How We Teach

Development of concept-based physiology lessons for biomedical engineering undergraduate students

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Submitted 29 February 2012; accepted in final form 8 March 2013

Nelson RK, Chesler NC, Strang KT. Development of concept-based physiology lessons for biomedical engineering undergraduate students. Adv Physiol Educ 37: 176–183, 2013; doi:10.1152/advan.00038.2012.—Physiology is a core requirement in the undergraduate biomedical engineering curriculum. In one or two introductory physiology courses, engineering students must learn physiology sufficiently to support learning in their subsequent engineering courses and careers. As preparation for future learning, physiology instruction centered on concepts may help engineering students to further develop their physiology and biomedical engineering knowledge. Following the Backward Design instructional model, a series of seven concept-based online lessons were created as prerequisite physiology training to prepare students to engage in a collaborative engineering challenge activity. This work is presented as an example of how to convert standard, organ system-based physiology content into concept-based content lessons.

NEARLY ALL BIOMEDICAL ENGINEERING (BME) undergraduate students are required to take physiology. ABET criteria for BME undergraduate programs require that “the program must demonstrate that graduates have: an understanding of biology and physiology, and the capability to apply advanced mathematics (including differential equations and statistics), science, and engineering to solve the problems at the interface of engineering and biology as well as the ability to make measurements on and interpret data from living systems, addressing the problems associated with the interaction between living and non-living materials and systems” (1). A few accredited BME programs do not include a physiology course in their core curriculum; instead, these programs focus on developing understanding of physiology as students engage in courses in their discipline. The remaining programs require one or two physiology courses taught either by core BME or other bioscience faculty members (Fig. 1). These physiology courses are usually prerequisite to discipline-level courses in BME curricula. In the undergraduate curricula of the ABET-accredited BME programs surveyed, there was no standard recommended semester in which these physiology courses are taken. When a course is required, biomedical engineering students in ~80% of the ABET programs are directed to take physiology before the end of the first semester of their third year. At this point students have completed most of their general core requirements and are beginning to take their first BME courses.

Physiology instruction should help prepare students to solve BME problems. Solving engineering problems requires both knowledge and innovation. Preparation for future learning is a proposed educational construct related to the ability to innovate. Because every problem cannot be anticipated, the preparation for future learning model suggests that instruction should focus on helping students develop their ability to learn as they encounter new situations by making connections to past learning (3). Physiology instruction, then, should aim to develop a prior knowledge that can support future learning (11). What students learn in an introductory physiology course becomes the acquired knowledge from which new connections are made as they continue to learn both new physiology topics and those in BME.

For BME students, only one or two physiology courses will form the basis of connected learning. In this constrained timeframe, what physiology content should be presented? As ongoing research expands our knowledge of physiology, covering all of the content may become a challenge for educators in these courses (4). It is important that BME students are prepared to fill gaps in learning as they advance in their subsequent courses and careers. When students have a solid understanding of general physiology concepts, they can continue to add specific content to their knowledge base. Instruction following a conceptual framework offers a potentially better structure upon which BME students can build new knowledge as they advance in the undergraduate curriculum.

Structuring instruction around concepts may influence how students develop knowledge representations. Schema theory focuses on the representations or schemata that a student brings to a learning situation. As students build knowledge, they make connections to prior learning. By making connections between schemata developed with prior learning and new information, students can build a network of structures that represent their knowledge (6). Schema theory views learning as making connections to an elaborate network of abstract mental structures that represents an individual’s knowledge (2). This would suggest that the concepts students learn become the schemata to which new information connects.

Focusing instruction on concepts in introductory physiology courses for engineering undergraduate students may better prepare them for future learning of physiology within the BME curriculum than courses that use an organ system presentation scheme. Whereas system-based taxonomy builds student knowledge around the function of individual organ systems, a concept-based approach builds knowledge around the physiology concepts that occur throughout the
have a quantitative frame of reference. Some of the core concepts, even those not designated as engineering concepts, the VaNTH concept taxonomy is engineering based, all of the balance. Energy, structure/function, levels of organization, and mass balance.

Several concepts occur in both: homeostasis, communication, ties between the VaNTH taxonomy and these core principles. Particularly on the needs of BME students, there are similarities to guide their physiology instruction, the question of how to develop new courses and revise existing courses becomes salient.

