysis) or acquired disorders of K^+ wasting.[1] While reduction in K^+ alters resting membrane potential,[2] the mechanism whereby hypokalemia produces weakness remains unclear. Axonal ion channel function may be investigated in vivo using novel excitability methods, recently adapted for clinical use.[3] In the present case, we used excitability techniques to investigate the cause of weakness in a patient with severe hypokalemia.

Case report. A 48-year-old Chinese man presented with an acute 3-day history of progressive, generalized weakness, with initial onset in the proximal lower limbs and later involving the upper limbs. There was no muscle pain. Intercurrent history included hypertension treated with enalapril and metoprolol. There was no family history of neurologic disease.

On neurologic examination, there was generalized limb weakness, graded as follows: Medical Research Council grade 3 for shoulder abduction and adduction; 4 for elbow and wrist flexion and extension; 5 for finger extension; 3 for hip flexion and extension; 4 for knee flexion, knee extension, and ankle dorsi- and plantarflexion. Tendon reflexes were normal. The remainder of the examination was normal.

Investigations established an initial serum K^+ of 1.7 mmol/L (normal 3.6 to 5.1 mmol/L) and normal serum Na^+, urea, and creatinine. Serum HCO_{3-} concentration was 34 mmol/L (normal 22 to 32 mmol/L). Thyroid function tests excluded thyrotoxic periodic paralysis (serum TSH 0.9 mU/L, normal 0.1 to 3.8; T3 4.1 pmol/L, normal 2.3 to 7.1; free T4 22.9 pmol/L, normal 9.8 to 23.8). Hypokalemic paralysis was initially diagnosed and K^+ replacement commenced at 15 mmol/h. Serum K^+ and limb muscle power returned to normal over 4 days.

Subsequent MRI of the abdomen demonstrated a left adrenal lesion. Basal aldosterone was elevated (1,398 pmol/L, normal <400 pmol/L) and serum renin was reduced (3.5 pg/mL, normal >5.4). Hyperaldosteronism was established following salt loading (basal aldosterone 1,398 pmol/L, post-loading 2,648 pmol/L). Left adrenalectomy revealed cortical adenoma, confirming Conn syndrome.

Methods. Excitability studies were undertaken following stimulation of the median nerve (figure 1A).[3] The patient gave informed consent to the procedures, which were approved by our regional and institutional review boards. The median nerve was stimulated at the wrist and compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis (APB). Stimulus-response behavior, threshold electrotonus (marker of internodal axonal function), current threshold relationships (measure of inwardly rectifying K^+ conductances), refractoriness (due to inactivation of transient Na^+ channels), superexcitability (determined by paranodal fast K^+ channels), and late subexcitability (determined by slow K^+ channels)[3] were recorded. Excitability was also assessed before and after maximal voluntary contraction (MVC) of APB against resistance for 60 seconds. Stimuli were delivered at 0.8-second intervals and rotated sequentially through channels (figure 1B). Excitability values were compared to previous normative values for a single subject (mean ± SD).[3] Values for MVC were compared to data obtained from 12 control subjects (age range 22 to 63 years).

Results. Excitability studies on day 2 (serum K^+ 2.4 mmol/L), established that the maximal CMAP amplitude was reduced (1.1 mV, normal 4.7 ± 1.3 mV). No response could be generated using a test stimulus of 0.2 millisecond, confirming that axons were of high threshold.

During acute hypokalemia, abnormalities were noted in threshold electrotonus (figure 2A), particularly during hyperpolarizing threshold electrotonus at the 90- to 100-millisecond interval (−246%, normal −121 ± 15%).

Prominent abnormalities were also noted during the recovery cycle (figure 2B). In particular, late subexcitability was increased with hypokalemia (29.8%; normal 14.8 ± 3.8%). Superexcitability was at the upper limit of normal (−28.2%, normal −25.3 ± 5.5%). Relative refractory period was normal (3.3 milliseconds, normal 3.1 ± 0.4). All excitability measures returned to normal following correction of hypokalemia with IV K^+ replacement (figure 2, C and D).

Excitability changes induced by MVC. To establish whether excitability changes were due to axonal hyperpolarization, a range of axonal excitability parameters were recorded before and after MVC of APB for 60 seconds. Activity alters resting membrane potential through effects mediated by the Na^+/K^+ pump,[4] with membrane depolarization during contraction, followed by an increase in Na^+/K^+ pump activity after contraction,[5] causing membrane hyperpolarization.

