INTRODUCTION

The cardiovascular response to exercise is influenced by several interactive neural mechanisms that evoke alterations in autonomic outflow, leading to changes in heart rate (HR), stroke volume, and total peripheral resistance that increases arterial blood pressure (BP) in an intensity-dependent manner (11, 12, 19). Central signals from the higher brain associated with the volitional component of exercise (i.e., central command) (42, 57), peripheral signals arising from mechanically and metabolically sensitive afferents fibers in contracting skeletal muscle (i.e., exercise pressor reflex) (27, 28, 33, 34, 50), and feedback from stretch receptors originating in the carotid and aortic arteries (i.e., arterial baroreflex) (10, 13, 14, 41, 43) are all involved. Although all three neural mechanisms are relevant for cardiovascular regulation during exercise, considerable attention has been given to the exercise pressor reflex due to its importance determining the magnitude of sympathoexcitation during muscular effort (1–4, 17, 18, 28, 37, 40, 46, 47, 51, 54).

The sensory component of the exercise pressor reflex comprises group III and IV skeletal muscle afferents that respond to both mechanical (i.e., muscle mechanoreflex) and metabolic (i.e., muscle metaboreflex) stimuli (28). In humans, the muscle mechanoreflex can be activated by mechanical stretch (22) or passive movement (35, 52, 56); however, its effects on cardiovascular responses appear small and transient. On the other hand, Alam and Smirk (2) first reported that the increases in arterial BP observed during isometric handgrip (IHG) exercise were partially maintained when the circulation of blood through the working skeletal muscles was arrested by suprastolic cuff occlusion just before the cessation of exercise. The classic work of Alam and Smirk employed a simple technique, commonly referred to as postexercise ischemia (PEI), to isolate the metabolic component of exercise pressor reflex (i.e., muscle metaboreflex). During this maneuver, metabolic by-products of muscle contraction, such as lactic acid, potassium, arachidonic acid products, and adenosine, are trapped and stimulate metabolically sensitive afferent fibers. Stimulation of these afferents results in an elevated arterial BP achieved by sympathetically mediated increases in systemic vasoconstriction and cardiac output (51). Overall, although it is well accepted that the skeletal muscle metaboreflex is one of the principal mediators of the cardiovascular response to exercise, PEI was widely used in scientific reports as a standard technique to isolate the skeletal muscle metaboreflex, but, to our knowledge, its use as a tool for teaching cardiovascular physiology for undergraduate students has not been previously reported.

Incorporation of active learning activities in conjunction with more traditional approaches to teaching in the classroom have proven to be more effective for student learning and retention compared with lecture alone (6, 21, 49). Therefore, this article describes a practical lesson methodology used in an undergraduate exercise physiology laboratory class that can guide teachers to demonstrate several aspects of cardiovascular regulation during exercise and report the perceptions of the students after the laboratory class. We hypothesized that our practical laboratory class will improve the students’ perceptions of their understanding of the cardiovascular regulation during exercise.
**Learning objectives.** The learning objective was that, on completion, the students should be able to describe and explain 1) the cardiovascular responses to IHG exercise; 2) the cardiovascular responses to isolated skeletal muscle metaboreflex activation via PEI; 3) the role of blood lactate as a trigger of skeletal muscle metaboreflex activation; and 4) the possible sex differences in cardiovascular responses to IHG exercise and PEI.

**Equipment and supplies.** The equipment and supplies used in this practical are as follows:

- Digital BP monitor
- Sphygmomanometer
- HR monitor
- Handgrip dynamometer with visual feedback
- Materials for blood analysis [capillaries (30 µL) with heparin, cotton, alcohol, rubber gloves, blood lancets, Eppendorf tubes with sodium chloride, and waste containers for blood and sharp materials]
- Lactate analyzer
- Timer (in min:s)

**METHODS**

**Ethical approval.** The present study was conducted in an exercise physiology class, which is a mandatory part of the second-year course of the Faculty of Physical Education at the University of Brasilia. The use of human subjects for these practical laboratory experiments may require ethical approval from your institution’s human research committee. The experimental pedagogical activity, including the employment of students as a human volunteer subjects and surveys, were approved by the University of Brasilia research committee (CAAE: 97916918.9.0000.0030), in accordance with the Declaration of Helsinki. All students are told that their participation as experimental subjects in the laboratory class is voluntary and that they can withdraw at any time. Each participant read and signed a specific informed consent form before the participation.