Over the years, many physiology concept-based taxonomies have been proposed. Whether emphasizing general models (9), unifying concepts (13, 14), core principles (7, 8), or core ideas (5), the pedagogical theme has been the same: present the core concepts and exemplify and elucidate with the physiological details. Agreement on a single taxonomy could be important, but an equally fundamental question is "How might a concept-based approach transform course design and classroom instruction?" As consensus develops on the core principles of physiology, and educators begin to define concept-based taxonomies to guide their physiology instruction, the question of how to develop new courses and revise existing courses becomes salient.

A concept-based taxonomy specifically targeting the needs of BME students was developed by physiology and engineering educators working with the Vanderbilt-Northwestern-Texas-Harvard/Massachusetts Institute of Technology (VaNTH) Engineering Research Center (ERC) in Bioengineering Educational Technologies (Fig. 2). This taxonomy emphasized unifying principles and concepts that repeat across physiology systems. The concepts were eventually categorized into four groups: introductory concepts, anatomical concepts, biological concepts, and engineering concepts (13, 14).

There have been recent efforts by physiology educators to establish core principles to be covered in a physiology course, which has led to a proposed list of 15 core principles (Fig. 3). Each of these core principles is a top-level concept that can be "unpacked" into component ideas that can be developed as learning objectives with measurable outcomes (7, 8). Even though the VaNTH ERC concept-based taxonomy was based particularly on the needs of BME students, there are similarities between the VaNTH taxonomy and these core principles. Several concepts occur in both: homeostasis, communication, energy, structure/function, levels of organization, and mass balance.

There are differences between the two lists as well. Because the VaNTH concept taxonomy is engineering based, all of the concepts, even those not designated as engineering concepts, have a quantitative frame of reference. Some of the core principles in the taxonomy developed by Michael et al. (7, 8) do not seem to have a counterpart in the VaNTH taxonomy (e.g., evolution, genes to proteins, and physics/chemistry). Some concepts in the VaNTH taxonomy (e.g., scaling in biological systems, biological units of measure, and physiological variables) do not emerge as single concepts among the core principles. Regardless of the specific concepts associated with different taxonomies, the overarching pedagogical goal of concept-based instruction is to provide students with a conceptual framework to support their current and future physiology learning.

In the present work, the VaNTH concept taxonomy for BME students was used as a framework for developing physiology lessons using the Backward Design instructional model (15). A single, 2-wk instructional unit focusing on physiology was created for the online instruction of undergraduate BME students. The unit lessons provided the prerequisite physiology background that students would need to effectively engage in a collaborative challenge-based learning activity that focused on biofluid engineering topics. All of the lessons and challenge activities were implemented in an online environment that allowed asynchronous and synchronous collaboration.

**Using Backward Instructional Design to Create Concept-Based Lessons**

Any discussion about developing courses or instructional materials benefits from reflecting upon instructional design principles. As a first step toward evaluating this question, we have....

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![Fig. 1. University departments teaching physiology courses required for biomedical engineering (BME) students in ABET-accredited programs.](http://advan.physiology.org/)

![Fig. 2. Concept categories and concepts of the Vanderbilt-Northwestern-Texas-Harvard/Massachusetts Institute of Technology (VaNTH) physiology taxonomy for BME students (13, 14).](http://advan.physiology.org/)
principles. Instructional design models are useful for aligning pedagogical goals with instructional materials of any kind. The Backward Design model (15) was used to frame the development of the concept-based lessons we describe in this report. Backward Design is a course design model that focuses attention first on the specific learning outcomes desired and then works backward from that point to determine how best to present course content to achieve those learning goals.

**Core Principle** | **Rank**
---|---
Cell membrane | 1
Homeostasis | 2
Cell-cell communications | 3
Interdependence | 4
Flow down gradients | 5
Energy | 6
Structure/function | 7
Scientific reasoning | 8
Cell theory | 9
Physics/chemistry | 10
Genes to proteins | 11
Levels of organization | 12
Mass balance | 13
Causality | 14
Evolution | 15

![Cell membrane](image1.png)

![Homeostasis](image2.png)

![Cell-cell communications](image3.png)

![Interdependence](image4.png)

![Flow down gradients](image5.png)

![Energy](image6.png)

![Structure/function](image7.png)

![Scientific reasoning](image8.png)

![Cell theory](image9.png)

![Physics/chemistry](image10.png)

![Genes to proteins](image11.png)

![Levels of organization](image12.png)

![Mass balance](image13.png)

![Causality](image14.png)

![Evolution](image15.png)

Fig. 3. Core principles in physiology with rankings compiled from responses to a survey of physiology faculty members asked to assess relative importance to the 15 core principles (8).