The threshold increase (channel 1) following MVC was greater in the patient with hypokalemia (figure 3A) than in controls (24.3%, normal 15.5 ± 3.1%) and failed to re-

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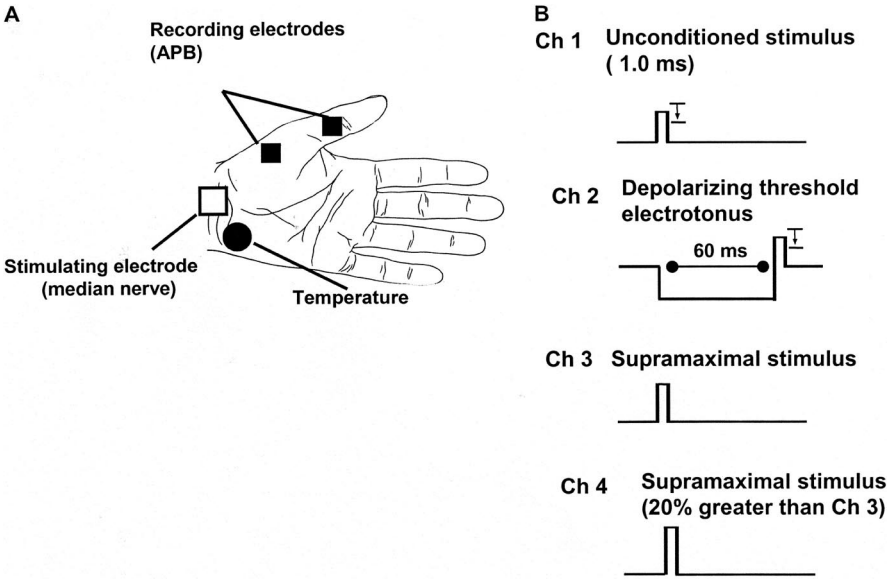

Figure 1. (A) Experimental paradigm. Excitability studies were undertaken following stimulation of the median nerve (clear squares) with the resultant compound muscle action potentials (CMAP) recorded from abductor pollicis brevis (APB) (filled squares). (B) Configuration of stimulus patterns. Vertical arrows indicate threshold tracking of test potential (set to 40% of the maximal potential). On channel (Ch) 1, a 1-millisecond stimulus was delivered and proportional tracking achieved the target response, set to 40% of the precontraction maximal CMAP. On channel 2, a depolarizing conditioning stimulus of 60-millisecond duration, set to 40% of threshold, preceded the test stimulus. On channel 3, a fixed supramaximal stimulus was delivered to produce a CMAP of maximal amplitude. A stimulus 10% greater than that on channel 3 was delivered on channel 4, ensuring that the CMAP on channel 3 was truly maximal. Stimuli were delivered at 0.8-second intervals and were rotated through the four channels sequentially.

turn to baseline within 10 minutes post-contraction (figure 3A). The change in threshold was accompanied by an increase in depolarizing threshold electrotonus (figure 3B), appropriate for axonal hyperpolarization, and again greater in the patient (33.4%, normal 21.2 ± 3.4%).

MVC induced conduction block, with a 73% reduction in the amplitude of the maximal CMAP (figure 3C). Maximal CMAP amplitude also failed to return to baseline within 10 minutes after MVC. There was no reduction in maximal CMAP amplitude for controls. The abnormalities in CMAP amplitude and depolarizing threshold electrotonus in the hypokalemic patient resolved with IV K^+ replacement.

Discussion. In this study, we used axonal excitability to investigate the mechanism of weakness in a patient with profound hypokalemia. There were major abnormalities in axonal excitability induced