**Traditional learning.** Figure 1 displays the timeline of events associated with the experimental procedures. Before the experimental laboratory class, a traditional 4-h lecture was conducted discussing the cardiovascular responses to exercise and the neural control mechanisms of circulation during exercise (i.e., central command, exercise pressor reflex, and arterial baroreflex). The traditional class included a lecture using images, scientific papers, answers, and discussion of students. To comprehensively understand the cardiovascular control at rest and during exercise, examples were given in both healthy young men and women, and in a range of populations, including elderly subjects and patients with hypertension, heart failure, diabetes, and Parkinson disease.

**Laboratory class.** The laboratory class was set during a practical laboratory exercise, which includes a total of 47 undergraduate students. To facilitate participation and visualization of experiments, the class was divided into two smaller groups, and each laboratory section had a 2-h duration. Eight students (4 men and 4 women) volunteered for the participation in the practical laboratory class. Subjects had to be asymptomatic, nonsmokers, normotensive, and non-diabetic. All subjects were using no prescribed or over-the-counter medications. Participants were requested to abstain from caffeinated beverages for 12 h and from strenuous physical activity and alcohol for a minimum of 24 h before laboratory class.

During the 2-h laboratory class, the first 30 min were allotted to review upcoming protocols and volunteer preparation. Each experimental protocol had a 25-min duration approximately. Importantly, we carried out the experiments in one man and one woman simultaneously to reduce the time spent during the laboratory class. Of note, to perform two experiments at same time point, we needed all equipment and supplies in duplicate. The final 40 min were used to consolidate and review data collection and to instruct students to prepare an individual homework assignment (see below).

After instrumentation, participants were positioned in a seated position (90° hip and knee flexion) and rested for ~10 min to allow stabilization of cardiovascular variables. An hydraulic handgrip dynamometer (Saehan, SH5001, Korea) was held in the dominant hand with the limb supported and the handgrip force exerted was placed in front of the subjects to provide visual feedback (Fig. 2A). Maximal voluntary contraction (MVC) was determined as the highest of three maximal efforts, each separated by 1 min. Each participant performed 90 s of IHG at 40% MVC, followed by 3 min of PEI, to isolate skeletal muscle metaboreflex, and 3 min of recovery. PEI was achieved by the rapid inflation of a cuff positioned around the exercising arm to suprasystolic pressure (240 mmHg) 5 s before the end of exercise. Arterial BP was measured in the nonexercising arm by a digital BP monitor (Omron, HEM-7200) and HR by a cardio frequencimeter (F5, Polar). The cardiovascular variables were measured at rest and during IHG, PEI, and recovery. Due to the time expended by the digital BP monitor to perform data collection (~30 s), we employed only one measurement in the final 60 s of each time point during experiments. Rating of perceived exertion (RPE) was obtained at the end of exercise using the OMNI-RES scale (0–10) (44). Importantly, in a future laboratory class, HR should be assessed via methods other than palpation of the carotid pulse, as this would invoke additional baroreceptor-mediated cardiovascular responses.

To improve engagement in the activity, students who did not serve as volunteer were instructed to perform verbal stimulation during experiments, and we selected students to 1) operate the computer; 2) perform cuff occlusion and release; 3) record BP and HR data; 4) record RPE data; and 5) operate the timer. The students must be instructed and familiarized with all equipment and procedures before hand.
For lactate analyses, blood samples were collected from the tip of the exercising finger with heparinized capillaries at rest and during PEI, and recovery (final 60 s). The collection of blood was performed by experienced teachers (A.L.T. and M.S.) using gloves, protective goggles, proper waste disposal, and local asepsis before and after sampling. A 25-μl blood sample was collected by capillary tubes and placed in Eppendorf tubes containing 50 μl sodium chloride. Blood samples were stored at −4°C until later analyses using the YSI method (YSI 1500 Sports, Yellow Springs Instruments) (Fig. 2B). All analyzers were calibrated and operated in accordance with the manufacturer’s instructions. Twenty-four hours after the completion of laboratory class, blood lactate results were sent to students via e-mail.

Homework. Each student was instructed to prepare an individual written practical report in the format of a condensed scientific paper consisting of the following sections: 1) Objectives, 2) Results, and 3) a brief Discussion with Conclusion. They are provided with detailed instructions on the writing of a scientific report and encouraged to use software such as Microsoft Word to write the report and Microsoft Excel to prepare figures. Specifically, to demonstrate the cardiovascular responses to exercise and metaboreflex activation, students were instructed to report data from all participants in each one of the hemodynamic variables (i.e., HR, systolic and diastolic BP) at rest and during IHG, PEI, and recovery. To further understand the possible sex-related differences in cardiovascular regulation, students were instructed to demonstrate the average changes (Δ) from rest in the hemodynamic variables during IHG and PEI comparing the subgroups of men and women. Additionally, to demonstrate the pivotal role of blood lactate as a trigger of skeletal muscle metaboreflex activation, students were instructed to show blood lactate responses at rest and during PEI and recovery in both sexes and average change from rest during PEI comparing men and women. Four days were given for the completion of homework.

