Teaching cardiac excitation-contraction coupling using a mathematical computer simulation model of human ventricular myocytes

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INTRODUCTION

At Seoul National University College of Medicine (SNUCM), the core course entitled Human Histology and Physiology, known as Human Physiology in short, is taken by first-year undergraduate medical students during the first semester. The course aims to provide students with comprehensive knowledge of basic physiological concepts, combined with microscopic structures, for the integrative understanding of major organ functions, except the nervous system. The Human Physiology course consists of 75 h of lecture and 60 h of practicum covering the themes of general cell physiology, including skeletal muscle function; heart and circulation; and respiratory, renal, gastrointestinal, and endocrine physiology. Microscopic histology of major organs and their tissues is also covered during the practicum. Students learn about neurophysiology separately in the course entitled Basic Neuroscience, which consists of 40 h of lecture and 40 h of practicum that include surface anatomy and dissection of human brains.

In Human Physiology, 7 h of physiology lectures cover 1) electrophysiology of cardiomyocytes and pacemaker cells; 2) cardiomyocyte excitation-contraction (E-C) coupling; 3) mechanics of cardiac cycle; 4) control of stroke volume and cardiac output; 5) electrocardiogram with basic understanding of arrhythmia; 6) autonomic control of heart; and 7) energy metabolism and heart failure. Before studying cardiac physiology, students learn basic principles of the Hodgkin-Huxley model of action potential (AP) and the concept of Nernst equilibrium potential to explain the direction of ionic movement, and the basic mechanism of E-C coupling in skeletal muscle.

Understanding E-C coupling of cardiomyocytes, along with the electrophysiological mechanisms of their characteristically long AP duration (APD) is an important learning goal in cardiac physiology (3). As can be found in the textbooks of medical human physiology (10), the relevant concepts and mechanisms taught to students include AP propagation to the T-tubule structure, activation of L-type voltage-gated Ca2+ channel (CaV), activation of ryanodine receptors (RyR) in the sarcoplasmic reticulum (SR), and Ca2+-induced Ca2+ release (CICR), and cross-bridge cycling of actin-myosin myofilaments generating contractile force. Relaxation-related processes, such as Ca2+ extrusion via Na+/Ca2+ exchanger (NCX) and SR Ca2+-ATPase (SERCA) are also explained in the lecture (Fig. 1).

Basic knowledge about the cardiac E-C coupling mechanism is delivered in the lecture using schematic drawings. It is then
followed by a written examination to evaluate students’ level of understanding. However, integrative interpretation of the interactive changes taking place in the above mechanisms is a challenging task for the instructor as well as students. For instance, the kinetics of interactions between the myofilaments and Ca\(^{2+}\) are nonlinear due to the complex conformational changes of the Ca\(^{2+}\)-binding troponin complex. Regarding the changes in intracellular Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_i\)), the complicated dynamic interactions between the voltage-dependent and calcium-dependent gating mechanisms of voltage-gated Na\(^+\) channels (Na\(_V\)), Ca\(_V\), and NCX are especially hard to understand through lecture only. In fact, the levels of [Ca\(^{2+}\)]\(_i\) are not homogenous in cardiac myocytes; the microdomains of subsarcolemmal space ([Ca\(^{2+}\)]\(_{sl}\)) and junctional space between the plasma membrane and T-tubule membrane ([Ca\(^{2+}\)]\(_{junc}\)) show different levels and speed of changes compared with those of the averaged cytosolic concentration of Ca\(^{2+}\) ([Ca\(^{2+}\)]\(_c\), Fig. 1). According to the multidomain model of the ventricular myocyte, [Ca\(^{2+}\)]\(_{sl}\) and [Ca\(^{2+}\)]\(_{junc}\) show about 10 times higher increases with faster kinetics than [Ca\(^{2+}\)]\(_c\) (27). However, the concept of subcellular domains of Ca\(^{2+}\) dynamics in cardiomyocyte is often skipped in the basic course of medical physiology, despite being important for the mechanisms of cardiotonic agents (e.g., digitalis) and heart failure. Furthermore, drastic change in [Ca\(^{2+}\)]\(_{sl}\) significantly influences the shaping of cardiac AP by altering the electrogenic NCX activity, which is a source of arrhythmogenic prolongation of APD.

