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Using lectures to identify student misconceptions: a study on the paradoxical effects of hyperkalemia on vascular smooth muscle

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INTRODUCTION

Students find specific topics in physiology challenging to understand. Numerous publications identify misconceptions or misunderstanding of critical concepts in this discipline (8, 16, 17, 22, 28, 30). Physiology may be perceived as a challenging subject due to its integrative nature, the requirement for causal reasoning, use of graphs and mathematics, and the tendency of students to try to memorize rather than understand and apply foundational concepts (16). Misconceptions, on the other hand, can arise from several sources, such as preconceived notions, nonscientific beliefs, conceptual misunderstandings, and other conflicting ideas on which students may have mentally fixated (18).

We identified a paradoxical concept during the teaching of physiology to medical students; this concept involves the physiology of hyperkalemia in vascular smooth muscle (SM), namely that of membrane hyperpolarization, vascular SM relaxation, and resultant vasodilation (9, 29). This observation is counterintuitive, as students are taught that the Nernst equation predicts cell depolarization with increases in extracellular K⁺ concentrations ([K⁺]) (7). Hyperkalemia typically causes depolarization, which results in skeletal muscle contraction and increases in tension; however, the cause of the depolarization and effect on specific tissues are crucial to one’s understanding. We aimed to identify the cause of misunderstanding of this paradoxical concept.

Two prerequisite concepts are required in order for students to understand this specific hyperkalemic paradox. First, acute hyperkalemia causes a local increase in K⁺ due to the increased activity of excitable tissues, and, second, acute hyperkalemia affects vascular SM, resulting in vasodilation and decreases in tension. Regarding the first concept, it is well known that acute hyperkalemia occurs during exercise, i.e., metabolic hyperemia or exercise-induced hyperemia. Active muscles release K⁺ ions into the local circulation, primarily through the delayed rectifier K⁺ and the ATP-sensitive K⁺ channels (24). While normal blood potassium levels are 3.6–5.5 mM (15), levels rise up to between 5.4 and 9 mM locally during exercise and take 3–5 min postexercise to return to basal levels (1, 11–13, 24, 32).

Second, activity-induced hyperkalemia mediates vasodilation of vascular SM, a response that is vital for the local control of blood flow, especially in the cerebral, coronary, renal, and skeletal vascular circulations (5, 7, 9, 23). At physiological membrane potentials (Vm), the elevation of extracellular [K⁺] from basal levels to 5–15 mM results in proportional vasodi-
lution and increases muscle blood flow (5, 12, 20, 23, 24). It should be noted that extracellular [K⁺] greater than ~15 mM results in the opposite effect: depolarization and vasconstriction of vascular SM cells (14, 20). Thus moderate elevations in serum K⁺ due to increased tissue activity caused by neuronal or muscle activation can paradoxically result in vascular hyperpolarization and vasodilation (29).

The mechanism involved in the initial steps of hyperkalemia-mediated SM relaxation is K⁺-induced vasodilation (9, 20). This is due, in part, to changes in the inward rectifier K⁺ (Kir) channel and the release of intracellular inhibition by Mg²⁺ and polyamines, which shifts the current-voltage curve to more positive values and increases the outflow of K⁺ ions (14, 20). Hyperkalemia also results in activation of the Na⁺-K⁺-ATPase pump (2–5, 7, 9, 20, 24, 26). Both of these effects result in hyperpolarization of the vascular SM, membrane voltage-dependent closing of the L-type calcium channels, and resultant relaxation and vasodilation of vascular SM (2–5, 7, 24, 26) (see Fig. 2A). Indeed, Na⁺-K⁺-ATPase pump activation overcomes the small depolarizing effects due to hyperkalemia (7). Additionally, SM cells have a more positive resting potential (between −35 and −55 mV), which explains how increases in extracellular potassium, especially when reaching hyperkalemic values, can promote hyperpolarization (6, 33) (see Fig. 2C). These changes in conductance, Na⁺-K⁺-ATPase pump activity, and higher resting Vm of vascular SM may contribute to a student’s incomplete understanding of the paradoxical effects of hyperkalemia. To clarify, we note that hyperkalemia is not the only effector of exercise-induced hyperkalemia (24).