Student perceptions. A paper-and-pencil survey to determine student perceptions was given after the completion of homework, and 10 min was given for its completion. Only the students who participated in both traditional learning and the experimental laboratory class were included in the survey (46 of the 47 students). The questionnaire was based on previous peer instruction studies in medical education (5, 8, 23, 45). Students were asked about their learning experience through a questionnaire consisting of 10 items on a 5-point Likert scale, ranging from strongly disagree to strongly agree. The questionnaire assessed the students’ self-perception of whether the experimental laboratory class improved their level of understanding of several aspects of cardiovascular regulation during exercise and the students’ attitude and actions.

Course exam performance. To determine the effectiveness of our pedagogical laboratory class, we compared the course exam performance between two different undergraduate exercise physiology classes that are taught by the same teacher. In one class, students did not experienced this experimental pedagogical laboratory class (i.e., the class of the anterior semester, n = 41), and, in the present class, students participated in the experimental laboratory activity (n = 47). Each course exam consisted of 10 questions (worth 1 point each), and the questions were different between classes, but all were related to general cardiovascular physiology, including cardiovascular responses to exercise and the neural control mechanisms of circulation during exercise. The class exam performance was divided based on the overall student score (minimum of 0 and maximum of 10 points) in three different scales: <5 points, between 5 and 6.9 points, and 7–10 points.

Statistical analysis. Usually, the number of volunteers is too low to consider variability and statistical significance. Thus the students used only the means of each variable. Considering second-year undergraduate students, we found that this approach is sufficient for the discussion of data and understanding of the cardiovascular physiology involved in the experiment. However, presentation of data variability can be useful to teachers who will use this protocol in class so that they know what to expect. In this sense, values are presented as means ± SD. Student perceptions and course exam performance were reported as the percentage. Based on previous reports (5), the questionnaire options of agree and strongly agree as well as disagree and strongly disagree were combined to better present the data in terms of positive and negative answers. A χ² test was used to compare the exam performance between the classes with and without the laboratory class. This analysis was conducted using Statistical Package for the Social Sciences (version 22, SPSS) for Windows, and the level of significance was set at P < 0.05. Graphical presentation can be performed using Microsoft Excel, Origin, or similar software.

RESULTS

Subject characteristics and resting hemodynamics variables are presented in Table 1.

Figure 3 shows systolic (A) and diastolic (B) BP and HR (C) responses at rest and during IHG, PEI, and recovery in men and women. The Student’s t-test was used to compare the means of each variable between groups. The significance was set at P < 0.05. Graphical presentation can be performed using Microsoft Excel, Origin, or similar software.

Table 1. Participant characteristics and resting hemodynamics variables

|                        | Men          | Women        |
|------------------------|--------------|--------------|
| n                      | 47           | 47           |
| Age, yr                | 19 ± 1       | 20 ± 1       |
| Body mass, kg          | 75.0 ± 10.5  | 59.8 ± 7.2   |
| Height, m              | 1.80 ± 0.05  | 1.61 ± 0.07  |
| Body mass index, kg/m² | 23.0 ± 2.4   | 23.0 ± 0.8   |
| MVC, kg                | 50.3 ± 12.8  | 32.0 ± 5.9   |
| Systolic BP, mmHg      | 121 ± 5      | 112 ± 5      |
| Diastolic BP, mmHg     | 72 ± 10      | 71 ± 4       |
| HR, beats/min          | 68 ± 7       | 74 ± 15      |

Values are means ± SD; n, no. of subjects. BP, blood pressure; HR, heart rate; MVC, maximum voluntary contraction.
Fig. 3. Systolic (A) and diastolic (B) blood pressure (BP) and heart rate (HR; C) responses at rest and during isometric handgrip (IHG) exercise, postexercise ischemia (PEI), and recovery in men (○; n = 4) and women (○; n = 4). Values are means ± SD. bpm, Beats/min.