As conventional lectures were allocated limited time in the physiology course, sufficient knowledge of cardiac E-C coupling based on the multidomain model of ventricular myocytes could not be delivered to the medical school students. Also, didactic teaching is not compatible with the integrative understanding of Ca\(^{2+}\) dynamics in cardiac E-C coupling. Against this background, starting from the first semester of 2017 in the Human Physiology course of SNUCM in 2017, we introduced the mathematical computer simulation model of human ventricular myocytes (Cardiac E-C_Sim) developed by us.

In general, simulation training is a participatory practice to reproduce processes or dynamics of any phenomenon in the real world. In the field of medicine, where functional performance is considered more important than any other area of professional education, training with human patient simulators (e.g., mannequins equipped with electromechanical devices) are widely used for the students to get hands-on practice and to increase their motivation of participation (1, 4). Unfortunately, however, the advantage of learning by using mecano-electric simulators (e.g., mannequins) is not suitable for the education of basic medicine. Instead, computer-based simulations of cells, organs, and human systems have been adopted (17, 22–24, 28).

In physiology education, the mathematical computer simulations of cellular and organ-level models have the ability to overcome the following difficulties: limitations of lecture-based learning in the integration of individual concepts, requirement of expensive instruments and well-trained techniques, and large-scale euthanization of animals in the conventional experiment-based practicum (9, 21, 24). The mathematical simulation models of the heart are not only a tool for the professional investigators, replacing animal experiments, but are also used in the education and training of medical school and postgraduate students, including biomedical engineering program students (2, 12, 17). Also, integrative
Cardiovascular physiology models are useful for the teaching of circulation physiology (6, 28). Computer-based mathematical simulations of the cardiomyocyte have been used for decades, and advanced models are available (19). To overcome the limitations mentioned above, we developed an interactive computer simulation of cardiac E-C coupling based on the original Grandi-Bers model of ionic description (8) and Negroni-Lascano model of myocyte sarcotendinous dynamics (18). As explained below, Cardiac E-C_Sim integrates the electrophysiology (ion channel kinetics and AP generation), Ca\textsuperscript{2+} dynamics (Ca\textsuperscript{2+} influx/efflux and organellar Ca\textsuperscript{2+} release/re-uptake), and Ca\textsuperscript{2+}-myofilament interaction accompanied by sarcomere length changes (Fig. 2). In the software development process, we focused on the following points: 1) intuitive understanding of the physiological phenomenon through real-time observation, 2) accessibility for students to modulate the parameters, 3) quantitative analysis of the data, with easily understandable graphical presentation, and 4) exporting the results for students solving the questions given by the instructor.

The goal of introducing computer simulation in the practicum was to let the students integratively interpret the concepts of cardiac E-C coupling. Also, by manipulating various user-interface parameters, students could mimic clinical situations where basic physiological knowledge can be applied to understand the pathological and pharmacological mechanisms. Here, we describe Cardiac E-C_Sim and its use within the Human Physiology course in SNUCM. In addition, we report the student survey feedback on this course. Students showed improved problem-solving ability through simulation-based learning (Cardiac E-C_Sim) and constructive discussions regarding the unique and dynamic cellular phenomena of cardiac E-C coupling.