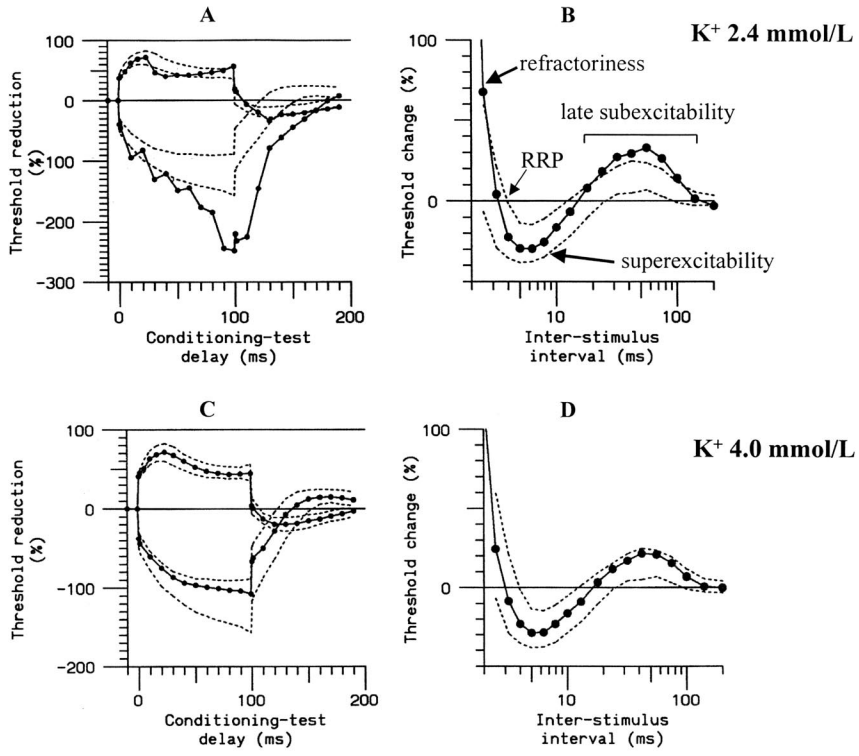

Figure 2. Threshold changes during threshold electrotonus using 100-millisecond duration polarizing currents set to ± 40% of the resting threshold (A, C). Changes are plotted as threshold reductions, with depolarization represented in an upward direction and hyperpolarization in a downward direction. The figure shows recordings from our patient (continuous lines with circles), during hypokalemia (A) and after K^+ replacement (C), with 95% CIs of mean data previously established for normal controls[3] (dotted lines). Recovery cycles (B, D) recorded from our patient with hypokalemia (continuous lines with circles) with 95% CI of mean data for normal controls (dotted lines). Refractoriness was measured as the percentage increase in threshold at a conditioning test interval of 2.5 milliseconds. RRP (ms) refers to the first intercept on the x-axis. Superexcitability, expressed as the percentage of change in the threshold current, was measured as the minimum mean of three adjacent points and late subexcitability (%) as the maximum mean of three adjacent points after 10 milliseconds.

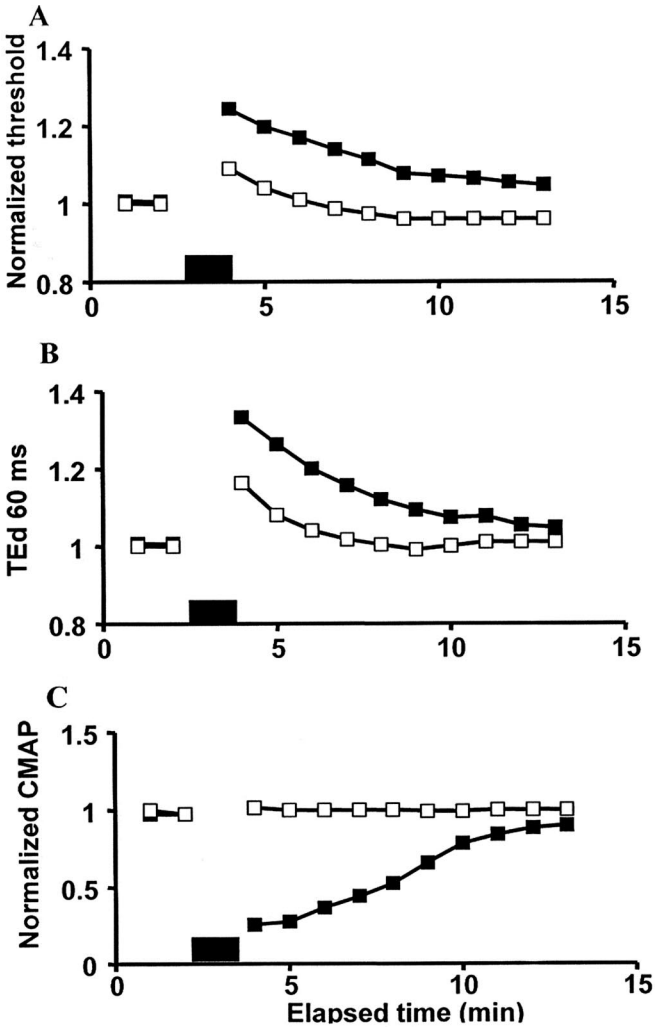

Figure 3. Excitability changes following maximal voluntary contraction, at serum K^+ concentrations of 2.4 mmol/L (filled symbols) and 4.0 mmol/L (clear symbols). Threshold and amplitude changes are normalized to precontraction values. Black bar indicates period maximal voluntary contraction. (A) Normalized threshold for a 1-millisecond stimulus. (B) Threshold electrotonus recorded using a depolarizing conditioning stimulus of 60-millisecond duration (Ted 60 millisecond), set to 40% of threshold. (C) Normalized maximal compound muscle action potential (CMAP) amplitude.

by hypokalemia; axons were of high threshold, with a fanning out of threshold electrotonus[6,7] and increased subexcitability, consistent with axonal hyperpolarization. Threshold tracking during the hypokalemic period demonstrated activity-dependent conduction block after normal activity, with resolution following IV K^+ replacement.