To identify flaws in logic regarding paradoxical hyperkalemia, we asked medical students a panel of questions as part of a didactic, first-semester basic sciences physiology lecture. We probed the understanding of the paradoxical effects of hyperkalemia. To test this hypothesis, we probed their understanding of three key physiological concepts: Vm, conductance, and SM response. This study was determined to be exempt by the St. George’s University’s Institutional Review Board (IRB), Ages, ethnicity, and overall academic performance of participating students were not collected in this IRB-exempt study. In-class questions were administered to two equivalent spring terms (cohort A = 476 and cohort B = 384) of first-semester basic sciences medical students at St. George’s University. The question set 1 was presented to cohort A, whereas the question set 2 was given to cohort B. This medical school recently underwent a change from a disciplines-based to a systems-based curriculum in 2016. All students involved in this study were from the systems-based curriculum.

The questions aimed to identify various potential misconceptions regarding the role of K⁺ in local control of blood flow based on the senior author’s previous experience teaching physiology and preparing exam questions. First-semester medical students were asked a sequence of questions to assess their understanding of the relationships between hyperkalemia and depolarization, in addition to their effects on SM. Questions were asked during a lecture after the professor explained that elevated K⁺ results in vasodilation due to the effects of local control. The mechanism of action, however, was not discussed until afterward, during the same lecture. This lecture shared similar content with both class terms (cohorts A and B) and was delivered by the same professor. The students’ responses were polled and collected using the TurningPoint clicker response system. The students were given 60 s to answer and discuss the questions among each other during each response interval.

We drafted two question panels for this study (Fig. 1, Tables 1 and 2, and appendix Tables A1 and A2). The first panel made use of the nested set model to evaluate the sequential effects of hyperkalemia. A nested set model is one in which each question relies on hierarchical data or information from its preceding or parent question. The second question panel was developed following the analysis of the initial question set (Table 1), as analysis of the first question set indicated a need to further assess comprehension of underlying physiological concepts (Table 2), such as DF and conductance. Thus the second question panel was administered in a similar manner for the similar first-semester cohort of medical school students.

RESULTS

First-semester basic sciences medical students were asked a series of questions to assess their understanding of the relationship between hyperkalemia and depolarization in vascular SM. The maximal response rate was 86.5% (n = 412/476) for question set 1 and 85.9% (n = 330/384) for question set 2. The first question set examined sequential relationships between hyperkalemia and depolarization (Fig. 1). The students demonstrated confusion regarding whether hyperkalemia

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**Fig. 1.** Diagram depicting logical flow of the different question sets. A: question set 1 probed the sequence of the effect of hyperkalemia as well as the direct effect on smooth muscle (SM). Since this question set evaluated sequential effects of hyperkalemia, we view them as nested or hierarchical. A nested set model is one in which each question relies on hierarchical data or information from its preceding or parent question. B: question set 2 addressed underlying mechanisms involved in the effect of hyperkalemia on SM (i.e., driving force and conductance) that were not addressed in the first question set. This set also addressed the effect of hyperkalemia on SM, but clarified the target muscle as vascular. This question set was termed as linear: the questions probed independent concepts. T, true; F, false.

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**TABLE 1.** First-semester basic sciences medical students were asked a series of questions to assess their understanding of the relationship between hyperkalemia and depolarization in vascular SM. The maximal response rate was 86.5% (n = 412/476) for question set 1 and 85.9% (n = 330/384) for question set 2.

| Question Set 1 | Question Set 2 |
|----------------|----------------|
| Hyperkalemia   | Hyperkalemia   |
| Depolarization | SM contraction |
| SM relaxation  | SM driving force |
| SM contraction | SM K⁺ conductance |
| 51.6% T        | 70.3% T        |
| 51.3% F        | 30.6% T        |
| 67.0% F        | 73.0% F        |

**METHODS**

We aimed to identify medical students’ conceptual errors in comprehension of the paradoxical effect of exercise-mediated hyperkalemia on SM. We evaluated students’ knowledge of three physiological concepts: Vm, conductance, and SM response. This study was determined to be exempt by the St. George’s University’s Institutional Review Board (IRB). Ages, ethnicity, and overall academic performance of participating students were not collected in this IRB-exempt study. In-class questions were administered to two equivalent spring terms (cohort A = 476 and cohort B = 384) of first-semester basic sciences medical students at St. George’s University. The question set 1 was presented to cohort A, whereas the question set 2 was given to cohort B. This medical school recently underwent a change from a disciplines-based to a systems-based curriculum in 2016. All students involved in this study were from the systems-based curriculum.