MATERIALS AND METHODS

**Structure of the educational course in SNUCM.** SNUCM has a 6-yr curriculum consisting of the first 2 yr of a premedical course and 4 yr of the medicine course, called the 2+4 system, which is the major system in the Republic of Korea. The first 2 yr of the medicine curriculum cover basic medical sciences, block-lecture style clinical medicine courses, and 10 wk of full-time research. It is followed by 2 yr of clinical medicine rotations in three affiliated hospitals. To get the primary physician license in Korea, at the end of the fourth grade, students have to pass the Korean Medical Licensing Examination. Most of the graduates with medical licenses undergo resident training programs in various specialties (31). The level of quality of medical education in SNUCM is strictly evaluated by the Korean Institute of Medical Education and Evaluation every 4 yr. The domestic evaluation is currently certificated by the World Federation for Medical Education.

The present study was carried out in two consecutive spring semesters (March to June) from 2017 to 2018 at SNUCM. A total of 304 students (150 students in 2017 and 154 students in 2018) in their first year of medical school participated in the study. First, 3 h of lectures were delivered on the following themes: 1) cardiac cell structure, myofilaments, and characteristics of the AP; 2) ionic currents and channels/transporters in cardiomyocytes; and 3) Ca\textsuperscript{2+}-myofilament interaction.
handling and E-C coupling processes. Then, 2 h of practicum were conducted using Cardiac E-C_Sim. The practicum, which is essential to pass the course, was conducted 2–3 days after the textbook-based lecture.

A file on Cardiac E-C_Sim was distributed 2 days before the practicum with the demonstration of the software, and students were instructed to submit individual reports of their results and discussion within 6 days after the practicum. The students were encouraged to discuss and answer the questions in the manual. During the class, students were instructed to recall the lectured contents, emphasizing the processes expected to be observed in the practicum.

The practicum was designed to have two parts: 30 min of introductory lecture with the demonstration of the software, and manual-guided conduction of the practicum. The class started with a brief description of the software interface and cardiac E-C coupling to recall the lectured contents, emphasizing the processes expected to be observed in the practicum.

The students then followed seven steps of virtual experiments on their own computers according to the manual provided by the teaching assistant. After completing the experiments, the students were instructed to submit individual reports of their results and discussion within 6 days after the practicum.

Description of the user interface of Cardiac E-C_Sim. Cardiac E-C_Sim comprises 1) Ca$^{2+}$-dependent contraction-relaxation component; 2) electrophysiology model of AP and ionic currents; and 3) multidomain model of Ca$^{2+}$ dynamics (functional, subsarcolemmal, and bulk cytosolic calcium compartments). Figure 2 shows the interface of Cardiac E-C_Sim that consists of 1) two mathematical diagrams and their parameter manipulation panels for the Ca$^{2+}$-binding kinetics of myofilaments and their contraction-relaxation cycles (A, B) and 2) two graph panels displaying the results of virtual experiments (C, D) located in the control panel of Fig. 2D. Table 1 shows the various parameters that students can select in the Display option. The “Reset constants and Calculate” button reproduces the initial results with the default parameter values. The “Calculate (refresh)” button erases the current graph and recalculates the results without resetting the parameters. The “Calculate (superimpose)” displays the recalculated graphs over the existing graphs without initializing the parameters. In the “Stimulus” panel of Fig. 2D, the students can control the electrical stimuli to trigger the AP of the virtual cardiomyocyte. In the “Run protocol”
In the first step, by clicking “Stimulate,” the students observe shortening of cell length with simultaneous plotting of \([\text{Ca}]_i\) changes (left display window) in the default condition. In the right display window, AP and \(I_{\text{Na}}\) current \(I_{\text{Na}}\) traces are plotted simultaneously. The representative results are shown in Figs. 3 and 4. Following are the brief explanations regarding the results from each step and related goals.

**Step 1:** Tutors demonstrate the calcium transient \([\text{Ca}]_i\) changes induced by a single AP and the accompanied contraction of cardiomyocyte reflected by transient changes of half sarcomere length (Half SL, Fig. 3A). Students can also observe the fast activation and inactivation of \(I_{\text{Na}}\) and transient changes in \([\text{Ca}]_i\), respectively (Fig. 3B).