Fig. 4. Average of changes (Δ) from rest during isometric handgrip (IHG) exercise and postexercise ischemia (PEI) in systolic (A) and diastolic (B) blood pressure (BP) and heart rate (HR; C) in men (solid bars, n = 4) and women (open bars, n = 4). Values are means ± SD. bpm, Beats/min.
Women blood lactate responses at rest and during PEI and recovery (these responses were more pronounced in men. Figure 5 shows PEI, arterial BP remained elevated in both sexes; however, exercise were greater in men compared with women. During PEI, arterial BP remained elevated in both sexes; however, these responses were more pronounced in men. Figure 5 shows blood lactate responses at rest and during PEI and recovery (A) and change from rest during PEI (B) in men (solid symbols/bars) and women (open symbols/bars). Blood lactate increased during PEI in women (Δ0.89 mmol/l) and further increased in men (Δ1.45 mmol/l). Importantly, RPE was similar between sexes (men: 7.8 ± 0.5 vs. women: 7.5 ± 0.5; means ± SD).

Table 2 includes the responses to survey questions from students who participated in both traditional learning and the practical laboratory class (n = 46). The results suggest that, before the laboratory class, some students were not confident of their understanding of cardiovascular responses to exercise.

Table 2. Students’ perception survey

| Statement                                                                 | Strongly Disagree/Disagree | Neutral | Agree/Strongly Agree |
|--------------------------------------------------------------------------|-----------------------------|---------|----------------------|
| I understood the cardiovascular responses to exercise well before the laboratory class. | 13 % 6 n                    | 30.4 % 14 n | 56.5 % 26 n         |
| The activity as a whole improved my understanding of the cardiovascular responses to exercise. | 0 % 8.7 n                   | 8.7 % 4 n   | 91.3 % 42 n         |
| The activity improved my understanding of the role of skeletal muscle metaboreflex as an important mediator of cardiovascular responses to exercise. | 8.7 % 4 n                   | 13 % 6 n    | 78.3 % 36 n         |
| The activity improved my understanding of the role of lactate as a trigger of skeletal muscle metaboreflex activation. | 4.3 % 2 n                   | 17.4 % 8 n  | 78.3 % 36 n         |
| The activity as a whole improved my understanding of the sex differences in cardiovascular responses to exercise. | 8.7 % 4 n                   | 15.2 % 7 n  | 76.1 % 35 n         |
| The activity reinforced or enhanced my appreciation for the importance of understanding the course content. | 0 % 0 n                     | 0 % 0 n     | 100 % 46 n          |
| The activity enhanced my desire to learn the course content. | 0 % 0 n                     | 15.2 % 7 n  | 84.8 % 39 n         |
| The laboratory class helped to improve my approach for studying the content for the course exam. | 2.2 % 1 n                   | 17.4 % 8 n  | 80.4 % 37 n         |
| I enjoyed the activity as a whole compared with lecture alone. | 0 % 19.6 n                  | 9 % 80.4 n  | 80.4 % 37 n         |
| I am more likely to want to study course material outside of class the more I understand it during class (compared with material that I did not understand during class). | 0 % 4.3 n                   | 2 % 95.7 n  | 44 % 44 n           |

Values are percentage and no. (n) of students who answered (n = 46 total responses).
cardiovascular regulation during exercise; students’ self-reported understanding of several aspects of cardiovascular responses to exercise and the neural control mechanisms of circulation during exercise. The class exam performance was divided based on the overall student score (minimum of 0 and maximum of 10 points) into different scales: ≤5 points, between 5 and 6.9 points, and 7–10 points. n, No. of students.

class, only 22% achieved the highest exam score (i.e., ≥7 points). On the other hand, when the second group of students were exposed to a laboratory class, 38.3% achieved a higher score.

DISCUSSION

The present study was undertaken to examine the effectiveness of a practical laboratory class using isolated skeletal muscle metaboreflex activation via PEI as a tool for teaching cardiovascular physiology for undergraduate students. The main findings are that 1) our laboratory class improved the students’ self-reported understanding of several aspects of cardiovascular regulation during exercise; 2) the activity improved the students’ appreciation for the importance of the cardiovascular physiology; and 3) students who participated in the present experimental laboratory class tended to have greater scores in the course exam compared with students who had the traditional lecture alone. In addition, since students felt that the activity increased their understanding of cardiovascular regulation during exercise, it is possible that the activity had an extended effect of increasing the desire to study the topic outside of class. Taken together, these results provide a simple and useful laboratory technique that could enhance students’ learning and may encourage exercise physiology teachers to demonstrate several aspects of cardiovascular regulation during exercise by using PEI as a simple technique to isolate the metabolic component of exercise pressor reflex in humans.