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results in depolarization of cells, as only 51.6% of students correctly identified the statement as true (Table 1, question 1A). This response suggested an incomplete understanding of DF, which relates equilibrium potential (V_{eq}) from the Nernst equation to V_{m}. This misunderstanding is likely attributed to the nested or hierarchical structure of the questions. Despite this result, a large proportion of students (67.0%) correctly indicated that depolarization does not result in SM relaxation (Table 1, question 2A). Lastly, a majority of students did not comprehend the effect of hyperkalemia on SM, with only 51.3% of the class indicating that hyperkalemia does not cause SM contraction (Table 1, question 3A).

Because question set 1 (Fig. 1) did not identify which specific concepts related to hyperkalemia were misunderstood, we devised a second set of questions to address a misunderstanding of the individual effects of hyperkalemia on DF, conductance, and SM contraction. Question set 2 (Table 2) was administered to the following year’s first-semester medical students (cohort B). There were 70.3% of students in cohort B who correctly identified that an increase in extracellular K^+ reduces the DF for that ion across the membrane (Table 2, question 1B). This suggests that students understood the concept of DF, defined as V_{m} minus V_{eq} for an ion (i.e., DF = V_{m} - V_{eq}), as well as the relationship of ion concentrations to the V_{m}. On administration of a subsequent question, only 30.6% of students understood that hyperkalemia increased the opening or conductance of specific K^+ channels in SM (Table 2, question 2B).

We then compared the results of the question sets for cohorts A and B, which yielded remarkable results. We note that question set 1 was nested, or dependent, on information from previously asked questions, whereas question set 2 was linear and independent of information from previous questions (Fig. 1). With respect to cohort A, comparison of questions 1A and 2A indicated that students had difficulty understanding the effects of hyperkalemia on depolarization and V_{m}. Comparison of questions 2A and 3A (Table 2) indicated that students correctly identified that hyperkalemia results in SM contraction, but struggled with the specific effects of hyperkalemia on SM. Directly addressing the individual concepts in question set 2 uncovered a lack of understanding regarding K^+ conductance in SM during hyperkalemic states.

Comparison of answers (cohort A versus B) provided insight regarding students’ understanding of lecture concepts, i.e., comprehension of ionic effects on V_{m} versus DF. Comparison of questions 1A and 1B (Table 2) suggested that the majority of students across cohorts exhibited an understanding of DF, but struggled to apply such a concept to V_{m} and depolarization. The third and final question in each question set was similar between cohorts. Interestingly, specifying the type of SM as vascular SM increased the percentage of correct responses (51.3 versus 73.0%) (Table 1, question 3A, vs. Table 2, question 3B). This latter finding suggested that students understand the general function of K^+ on tissue without necessarily understanding the mechanism.

**DISCUSSION**

Medical students experience difficulty understanding the paradoxical effects of exercise-mediated hyperkalemia in SM because it is an exception to textbook electrophysiological responses of skeletal muscle and nerves to hyperkalemia. In brief, this paradoxical effect results in hyperpolarization and vasodilation due to increased conductance of K^+ channels instead of hyperkalemia causing depolarization and cell activation. Although the V_{eq} of K^+ will become less negative, the increase in relative permeability to K^+ will dominate the V_{m} and result in hyperpolarization (6) (Fig. 2, A and C).

This study uncovered three misconceptions related to hyperkalemia: membrane depolarization, K^+ conductance, and SM relaxation. In this study, 51.6% of students correctly identified that hyperkalemia resulted in depolarization. This result is higher than a separate study of undergraduate students, of which only 36.5% demonstrated conceptual understanding in which increases in extracellular [K^+] from 3 to 5 mM results in depolarization in skeletal and neuronal cells (24). This is perhaps due to a lack of understanding of the [K^+] gradient across the cell membrane, whereby small changes in extracellu-

### Table 1. Hyperkalemia question panel used in lecture for cohort A

| Question No. | Question                                                                 | Correct, % | N (Correct/Total) | Correct Response |
|--------------|--------------------------------------------------------------------------|------------|-------------------|-----------------|
| 1A           | Does hyperkalemia cause depolarization? Concept: hyperkalemia and depolarization/V_{m} (general) | 51.6       | 208/403           | True            |
| 2A           | Does depolarization cause SM to relax? Concept: depolarization/V_{m} effect on SM | 67.0       | 276/412           | False           |
| 3A           | Does hyperkalemia cause SM to contract? Concept: hyperkalemic effect on V_{m} and resultant effect on SM | 51.3       | 197/214           | False           |

N, no. of student responses. Total registered students = 476. SM, smooth muscle; V_{m}, membrane potential.