**Step 2:** Students observe the calcium influx via \(C_a\) (Fig. 3C) and the \([\text{Ca}]_i\) increase owing to \(C_a^{2+}\)-induced \(C_a^{2+}\) release via RyR in SR (CICR, see step 3).
modulated the changes of physiological parameters by reducing Na\(^{+}\) channel current (I\(_{Na}\); A), membrane potential (V\(_{m}\); B), intracellular Ca\(^{2+}\) concentration ([Ca\(_{i}\); C], and half-length of a sarcomere (Half SL; D) while elevating extracellular K\(^{+}\) concentration from 5.4 to 8, 10, and 12 mM. E–F: changes of L-type Ca\(^{2+}\) channel current (I\(_{CaL}\); E), open probability of ryanodine receptor (PoRyR; F), [Ca\(_{i}\); G], and Half SL (H) after reducing the amplitude of I\(_{Ca}\), by reducing it from 1.00 to a 0.75, 0.50, and 0.25 ratio for mimicking calcium channel blocker. I–L: for observing the effects of digitalis, students modulated the changes of physiological parameters by reducing Na\(^{-}\)-K\(^{+}\) pump activity (I_{NaK}; I), I_{NaCa} (J), [Ca\(_{i}\); K], and Half SL (L) from 1.00 to a 0.75, 0.50, and 0.25 ratio.

Step 3: Students observe the RyR open probability (PoRyR) change (Fig. 3, D and E). Also, the spatial difference in the changes of Ca\(^{2+}\) concentration is compared, i.e., bulk cytosol ([Ca\(_{i}\)], subsarcolemmal [Ca\(_{s}\)], and junctional space concentration ([Ca\(^{2+}\)\(_{junc}\); Fig. 3E) according to Grandi-Bers’ model (8).

Step 4: Students observe the kinetics of Ca\(^{2+}\)-troponin binding (Fig. 3G).

Step 5: Students are guided to observe the two major types of Ca\(^{2+}\) removing mechanisms: SR Ca\(^{2+}\)-ATPase (SERCA; Fig. 3H) and Na\(^{+}\)/Ca\(^{2+}\) exchanger (NCX; Fig. 3, I and J).

Step 6: Students observe the effects of fatal hyperkalemia causing cardiac arrhythmias and arrest (13, 30). Hyperkalemia induces voltage-dependent inactivation of Na\(_{v}\) (29) and subsequent decrease of AP amplitudes (Fig. 4, A–D).

Step 7: The effect of calcium channel blockers (CCB) is stimulated by reducing the activity of Ca\(_{v}\) (Fig. 4, E–H). Also, the effects of digitalis, a cardiotonic herbal agent containing ouabain (11), are simulated by reducing the activity of Ca\(^{2+}\)-K\(^{-}\)-ATPase (Na\(^{+}\) pump, Fig. 4I), which reduces the Ca\(^{2+}\) efflux via NCX (Fig. 4J), resulting in increased calcium transient and the shortening of half sarcomere length (Fig. 4, K and L).

At every step of these virtual experiments, students are not informed about the expected results. Also, students are guided to try different values of input parameters to compare the results of the virtual experiments. In the procedure, tutors facilitate active discussions within students to solve questions based on the electrophysiological properties of the cardiomyocyte. After conducting the seven experiments according to the manual, the students were further encouraged to freely change the parameters in combination and discuss results in small groups.

Study design. To assess students’ opinions about the computer simulation program and the practicum, we designed a questionnaire-based survey. Students rated the questionnaire consisting of 19 affirmative-form statements (Fig. 5) on a 5-point Likert-type scale: strongly disagree, disagree, neither agree nor disagree, agree, and strongly agree. The questionnaire aimed to assess the students’ perceptions of their learning using simulation. Due to the voluntary and anonymous nature of the survey, the investigation failed to involve all of the students who took the class. Of the 301 students in the class, 202 (67.1%) responded to the questionnaire. For analysis, the 19 questions were categorized into 9 subjects, according to the purpose of the survey (Fig. 5).