Hyperaldosteronism per se would not be expected to cause these excitability changes. Any effect of aldosterone on motor nerve excitability would be mediated through alteration in serum K^+ rather than by a direct hormonal effect on motor nerves.[8]

It must be acknowledged that alteration in muscle membrane excitability may contribute to the activity-dependent changes recorded in the present study, as moderate K^+ deficiency may lead to muscle membrane hyperpolarization. The distinction between muscle and nerve factors is not clear-cut, although nerve excitability measures are generally accepted to be determined by local factors at the stimulating electrode[6] and therefore more likely to reflect neural rather than muscle excitability. Arguing against a significant muscle contribution to the clinical weakness, previous in vitro studies showed that extreme K^+ deficiency leads to muscle membrane depolarization, opposite to the changes demonstrated in the present case.[9]

While changes in threshold electrotonus were consistent with hyperpolarization, the increase in subexcitability would be unexpected.[6] Subexcitability is determined by activation of nodal slow K^+ channels and the difference between membrane potential (E_r) and potassium equilibrium potential (E_k). Hypokalemia leads to reductions in extracellular K^+, such that ($E_r - E_k$) increases,[6] suggesting that hypokalemia is driving axonal hyperpolarization. It is important to emphasize that these excitability changes are unlikely to be those observed in hypokalemic periodic paralysis due to a primary muscle membrane channel defect and in which there is a short-term shift of K^+ into cells[1] rather than the large deficit in total body K^+ described in the present case.

Activity-dependent conduction block was first demonstrated in demyelinated nerve fibers that became hyperpolarized by tetanization.[5] Conduction failure was prevented by applied depolarization, establishing that activity-dependent conduction block was due to axonal hyperpolarization causing decreased excitability of the blocking node.

This phenomenon has recently been demonstrated in patients with demyelinating neuropathies, such as chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy.[7] In the present case, there were no clinical or neurophysiologic features to suggest demyelination. The rapid clinical improvement with K^+ replacement would also not be consistent with demyelination. The mechanism of activity-dependent conduction block is intrinsically linked to hypokalemia and its effects on the Na^+/K^+ pump, supporting earlier studies demonstrating axonal hyperpolarization due to extracellular K^+ depletion.[10]

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Posterior circulation infarct after bronchial artery embolization and coiling

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A 51-year-old left-handed woman developed acute hemoptysis. The day after admission, her bronchoscopy showed active bleeding in the apical segment of the right upper lobe. Pulmonary angiography showed a small vascular lesion in the apex. The right bronchial artery was embolized using 300- to 500-μm Embosphere microspheres and three 2 x 10–mm coils. The patient had a headache the following day. Noncontrast CT showed multiple hypodensities in the cerebellum. Follow-up MRI showed multiple areas of infarct.

Her echocardiogram showed no evidence of an intracardiac source of embolism. No bubble testing was done.

Her exam showed a slight vertical skew of her eyes, with slight horizontal hypometria and vertical nystagmus. Her right arm was slower than the left for rapidly alternating movements. Finger–nose–finger testing showed postpointing bilaterally. Her right arm drifted downward during arm extension while standing (Romberg testing).

Her Mini-Mental State Examination score was 23, with her missing the day and date, the county, town or city, and one item on distant recall. We do not think her missing the county and town or city pertinent as she was transported from another hospital. Her clock and intersecting pentagons were correct. Her sentence was grammatically correct and showed good penmanship. Her affect was flat. No telangiectasias were seen on her skin or tongue.

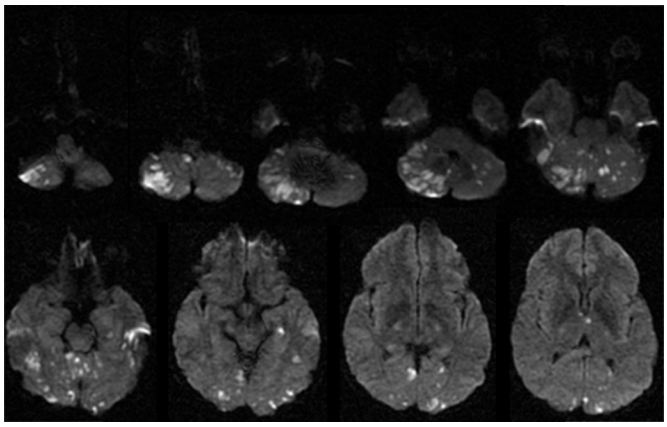

Figure. Diffusion-weighted images go from inferior to superior from left to right and top to bottom. They show multiple areas of same-size focal infarcts in a posterior circulation distribution. Imaging was performed 2 days after the right bronchial artery embolization.

Infarction with only posterior circulation distribution due to cardiac or idiopathic source of embolism has been reported.[1] We wonder if other incidents such as this may occur without being detected owing to the minimal symptoms, similar to that seen with some patients after coronary artery bypass graft (figure).[2]

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