### Table 2. Hyperkalemia question panel used in lecture for cohort B

| Question No. | Question                                                                 | Correct, % | N (Correct/Total) | Correct Response |
|--------------|--------------------------------------------------------------------------|------------|-------------------|-----------------|
| 1B           | Hyperkalemia decreases driving force across SM membranes. Concepts: hyperkalemia driving force SM | 70.3       | 230/327           | True            |
| 2B           | Hyperkalemia increases potassium conductance across SM membranes. Concept: hyperkalemia conductance SM | 30.6       | 101/330           | True            |
| 3B           | Hyperkalemia causes vascular SM to contract. Concept: hyperkalemic effect on V_{m} and resultant effect on SM | 73.0       | 240/329           | False           |

N, no. of student responses. Total registered students = 384. SM, smooth muscle; V_{m}, membrane potential.
Fig. 2. Hyperkalemia has differential effects on different tissues, resulting in relaxation of vascular smooth muscle (SM) and activation of excitable tissues (skeletal muscle (Skel m) and nerve). A: hyperkalemia results in a decrease in the driving force (DF), which is offset by increased K⁺-induced K⁺ conductance through the inward rectifier K⁺ (Kir) channels. The increased K⁺ conductance and hyperpolarization results in the closing of L-type voltage-gated Ca²⁺ channels, with a concomitant decrease in cytoplasmic Ca²⁺ and vascular SM relaxation and vasodilation. B: in contrast, hyperkalemia in excitable tissues results in decreased DF, which in turn reduces K⁺ efflux and results in depolarization. The depolarization results in opening of Ca²⁺ channels and activation. C and D: the membrane potential (V_m) changes with hyperkalemia. C: the resting V_m of SM under physiological loading is approximately −35 to −55 mV. Since V_m is further away from equilibrium potential (V_eq), there is greater DF upon K⁺ ion channel opening. This also leaves more “room” for hyperpolarization. D: in excitable tissues, the DF is less as V_m is closer to V_eq. The combination of lower DF and the absence of K⁺-induced K⁺ conductance through the Kir channels results in depolarization instead. [Ca²⁺], Ca²⁺ concentration; E_K, equilibrium potential for K⁺; [K⁺], K⁺ concentration.

lular K⁺ have profound effects on the V_m (28). However, the specific question, “Does hyperkalemia cause depolarization?” is not clear, as the response depends on the cell type. In neurons and striated muscles, the answer would be true, but even still the answer depends on both the concentration of neurons and striated muscles, the answer would be true, but is not clear, as the response depends on the cell type. In specific question, “Does hyperkalemia cause depolarization?” the conductance is related to DF as follows: 

\[ \frac{g_{Kir}}{(DF)} = \frac{g_{x}}{V_{eq} - I_{x}} \]

where \( I_{x} \) represents current flow, and \( g_{x} \) represents conductance. K⁺ conductance in vascular SM is different than that of skeletal muscle and nerves. The rise in extracellular K⁺ results in K⁺ conductance of greater magnitude in vascular SM than excitable tissues (Fig. 2). This observation is counterintuitive, as students have been taught that the Nernst equation predicts cell depolarization with increases in extracellular [K⁺] (7).

The exact mechanism of K⁺ channel response in SM versus striated muscle is currently unclear; however, studies of coronary vasculature indicate that several K⁺ channels are involved in metabolic K⁺-mediated vasodilation (4). Furthermore, the probability of opening K⁺-sensitive K⁺ channels increases in states of hyperkalemia (10), yet the specific K⁺ channel molecular subtype has not been definitively identified (4). A detailed explanation of the specific K⁺ ion channel responsible is beyond the scope of this study, but one theory states that the regional hyperkalemic effect greatly increases the conductance of overlying Kir channels in SM more strongly than that of regional skeletal muscle and nerves due to a greater receptor density of more reactive isoforms of the channel (2). This enormous increase in Kir channel conductance accounts for the hyperpolarization to equilibrium potential for K⁺, despite the simultaneous loss of K⁺ channel conductance. Thus the biophysical properties of the Kir2 channel explain how small increases in external K⁺ can act as a powerful vasodilatory force, directly generating rapid and profound hyperpolarization and dilation of the arterioles (14). Moreover, changes in K⁺ levels are expected to be greater in the local microenvironment compared with the overall concentration in blood: hence the term local control of blood flow.