Statistics. Results are presented as means ± SD. Unpaired Student’s t test was used, and P < 0.05 was considered significant. The numbers of students in each analysis are mentioned in Fig. 6 and in relevant context.

RESULTS AND DISCUSSION

Student feedback. In 2017 and 2018, 100 of the 148 students (67.5%) and 102 of 153 students (66.7%), respectively, responded to the questionnaire. In addition, we requested the students to share their comments or feedback regarding the simulation practicum class. The feedback is summarized in Fig. 5. The overall responses based on the nine categories are described below.

1. Understanding of learning objectives: The students evaluated themselves to rate their level of understanding of the learning goals, and their feedback was positive in...
general. The scores of question 1 (Q1) and Q2 were 3.71 ± 0.909 and 3.64 ± 0.894 (n = 202 students), respectively, which indicated that the learning objectives of both the overall class and each of the seven experiments were successfully understood. About 10% (21 out of 202) of the students found it difficult or very difficult to understand the learning goals.

2. The completeness and convenience of simulation program: The students made a positive assessment of the program interface and control panel (Q4: 3.84 ± 0.921). Consistent with the assessment, we observed that the students showed faster performance of the protocol at the latter half of the practicum. At first, we were concerned that the interface would be too complex for the students. However, most of them found little or no difficulty in using Cardiac E-C_Sim. Only 13 students responded that they had difficulty in understanding the meaning of the parameters (Q3); 16 students had some difficulty in handling the program interface (Q4); and 18 students had difficulty in handling export data interface (Q5). Students also mentioned that the graph was difficult to read. Although the results were indicated in different colors, it was still challenging for students to understand the arrangement of the graph. The students also highlighted that it was difficult to import the output in text file format. Since Cardiac E-C_Sim exports all variable values to a text file, i.e., ascii.txt, to analyze the result from different conditions, they had to be stored and compared using spreadsheet programs. Students suggested improvement of the process of exporting the values as an image file rather than a text file (e.g., image capture function). Considering the negative opinions toward the graph display areas in the bottom panels of the interface, further modification is required to improve the interface panels.

3. Understanding of study materials: The students’ evaluation of the three questions (Q6–Q8) was moderately positive: Q6: 3.60 ± 0.096, Q7: 3.65 ± 0.987, and Q8: 3.77 ± 0.829. In the process of designing the practicum, along with the structure of the user interface, we thought that learning materials should not be difficult to understand. Although not shown here, we provided PDF files containing step-by-step instructions and learning materials that were helpful for students to conduct the practicum. The students also answered that the practicum procedure was well structured (Q8). However, despite the generally favorable response to the structure of the practicum, the level of understanding of the manual was relatively low (Q6).

4. Interest in practical class: A majority of the students appeared more than moderately interested in the class.
(Q9: 3.64 ± 0.016). Since the practicum is a part of the physiology course, the students are assessed by their reports for their practicum, as well as the written exam focusing on the lecture-based learning contents with specific goals. Compared with the written exam, the evaluation and scoring criteria of the students’ reports could be subjective. Furthermore, owing to the competitive atmosphere in the first-year class of medicine, students made the appeal that reports without volume limits lead to overly competitive minds that also made the practicum less interesting. It was necessary to develop a more structured format of the report (e.g., predefined font size and total pages) to lessen the burden on the students.