The Backward Design process is the same whether instruction is being designed for a series of introductory courses or a single lesson. The first step is to identify the results expected from the instructional unit (i.e., course or lesson). Second, with the expected results articulated, acceptable evidence for achievement is determined: how should students be able to demonstrate their new knowledge? When the learning objectives and assessments are in place, planning the learning experience and developing the course materials are the final steps.

**Step 1: identifying desired results of the concept-based lessons.** Because our goal was to develop concept-based physiology instructional materials to prepare BME students for future learning in biomedical engineering, we first developed BME learning modules that require physiology content knowledge. These modules used challenge-based learning activities that required undergraduate BME students to work in small groups to develop a solution to an engineering challenge question. Challenge-based instruction engages students with open-ended problems to improve their ability to apply learning to both current and novel situations. Each small group of students was presented with one of two challenge questions that focused on a biofluid topic (Fig. 4). One question required the students to explore giraffe hemodynamics as they addressed the concern of the blood rush to the giraffe’s head as it bent down to drink water. The other question required students to consider issues associated with deep diving and the limits of human exposure. Both questions were presented in a scenario that put the students together as a team of interns who were tasked with providing a solution to the problem in the form of a final report. Students were encouraged to generate potential solutions, seek multiple perspectives on the problem,

![The Giraffe Challenge](image16.png)

You are one of a small group of interns working at the Zmahahi Wildlife Park. The park has just received word that they will get a large donation from Thurston and Lovey Howell to build a new habitat for the giraffes in the park. There is one slight obstacle, however. Lovey Howell is reluctant to give the money to Zmahahi because she is concerned about the welfare of the giraffes. She insists that the water troughs for the giraffe habitat be placed 12 feet in the air so the giraffes do not have to lower their heads to drink. It is up to the interns to present scientific evidence to convince Mrs. Howell that placing water at head level for the giraffe is not necessary as the giraffes will not be distressed when they bend their heads to drink from the ground.

You will soon begin working with the other interns on this important challenge; but first you should review some important physiology concepts. You will do this by working through the physiology training module linked below.

![The Diving Challenge](image17.png)

You are one of a small group of interns working at Big Petroleum. The company has just received word that an oil well along the coast of the United States has failed and oil is leaking from an uncapped well 5000 feet below sea level. Your group has been tapped for public relations damage control. The governors of the coastal states insist that diving teams be employed to cap the well immediately. It is up to the interns to present scientific evidence to the governors to convince them that divers would not be able to work under these conditions, helping them to understand the process more clearly.

You will soon begin working with the other interns on this important challenge; but first you should review some important physiology concepts. You will do this by working through the physiology training module linked below.

Advances in Physiology Education • doi:10.1152/advan.00038.2012 • http://advan.physiology.org
after completing the physiology training, the student will be able to:
- Recognize the main points of cell theory
- Identify elements of process of filtration
- Compare and contrast the structure and function of the four major tissue types
- Predict change in blood flow related to heart valve insufficiency
- Analyze a hematocrit value
- Cite examples of the function of blood
- Differentiate blood vessels by function
- Assess effects of capillary filtration given changes in typical pressures
- Summarize function of blood-brain barrier
- Recognize that a pressure gradient is required for respiration

Fig. 5. Learning objectives for physiology training supporting the challenge-based learning activity for undergraduate BME students.