The last misconception identified involves the relationship between hyperkalemia and SM relaxation. It is well known that K⁺ mediates local control of blood flow, depending on the level of metabolic activity of skeletal muscle. Students, however, appear to struggle in understanding differences between the traditional depolarization and the paradoxical hyperpolarization response in states of high extracellular K⁺. The information is likely compartmentalized (15), thus making it difficult to layer new and disparate information onto the existing schema. As a result, mild exercise-induced hyperkalemia is an excellent example to use when teaching about the local control of blood flow.

An additional relevant concept that was not addressed in this study is that vascular SM has a more positive V_m (between approximately −35 to −60 mV) under physiological intravascular pressure (40 mmHg) (9, 14, 19). This allows for a much larger DF and propensity for depolarization than skeletal muscle (Fig. 2, C vs. D). Unloaded blood vessels, however, have a V_m of −70 mV, which is not physiological, and skeletal muscle has a V_m of approximately −80 mV (9). This more positive V_m in vascular SM, under physiological conditions, explains how increases in extracellular K⁺ (hyperkalemia range) can promote hyperpolarization (Fig. 2C). In skeletal muscle and nerve cells, hyperkalemia raises the V_m and thus decreasing the DF for K⁺ ions, reduces the potential for repolarization, and causes the expected depolarization (Fig. 2C). Conversely, in vascular SM, the physiological V_m of arteriolar cells is −35 to −50 mV, which is still even more positive than the V_eq of −76 mV for an extracellular [K⁺] of 8 mM and an intracellular [K⁺] of 140 mM (14). Increased levels of K⁺ promote the opening of Kir due to the release of intracellular inhibition by Mg²⁺ and polyamines, which shifts the current-voltage curve.
to more positive values (14). This concept is likely contributory to students’ misunderstanding of this topic. We have diagramed how the changes in the resting $V_{m}$ of vascular SM and excitable tissues affect both the $V_{eq}$ and DF (Fig. 2).

**How to improve on teaching.** In this study, we identified essential student misconceptions related to physiological concepts of $V_{m}$, conductance, and SM response. Herein, we delve deeper into these misconceptions as well as propose a new method to teach this complex physiological concept using a visual aid that compares and contrasts the effect of hyperkalemia on cellular mechanisms, $V_{m}$, DF, and conductance in various tissues (Fig. 2).

The $V_{m}$ question (Table 1, question 1A) was perceived as a tricky question based on student feedback. This may be because information on the rate of plasma $[K^+]$ change was not provided in the question. The rate of $[K^+]$ change has profound effects on $V_{m}$, as a rapid increase results in depolarization, whereas a gradual increase in concentration can cause hyperpolarization. In the former case, a cell can initially have an action potential with a subsequent depolarization block or accommodation of voltage-gated Na$^+$ channels, since inactivation gates are not reset at higher $V_{m}$. In contrast, slow and steady elevations of K$^+$ result in gradual membrane depolarization. This gradual depolarization results in the inactivation of voltage-gated Na$^+$ channels and increased K$^+$ conductance due to the opening of KIR channels and thus hyperpolarization. Clinically, the end effect of hyperkalemia in both situations is a lack of muscle contraction.

K$^+$ conductance was central to students’ misunderstanding of the paradoxical effect of hyperkalemia in SM. Education materials may be a likely source of this issue, as textbooks may not include mechanisms if they are not clearly elucidated, as suggested by Michael et al. (17). The most obvious explanation is that students are not properly taught the different subtypes of K$^+$ channels, some of which lead to the observation of the paradoxical behavior of hyperkalemia in vascular SM. In our study, question sets were presented to students after explaining the relationship between K$^+$ and vasodilation but before teaching about the underlying mechanisms of K$^+$ conductance. It is expected that the students’ performance would improve once these two underlying concepts were explained in conjunction. Clearly delineating between the two responses to hyperkalemia, primarily due to K$^+$-mediated K$^+$ conductance in vascular SM and the response of the different tissues, may reduce this confusion. As a result, we created Fig. 2 to clarify this matter and highlight the different effects of hyperkalemia on various tissues.