5. Learning efficacy of practical class: Although relevant lecture classes were conducted before the practicum, the students gave the lowest score to the question regarding background knowledge of cardiac E-C coupling (Q10: 3.19 ± 1.098). Also, the specific positive effect on the improvement of the knowledge delivered by the previous lecture was not as high (Q11: 3.52 ± 1.051). Interestingly, students answered that the practicum helped to broaden their understanding of cardiac physiology (Q13: 3.86 ± 0.847), whereas assessment of the question about motivation was slightly lower (Q12: 3.60 ± 1.021). The relatively positive response to Q13 coupled with the low score of Q10 reflects an insufficient level of understanding through only lecture-based learning. In fact, among the total 202 students who responded to the questionnaire, 111 said that their understanding of cardiac physiology increased after the practicum (Q11), 116 said that they were motivated by the practicum to study further about the related topics (Q12), and 143 responded that the practicum was a great help in understanding heart physiology (Q13).

6. Comparison with conventional practicum and lecture: Although the computer simulation-based practicum could be helpful for the detailed understanding of cardiac E-C coupling, it appeared not to be as impressive as a conventional practicum, such as human ECG recording (Q14: 3.63 ± 0.925). Also, the learning efficiency did not appear superior to the conventional textbook-based lecture (Q15: 3.66 ± 1.017). The delivery of concise knowledge via lecture could be more efficient for the first-year medical students with a condensed curriculum. The student might also feel that the specific learning goals of the simulation-based practicum are redundant and surplus. However, considering the positive response to the question regarding understanding of cardiac physiology (Q13), we interpret that the simulation class was helpful for the integrative understanding and was not just a redundant ancillary learning step.

7. Approval level of practical class: An introductory review lecture at the beginning of the practicum was evaluated positively by the students (Q16: 3.82 ± 0.926). Also, the summary lecture at the end of the practicum was quite helpful (Q17: 3.77 ± 0.893).

8. Efficacy of discussion: Students responded that the active group discussion was most helpful in the practicum (Q18: 3.87 ± 0.876), which was quite encouraging.

9. General critique: To assess students’ overall evaluation of the simulation practicum, we inserted the question, “I would recommend the simulation class to the juniors,” in the survey to which the students answered positively, suggesting that they were generally satisfied with the practicum (Q19: 3.81 ± 1.027).

Free opinions. Overall, most of the students’ responses were positive and encouraging. Of the 26 free opinions in the 2-yr survey (11 in 2017 and 15 in 2018), 19 were positive for the practicum. A total of eight students described their increased understanding of cardiac physiology through the simulation practicum: “Through the practicum, I was able to get a deeper understanding of what I had learned in the text-book based lecture,” and “The parts that I did not understand well during the class were clarified through practical class.”

During the practicum, the students were instructed to make small groups of three to four peer students and discuss the results with each other. Students preferred small-group discussions: “It was much helpful to understand the details because the facilitator was closely available. I think this is a good way to teach a small group,” and “What I was able to discuss freely with my friends helped me to get used to the simulation.”

Seven students gave negative opinions related to the timing of the practicum: “The interval between the lecture and the practicum was too short to understand all the details of the lecture before the practicum.” Also, two students pointed out that the graphic-exporting interface was not convenient: “The graph area is difficult to understand because it contained too much information in one graph,” and “I hope the results are exported in graphical format. It was difficult to handle the results with an MS-Excel.”

During the practicum, students not only conducted virtual experiments, but also predicted and observed the results in offered conditions such as hyperkalemia, effects on CCB, and digitalis. While modulating the program by themselves, students could appreciate that the textbook and lecture-based knowledge is actually observed in the simulation, which has the effect of strengthening the knowledge. We interpret that the generally favorable opinions of the practicum using Cardiac E-C_Sim could be due to an intellectual reward from the
immediate presentation of reasonable results. Nevertheless, we have to admit that the mean scores of the questionnaire were not as high as we initially expected; none of the mean values were higher than 4.0 (Fig. 5). Since the program used in this study (Cardiac E-C_Sim) is aimed to be used in graduate course training, as well as in the undergraduate medical college, it might have frustrated the students who did not fully understand the details of E-C coupling. In fact, the level of “background knowledge on E-C coupling before the practicum” got the lowest response score in the questionnaire (Fig. 5).