Table 1. Specific physiology subtopics selected for inclusion in the online lessons

<table>
<thead>
<tr>
<th>Concept</th>
<th>Subtopics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levels of organization in the body</td>
<td>Cell theory, the four basic tissue types, organs and list of organ systems, Cell membrane, heart structure and anatomy, plasma, the blood-brain barrier, the blood-cerebrospinal fluid barrier</td>
</tr>
<tr>
<td>Compartmentation</td>
<td></td>
</tr>
<tr>
<td>Structure-function relationships</td>
<td>Structure and function of tissue types, pulmonary and systemic circuits, major vessel anatomy of the head and neck</td>
</tr>
<tr>
<td>Molecular interactions</td>
<td>Formed elements, viscosity, functions of blood, gas transport in blood, the gas law: Henry, gas exchange at lungs and tissues</td>
</tr>
<tr>
<td>Biological energy</td>
<td>Metabolic requirements of the brain, cerebral blood flow</td>
</tr>
<tr>
<td>Mechanics: movement and associated forces</td>
<td>The heart as a pump</td>
</tr>
<tr>
<td>Elastic properties</td>
<td>Arteries, arterioles, veins, venules; cardiac muscle cells and tissue</td>
</tr>
<tr>
<td>Bioelectricity</td>
<td>Events of a heartbeat</td>
</tr>
<tr>
<td>Emergent properties of complex systems</td>
<td></td>
</tr>
<tr>
<td>Biological units of measure</td>
<td>Formed elements, hematocrit, the cardiac cycle, cardiac output, stroke volume</td>
</tr>
<tr>
<td>Physiological variables</td>
<td></td>
</tr>
<tr>
<td>Scaling in biological systems</td>
<td></td>
</tr>
<tr>
<td>Biological transduction (molecular/sensory)</td>
<td>Baroreceptors, chemoreceptors</td>
</tr>
<tr>
<td>Communication and coordination</td>
<td>Structural overview of the central nervous system, neural tissue, cerebrospinal fluid, the events of a heartbeat, capillaries, metarterioles, anastomoses</td>
</tr>
<tr>
<td>Homeostasis/dynamics and control systems</td>
<td>Cellular homeostasis, baroreceptors, chemoreceptors</td>
</tr>
<tr>
<td>Mass flow (transport)</td>
<td>Membrane transport, diffusion, filtration, facilitated diffusion, active transport, carrier-mediated transport, the gas law: Fick, alveoli, bulk flow, blood flow, pulmonary circulation (flow of blood and air), capillary exchange</td>
</tr>
<tr>
<td>Mass balance</td>
<td>Starling forces and net filtration pressure</td>
</tr>
<tr>
<td>Heat balance</td>
<td></td>
</tr>
<tr>
<td>Pressure-flow-resistance</td>
<td>Blood pressure, mean arterial pressure, cardiac output, respiratory system structures, lung structure and anatomy, gas laws: Dalton and Boyle, pulmonary circulation (flow of blood and air)</td>
</tr>
</tbody>
</table>
atives, but the specificity of each objective would be equivalent to those presented here.

Step 3: Planning the concept-based physiology instruction.
The desired results and specific learning objectives informed the choice of content to include in the physiology lessons. From a review of several introductory physiology texts, specific physiology subtopics were selected for inclusion in the online lessons (see Table 1 for details). Subtopics were chosen based on two criteria: 1) the topic provided students with necessary background information to solve the engineering challenge and 2) the physiology subtopic itself did not require background information not presented in the lessons. The subtopics chosen were narrowly targeted since the amount of student engagement time was limited. Each lesson targeted one or two learning objectives and was designed to be completed by the student in 30–45 min.

Designing instructional material based on a conceptual framework requires a shift in thinking about how physiological details are presented to students. The subtopics as selected from the physiology textbooks were structured according to systems. If this targeted content was placed in a series of seven system-based lessons, the lesson topics would include, in order, cells, tissues, the cardiovascular system, the respiratory system, blood, blood vessels, and the central nervous system. Developing the concept-based lessons required a realignment of this system-based presentation of topics. The VaNTH conceptual taxonomy (13, 14) was used to frame the concept-based lessons. The 19 concepts of the VaNTH taxonomy were aligned into 7 lessons. To integrate these subtopics in the lesson content, the associated VaNTH concepts were clustered in seven groups of like concepts and given a representative lesson name (Fig. 6). To achieve the best fit concepts grouping for this learning activity, the amount of content to be included in each category was considered along with trying to maintain lessons that fit the 30- to 45-min timeframe.