**Clinical applications.** How do educators relate local control of blood flow to clinical applications as well as pathological hyperkalemia? Transient alteration of blood K$^+$ levels can be induced pharmacologically, such as with diabetic medications or with exercise. Dapagliflozin utilizes voltage-gated K$^+$ channels to cause vasodilation in SM (31). Interestingly, elevated K$^+$ and catecholamine levels during exercise are not cardiotoxic, in part due to simultaneous synergistic minimization of harmful effects (21). However, in the postexercise period, the most significant cardiogenic risk occurs when plasma K$^+$ levels are low, while the adrenergic tone remains high (25).

Pathological hyperkalemia can be acute or chronic. Acute hyperkalemia is generally attributed to intercompartmental shifts in the distribution of K$^+$ and can be associated with exercise, diabetic ketoacidosis, and cell lysis (i.e., major trauma, burns, and shock). During chronic hyperkalemia, there is an increase in total body K$^+$, which may cause cardiac arrhythmia and skeletal muscle paralysis, as well as diseases such as prolonged QT syndrome, epilepsy, and type 2 diabetes mellitus (27). Pathologies such as hypertension, obesity, stress, and ischemia have been linked to decreased activity of KIR channels (10). Finally, downregulation or inactivation of these channels is increasingly seen as instrumental in the increased excitability of vascular SM found in pathological conditions such as hypertension, hypercholesterolemia, and diabetes (9).

**Limitations of the study.** We discovered variations in the number of student responses to each question, which was attributed to both the number of students attending the lecture, as well as their ability to respond within the 60-s time frame allotted per question (Tables 1 and 2). Mechanical error with the clicker response system may contribute to this difference as well. Students were also allowed to discuss the questions before responding; thus polling may reflect a higher group value rather than an individual’s knowledge. The aim of this study, however, was to identify cognitive gaps in students’ knowledge regarding the effects of hyperkalemia on SM cells, and we are confident that the aforementioned limitations did not prevent the achievement of our aim.

**Conclusion.** Students appear to struggle with the effect of hyperkalemia on SM cells, which elicits paradoxical hyperpolarization and relaxation. There may be dissonance between the canonical teaching of hyperkalemia and depolarization versus the paradoxical hyperkalemia effect in SM. This misunderstanding is likely due to the concept of regulation of specific and special K$^+$ conductance. We discuss paradoxical hyperkalemia in the context of pathological hyperkalemia and introduce a potential teaching tool to illustrate divergent cellular responses and improve student learning outcomes.

**APPENDIX**

Hyperkalemia question panels were used in the lecture for cohorts A and B (Tables A1 and A2, respectively). These tables expand on the number of answer choices, as well as the correct answer choice for each question.

| Question | Answer Choices | Correct Answer |
|----------|----------------|----------------|
| 1A | Does hyperkalemia cause depolarization? Concept: hyperkalemia and depolarization (general) | True, False, Unsure | True |
| 2A | Does depolarization cause SM to relax? Concept: depolarization effect on SM | True, False, Unsure | False |
| 3A | Does hyperkalemia cause SM to contract? Concept: hyperkalaemia effect on $V_{m}$ and resultant effect on SM | True, False, Unsure | False |

SM, smooth muscle; $V_{m}$, membrane potential.

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Table A2. Questions used in lecture from cohort B

| Question No. | Question                                                                 | Answer Choices | Correct Answer |
|--------------|--------------------------------------------------------------------------|----------------|----------------|
| 1B           | Hyperkalemia decreases driving force across SM membranes. Concept: hyperkalemia | True, False    | True           |
| 2B           | Hyperkalemia increase potassium conductance across SM membranes. Concept: hyperkalemia | True, False    | True           |
| 3B           | Hyperkalemia causes vascular SM to contract. Concept: hyperkalemia effect on Vm and resultant effect on SM | True, False    | False          |

SM, smooth muscle;  \( V_m \), membrane potential.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

I.V.M. conceived and designed research; I.V.M. performed experiments; S.J.B., J.G., B. Bauer, M.P., N.S., L.B., D.B., and I.V.M. analyzed data; S.J.B., J.G., B. Bauer, M.P., N.S., L.B., D.B., and I.V.M. interpreted results of experiments; S.J.B. and I.V.M. prepared figures; S.J.B., J.G., B. Bauer, M.P., N.S., L.B., D.B., M.C., and I.V.M. edited and revised manuscript; S.J.B., J.G., B. Bauer, M.P., N.S., L.B., D.B., M.C., and I.V.M. approved final version of manuscript.

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