**Learning outcomes.** SNUCM conducts four regular tests in each semester of the physiology course. We compared the scores of the cardiac physiology section for 3 consecutive yr (2016–2018) to evaluate whether the simulation-based practicum improved the understanding of cardiac physiology (Fig. 6). Because students (2017 and 2018) have participated in the practicum for 2 yr, we compared the exam scores with those of the student in 2016 when the simulation-based practicum was not adopted.

The same professor had given the cardiac electrophysiology and E-C coupling lectures each year with identical lecture materials based on the essential learning goals selected by the faculty of SNUCM Physiology Department. The questions of the regular examination are constructed to assess the learning goals (3 to 4 items per hour) clearly presented to the students. Although the questions of the regular examination are not the same throughout the 3 yr, since the teaching professor and the learning goals were not changed, we cautiously assumed that the level of examination was not different in the 3 yr. As the entire course of cardiac physiology was identical except for the addition of the practicum using Cardiac E-C_Sim, we could minimize the other factors interfering with the scores.

The cardiac and circulatory physiology parts correspond to the second exam composed of 40–45 questions. Among them, 14–17 questions are about cardiac physiology, having the same total score in the 3 yr (Table 2). About 20% of the questions tested the students’ recall of universal and specific knowledge or not (knowledge). One-half of the questions referred to the understanding of facts and ideas by organizing, comparing, interpreting, and giving descriptions about cardiac physiology (comprehension). The rest of the questions tested the application of knowledge acquired in the practicum (application) and the functions of ion channels and transporters. The percent normalized score of the cardiac physiology test was 59.2 ± 6.21, whereas the total score of physiology was 80.0 ± 9.23 in the year 2016, suggesting that students showed relatively incomplete understanding of cardiac physiology. In the years 2017 and 2018, the scores of cardiac physiology were 79.8 ± 7.38 and 78.2 ± 4.39, respectively. The total scores in 2017 and 2018 were 81.0 ± 6.35 and 75.0 ± 4.19, respectively (Fig. 6).

Taken together with the scores of examination and students’ feedback, we cautiously conclude that the practicum designed using Cardiac E-C_Sim has contributed to improved understanding of cardiac physiology.

The improved outcome might owe to a kind of spaced-repetition effect of the practicum (20, 26). Repetitive learning of cardiac physiology within the interval of a few days through the simulation-based practicum could have helped the students in memorizing the key concepts and their deep understanding. Nevertheless, one could ask whether a single practicum class of 90 min would produce such a significant effect on the examination score. In fact, the monthly examination is a knowledge-based test, not a performance skill. The lecture for theoretical background in the practicum and the question-and-answer session might have provided an additional chance of understanding cardiac physiology, which was not provided in 2016. Careful interpretation is required to compare the effectiveness of the computer simulation practicum in the written examination.

**Lessons for using computer simulation model for students.** The present study explores courses with an application of physiology simulation in basic medical education. As a whole, we could safely conclude that the practicum using Cardiac E-C_Sim was helpful for the students, as well as the instructors designing the physiology practicum without using animal experiments. In some cases, the sophisticated levels of Cardiac E-C_Sim allowed for “virtual experimental research” by motivated students. In the winter vacation of 2017, three premedical student volunteers learned basic electrophysiology by tutoring using Cardiac E-C_Sim. They were then motivated to learn the cardiac pacemaker using another simulation program and conducted virtual experiments on the putative role of NCX in pacemaker potential. The students presented the results in a Computer-Simulation Based Students Research Festival supported by the Korea Research Foundation, the EDISON Challenge (15).