With the concept grouping established, the physiology content was associated with the predominant concept or concepts and placed in one or more of the seven lesson groups. Some physiology topics were presented to the students as part of multiple concepts. Topic areas were introduced, associated with one concept in an early lesson, and then further developed with a different concept in a later lesson. The presentation of the formed elements subtopic is an example of this strategy. The content related to red blood cells was distributed between two concepts: molecular interactions and physiological variables, which were found in two different lessons. As another example, information about baroreceptors and chemoreceptors was presented to support the development of both the biological transduction and homeostasis/dynamics and control systems concepts. In each of these examples, the physiological details of the subtopic that supported or provided evidence of one particular concept were the only aspects presented in the lesson.

In the lessons, each concept was first presented and defined (see Fig. 7 for an example). After the concept was defined, the related subtopic information was developed in a lesson format. Unlike a system-based presentation, which builds from cells to tissues to organ systems to organs, the concept-based presentation did not have an established order. However, it was important for introductory topics to be covered in early lessons so that knowledge could build. In the form and function lessons, concepts often considered fundamental were introduced. In the form lesson, these included cell theory, the structures of the cell membrane, tissue types, and plasma elements. The function lesson took a second look at some of these subtopics as students then considered the function of the cell membrane and tissues and identified blood components and functions. Additionally, within each of the seven lessons, the order in which the concepts were presented was flexible. This allowed for the complexity of the individual lessons to build. For example, the concept of homeostasis, dynamics, and control systems was presented before mass transport in the control systems lesson, with content related to homeostasis supporting the advanced topic of mass transport. Figure 8 shows a process diagram of the conversion of the instructional unit from a system-based structure to a concept-based structure.

Step 4: Developing the course materials. Multimedia lessons were created using the Moodle lesson activity tool. Online materials on the Moodle course site included the physiology lessons, a series of four biofluid lessons that provided specific information related to each challenge question, a discussion forum for group collaboration, and a wiki for the collaborative development of the solution. Although not required viewing, the learning objectives for each lesson were presented as a text file that the students could view. Before moving to the next lesson, students were required to complete a set of review

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**Table 1: Realigned concept-based taxonomy lessons for the physiology learning module for undergraduate BME students.**

<table>
<thead>
<tr>
<th>Lesson</th>
<th>Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesson 1:</strong></td>
<td>Levels of organization in the body</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Compartmentation</td>
</tr>
<tr>
<td><strong>Lesson 2:</strong></td>
<td>Structure/function relationships</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Molecular interactions</td>
</tr>
<tr>
<td><strong>Physical Properties</strong></td>
<td>Biological energy</td>
</tr>
<tr>
<td><strong>Lesson 3:</strong></td>
<td>Mechanics: movement and forces</td>
</tr>
<tr>
<td><strong>Physical Properties</strong></td>
<td>Elastic properties</td>
</tr>
<tr>
<td><strong>Lesson 4:</strong></td>
<td>Bioelectricity</td>
</tr>
<tr>
<td><strong>Variables &amp; Measurement</strong></td>
<td>Emergent properties of complex systems</td>
</tr>
<tr>
<td><strong>Lesson 5:</strong></td>
<td>Biological transduction</td>
</tr>
<tr>
<td><strong>Information Processing</strong></td>
<td>Communication and coordination</td>
</tr>
<tr>
<td><strong>Lesson 6:</strong></td>
<td>Homeostasis/Dynamics &amp; Control Systems</td>
</tr>
<tr>
<td><strong>Control Systems</strong></td>
<td>Mass flow (transport)</td>
</tr>
<tr>
<td><strong>Lesson 7:</strong></td>
<td>Mass balance</td>
</tr>
<tr>
<td><strong>Pressure/Flow</strong></td>
<td>Heat balance</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td>Pressure - Flow - Resistance</td>
</tr>
</tbody>
</table>

Fig. 6. Realigned concept-based taxonomy lessons for the physiology learning module for undergraduate BME students.
questions that assessed their understanding of the lesson content. Using the quiz tool in Moodle, formative feedback was automatically provided to the respondent at the end of the quiz. This gave students an additional opportunity to review the material. Wiki technology was incorporated to allow students to construct their final reports. The students could write on the wiki either individually or collaboratively, and each revision was documented. Additionally, the groups met in the multiuser virtual environment Second Life for a brainstorming meeting and a final wrap-up meeting as they developed their final solution and wrote their report in the Moodle wiki (10, 12). The concept-based physiology lessons developed for this learning activity can be viewed online (https://courses.moodle.wisc.edu/prod/course/view.php?id=66).