The present activity learning used a traditional approach proposed in 1937 by Alam and Smirk (2) to isolate the metabolic component of exercise pressor reflex (i.e., muscle metaboreflex) with PEI. During PEI, arterial BP remained elevated compared with resting values, whereas HR returned to baseline. These cardiovascular responses observed by Alam and Smirk were ratified later by several authors, and, consequently, the muscle metaboreflex was not considered to influence HR after IHG, but was believed to raise arterial BP via an increase in sympathetically mediated peripheral vasoconstriction and cardiac output (51). However, a less well-appreciated observation is that HR remains elevated during metaboreflex activation with PEI after leg exercise (1), suggesting that the limb or mass of exercising muscle also influences HR during PEI. In addition, recent studies showed that HR responses to PEI are influenced by the exercise modality and intensity, size of the exercising muscle mass (16), and participant body position (51). These aspects could be further discussed by teachers in their classes.

PEI technique requires simple and easily handled equipment; however, in our laboratory class, we employed blood sample analysis to further demonstrate the pivotal role of blood lactate as a mediator of skeletal muscle metaboreflex activation. Of note, we used a gold standard YSI method (Yellow Springs) to measure blood lactate, but future laboratory classes can perform this using a portable lactate analyzer, which is able to process blood samples simply and quickly (31). However, if teachers are unable to collect blood samples, we encourage performing this laboratory class without lactate analysis. Furthermore, to demonstrate the importance of blood lactate as a critical mediator of skeletal muscle metaboreflex activation, we recommend introducing during traditional learning the classic work of Professor Paul Fadel in patients with myophosphorylase deficiency (i.e., McArdle’s disease), who cannot metabolize intramuscular glycogen and do not generate lactic acid in exercising muscles (15). Another suggestion for future laboratory activity is to collect data in a trial without muscle ischemia. By performing this trial, hemodynamic variables will increase during exercise and rapidly return to baseline during recovery (30).

An important point that should be considered is the potential sex differences in the cardiovascular responses at rest and during exercise. Indeed, several studies have shown attenuated muscle metaboreflex activation in women compared with men (9, 25), but the precise underlying mechanisms remain unclear. It is well established that cardiovascular control is markedly different between men and women (26, 29, 38, 48, 53, 55), in part because of the effects of female sex hormones (i.e., estrogen and progesterone) on the cardiovascular system (32). Recently, we found that spontaneous cardiac baroreflex sensitivity and parasympathetic indexes of HR variability were enhanced during PEI in men but not (or less increased) in women (48). In addition, Notay et al. (36) reported that handgrip MVC was important for the larger BP responses to IHG exercise observed in men compared with women. Collectively, these findings could contribute to the sex differences in arterial BP regulation during PEI. Interestingly, in our laboratory class, we are able to demonstrate the sex-related differences in cardiovascular responses to exercise and skeletal muscle metaboreflex activation, even with a very small sample size (4 men and 4 women). However, as highlighted before, we did not perform robust statistical analyses to confirm these results.

Question and answers to follow up this activity. Here we suggest some key discussion questions that could be used as a follow up to this activity other than the laboratory report.
format. The answers to each one of the questions can be discussed in class by using the referenced papers.

1. What effect does arterial baroreflex have on HR during PEI? (Refs. 20, 48)
2. What effect does Parkinson’s disease have on muscle metaboreflex-mediated hemodynamic responses to exercise? (Ref. 47)
3. What effect does hypertension have on muscle metaboreflex-mediated hemodynamic responses to exercise? (Ref. 7)
4. What effect does diabetes have on muscle metaboreflex-mediated hemodynamic responses to exercise? (Ref. 24)
5. What effect does exercise intensity have on hemodynamic responses to muscle metaboreflex activation? (Ref. 18)

Conclusion. In summary, the present study describes a practical lesson methodology used in an undergraduate exercise physiology laboratory class that can improve students' learning and guide teachers to incorporate the use of isolated skeletal muscle metaboreflex activation via PEI as a tool for teaching cardiovascular physiology for undergraduate students.

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

AUTHOR CONTRIBUTIONS
A.L.T. conception and design of research; A.L.T. and M.S. performed experiments; A.L.T., M.S., and L.C.V. interpreted results of experiments; A.L.T. prepared figures; A.L.T. performed experiments; A.L.T., M.S., and L.C.V. analyzed data; A.L.T., M.S., and L.C.V. approved final version of manuscript.

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