The effects of simulation training in medical education were addressed in general areas of Miller’s learning pyramid (5, 16). Miller’s learning pyramid can be further subdivided into Bloom’s taxonomy. Bloom divided educational objectives into three domains: cognitive, affective, and psychomotor domains. The cognitive domain is divided into knowledge, comprehension, application, analysis, synthesis, and evaluation. The affective domain is divided into receiving, responding, valuing, organizing, and characterization. The psychomotor domain is divided into reflex movements, fundamental movements, perceptual abilities, physical abilities, skilled movements, and nondiscursive communications (25). Meta-analysis based on Bloom’s taxonomy, which analyzed the effects of simulation education on nursing education in parallel with medical education, exhibited significant effects on knowledge, critical thinking, problem-solving, clinical judgment, and communicative skills in the cognitive domain. In the affective domain, the effects were significant in confidence and satisfaction, while clinical performance was significant in the psychomotor domain (14).

While Cardiac E-C_Sim is not equivalent to human patient simulators in clinical medicine, we could explore Bloom’s

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**Table 2. The number of questions in the cardiac physiology examination**

| Year | Knowledge | Comprehension | Application | Total No. |
|------|-----------|---------------|-------------|-----------|
| 2016 | 4         | 7             | 6           | 17        |
| 2017 | 3         | 8             | 5           | 16        |
| 2018 | 3         | 8             | 3           | 14        |

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taxonomy to examine the effects of a mathematical simulation-based practicum in physiology education. From the student survey of the present study, we could get a hint of the effects of simulation training on the cognitive and affective domain, especially the motivation in the affective domain of Bloom’s taxonomy. In terms of the cognitive domain, the operational definition of the degree of “comprehension” was defined by focusing on how much the contents were understood and interpreted. Therefore, Q11 on the student survey was to confirm how well the comprehension within the cognitive domain was achieved. Q12 intended to evaluate the effectiveness of the training by implementing affective domain as an operational definition of “motivation for learning.”

Directions for future improvement. The survey results and learning outcomes of students suggest that the computational model could be a useful educational tool. Also, computer-based learning helps the students to visualize sophisticated concepts of physiology without sacrificing animals, and it also saves their time. The students could actively discuss the acquired results and the primary knowledge with colleagues in a practical class, which widens and deepens their understanding. Taken together, we report the usefulness of Cardiac E-C_Sim to deepen the understanding of heart physiology through active learning rather than didactic lecture-based learning.

Despite the positive impression for the instructor and generally favorable responses from the students participating in the practicum, the present study analyzing the questionnaire has some limitations: 1) the total percentage of responses to the questionnaire was not satisfactorily high; 2) comparison with the practicum classes of other subjects (e.g., human respiratory function test) was not explicitly included; and 3) a follow-up questionnaire to the same class was not designed to evaluate the long-term results.

While we have already made some improvements based on the students’ opinions in the practicum of year 2017, there are still some points to be improved in the practicum. J) The students highlighted that it was difficult to export the output in text file format, suggesting the improvement of easy export values as a picture file rather than a text files (e.g., image capture function). 2) The current Cardiac E-C_Sim requires modification to implement the pathophysiological conditions, such as failing heart. 3) In addition to E-C coupling, it would also be helpful to provide a simulation model of a cardiac pacemaker, i.e., SA node cell model (7). Finally, apart from the simulation model per se, a simplified criteria of report scoring could be considered. An alternative evaluation system, such as pass-or-fail evaluation, should be developed to relieve the burden of students, which is important to maintain the students’ interest and motivation.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Y.K.J., J.B.Y., C.H.L., and S.J.K. conceived and designed research; Y.K.J.J. and J.W. performed experiments; Y.K.J.J., J.W., and S.J.K. analyzed data; Y.K.J.J., H.Y.Y., and S.H.L. interpreted results of experiments; Y.K.J.J. prepared figures; Y.K.J.J. and K.J.H. drafted manuscript; H.Y.Y., S.H.L., and S.J.K. edited and revised manuscript; S.H.L. and S.J.K. approved final version of manuscript.

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