DISCUSSION

In this work, concept-based physiology lessons were developed to prepare BME undergraduates to use physiology knowledge in future BME courses. We used the VaNTH...
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taxonomy, which was designed for BME curricula, to define the concepts, but it is not so different from other taxonomies that the process herein described for creating concept-based lessons is exclusive to this engineering taxonomy. Each taxonomy parses physiology content into a list of concepts that guide understanding of physiology. The concepts associated with each taxonomy are found throughout the physiological content students learn in introductory or survey courses.

By anchoring the physiology lesson development around the specific learning goals for BME students, concept-based lessons were created to prepare students to engage with one of two engineering challenge activities: giraffe hemodynamics or deep diving. The Backward Design process was used because it focused the development of the lessons specifically on learning outcomes. In this example, the learning objectives included physiology knowledge that supported the students’ exploration of new engineering topics related to biofluids. That particular learning goal focused the choice of subtopics to include in the lessons.

The flexibility to realign the 19 concepts of the VaNTH taxonomy into 7 lessons was essential. When developing instructional materials on a small scale like this physiology training for engineering challenge modules, it was important that each element served a pedagogical purpose. Grouping the concepts around the targeted physiology subtopics allowed the lessons to be focused. Nineteen concepts, seven lessons, and the list of necessary subtopics were the three design factors that influenced how the concepts were aligned. An optimal combination of concepts for each lesson eventually surfaced for this specific learning situation. If a different concept taxonomy had been chosen, the lesson grouping that best fit the course objectives would likely have been different.

From a student perspective, many obvious differences can be found when we compare the end product of seven concept-based lessons to seven system-based lessons. First, the lesson names will completely differ. Second, the topics will ultimately be presented in a different order. Third, within the lessons, the headings used to highlight the subtopics will not be the same. A comparable set of system-based lessons might build on cellular physiology, cardiovascular physiology, respiratory physiology, and neural physiology. Contrast this with the concept-based lessons built around form, function, physical properties, variables and measurements, information processing, control systems, and pressure-flow-resistance. The building blocks of the concept-based lessons are an array of concepts that make learning physiology in this manner distinctive.

From the instructor’s perspective, we found that creating concept-based lessons does not involve extensive rewriting of system-based content. Although new material may need to be created to provide instructional descriptions of the concepts, content describing the subtopics from a system-based lesson can simply be presented in a different order and elaborated on as an example of how the concept manifests in particular organ systems. Introduction of a concept before providing details of the physiology examples from different systems may allow students to learn more holistically as they form connections to gain an understanding and an appreciation of the new physiology knowledge.

Summary

A concept-based introductory physiology course may be particularly effective for BME students. BME undergraduate students will likely take one or two physiology courses in their academic career. With exposure to all concepts of a taxonomy, engineering students could gain an appreciation of the complete conceptual framework of physiology. Additionally, within this framework, students could connect new physiology information encountered over a lifetime, allowing future physiology learning to develop. By learning the concepts that describe all physiology processes, students may more easily create mental models or schemas that serve as connections for learning transfer.

Biomedical engineers will be required to continually fill in the gaps in their physiology knowledge as they acquire new BME knowledge. The ability to fill those gaps may not rely as much on what a student learned in an introductory physiology course as what they were able to continue to learn about physiology after taking an introductory course. We hope to explore in future work whether the concept-based approach effectively prepares engineering students for future learning, placing them in a position to become lifelong learners of physiology. In addition, in future work, the design model used for this learning activity for undergraduate engineering students could be applied with different concept taxonomies again on a small scale with a specific learning focus or within a larger course where more content is presented.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: R.K.N. conception and design of research; R.K.N. analyzed data; R.K.N. interpreted results of experiments; R.K.N. prepared figures; R.K.N. drafted manuscript; R.K.N., N.C.C., and K.T.S. edited and revised manuscript; R.K.N., N.C.C., and K.T.S. approved final version of manuscript.

REFERENCES