Quantitative Circulatory Physiology: an integrative mathematical model of human physiology for medical education

Sean R. Abram, Benjamin L. Hodnett, Richard L. Summers, Thomas G. Coleman, and Robert L. Hester

Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi

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In the pursuit of providing the most comprehensive medical educational experience possible, many healthcare training centers around the world are employing elaborate mathematical models (simulations) that mimic clinical problems often encountered in the practice of medicine. Simulation, as defined by John Doyle (4), is an "artificial representation of a complex real-world process with sufficient fidelity to achieve a particular objective, usually for the purposes of training or performance testing." The Quantitative Circulatory Physiology (QCP) model discussed in this article has been effective in fostering the development of skills in the areas of diagnosing, evaluating, and treating future patients by providing first-year medical students and others with an opportunity to understand concepts essential to integrative physiology.

Throughout the latter half of the 20th century and into the present, computer simulation has been viewed as a cost-effective educational instrument that allows pre-/postgraduate students in the basic sciences, engineering, and healthcare professions to learn a bevy of skills essential to their respective crafts. For example, simulation allows for the creation of a disturbance and the ability to track the response without causing harm to the patient/animal or encouraging exorbitant increases in a medical facility’s budget (1). Also, new and exploding technology, with respect to computer resourcefulness, literally allows the student 24-h access to an educational tool that promotes acquisition of skills that are often required during the indepth study of physiology as well as other scientific disciplines. Arguably, the most important component associated with computer simulation-enhanced education is the fact that it facilitates the learning of physiology using a systems analysis approach. For example, in the laboratory and/or clinical setting, situations often arise that do not allow for the administration of particular pharmacological agents, due to adverse effects rendered systemically. This problem is somewhat circumvented in biomedical research by the ability to perform in vitro experiments. Although they have contributed mightily to our understanding and ability to extrapolate data, in vitro studies are not always indicative of what is seen when whole animal research is conducted (9). It is in the previously mentioned realities that computer simulation finds its niche. Mathematical modeling allows the clinician and/or biomedical researcher to perform experiments that are presently not possible in today’s world of complex medicine and biomedical research. Last, but certainly not least, is the fact that simulation provides an ethical medium by which the scientist is not limited by boundaries or the confinements of research and research. Last, but certainly not least, is the fact that simulation provides an ethical medium by which the scientist is not limited by boundaries or the confinements of research and modern day medicine, i.e., moral, ethical, and legal pitfalls.

QCP is a dynamic mathematical model composed of 4,000 variables and equations based on published responses generalized to the population. With the initial concentration focusing on the circulatory system, QCP’s capability and effectiveness have increased over the past three decades with the incorporation of many other physiological systems, e.g., the nervous, respiratory, and endocrine systems. Previously published departmental studies (2, 5) using mathematical modeling have focused on cardiovascular function and complementary systems. Although the majority of the text is dedicated to helping the reader understand how QCP operates and the physiological responses to exercise, an additional purpose of this article is to highlight the educational benefits of incorporating a tool such as QCP into the training and curriculum of the competent medical scientist.

Features of QCP

QCP allows the user to adjust many characteristics of the patient’s physical environment, from global conditions such as altitude to local qualifiers such as temperature, humidity, and barometric pressure. Other external parameters that can be adjusted include the partial pressures of individual gases in
inspired air and the nutritional composition of ingested food and fluids. Control of the patient’s daily routine schedule allows the user to adjust basic functions such as sleeping, working, and feeding on an hour-to-hour basis, whereas the “Exercise” panel facilitates studying the effects of differing types of exercise on both short- and long-term scales (Fig. 1).

Various panels such as the “Organ Details” and “Basic Physiology” button groups allow the user to investigate and adjust physiological parameters on a more indepth basis (Fig. 2). Panel features include graphical data displays, information buttons, and adjustable variables. The use of these features is shown in Fig. 3, which details the panels for angiotensin where the rates of secretion, degradation, and metabolism can be manipulated. In some instances, pathophysiological states can be mimicked through the use of radio and slider buttons that allow hormone levels to be clamped or fixed at a given level (Fig. 3).

In addition to the manipulation of physiological parameters, QCP allows the user to administer pharmacological agents to treat a simulated patient. Currently, four drugs are available for interventional treatment: chlorothiazide, digoxin, furosemide, and midodrine. Additional drugs can be added as the quantitatively relationships regarding their physiological function are determined. Several additional treatment options are available in the QCP model, including placing the patient on a ventilator, administering fluids via an intravenous drip, and performing a blood transfusion.

Sample Simulation: the Exercise Simulation

Exercise is physiologically one of the most exertive cardiovascular events to which many individuals consistently submit themselves. Exercise is used to achieve overall better health and to protect from diseases such as diabetes, hypertension, and obesity. The QCP model can be used as a teaching aid to reinforce core physiological concepts through the simulation of a simple exercise regimen. This section outlines the steps in setting up a simple exercise protocol for teaching purposes, followed by a comparison of the simulation with expected results based on basic physiological principles.

Steps in setting up a simple exercise protocol. The sequence is as follows: displaying the correct panels (multiple screens that display the model’s variables and parameters), loading the

Fig. 1. External parameters, such as altitude and temperature, can be adjusted on the “Environment” panel. Inspired air and diet composition can be manipulated using the “Air Supply” and “Diet” panels. The “Exercise” panel allows the user to set exercise bike or treadmill regimens.
initial conditions, placing the subject in the correct exercise position, and beginning a treadmill exercise regimen.

**STEP 1.** Start the QCP program.
**STEP 2.** Access the “View” main menu and select “Organ Details.” (“Clinical” buttons and “Basic Physiology” buttons should already be checked.)
**STEP 3.** Access the “Orthostasis” panel (Fig. 4). Select the radio button under “Posture Control” labeled “Suggest - Standing.”

At this point, the subject is now in the standing position required for exercise. Before the exercise simulation is begun, a control period should be simulated to account for positional changes in blood pressure and heart rate that occur when moving from a lying to standing position.

**STEP 4.** Access the “Monitor” panel to view the blood pressure, respiratory rate, temperature, and heart rate that occur during the control period.
**STEP 5.** Access the “Go” main menu and select “1 Hour.” Another useful tool is the “Mark” function. This tool allows the user to place a vertical line on the graphs. Placing a mark on the graphs allows the user to better see the changes that occur during the exercise simulation.
**STEP 6.** Right-click any of the graphs on the screen and select “Graph - Mark.” Select “All Graphs” under the “Apply To” box.

Now that the graphs are marked, the exercise protocol can begin. This regimen simulates treadmill exercise on a 2% incline at a speed of 2 miles/h.
STEP 7. Access the “Exercise” panel (Fig. 4). Select the radio button under “Control - Type” labeled “Treadmill.” Adjust the slider bars in the “Treadmill” box until they read “Speed (MPH) = 2” and “Grade (%) = 2.”

STEP 8. Access the “Monitor” panel again to view the changes in blood pressure, respiratory rate, temperature, and heart rate that occur during the exercise period.

STEP 9. Access the “Go” main menu and select “30 Min.” At this point, the user should be able to see an increase in the blood pressure, respiratory rate, temperature, and heart rate (Fig. 5). By accessing the various panels of the “Basic Physiology” and “Organ Details” groups, the user can further examine other physiological changes that occurred during the exercise regimen. As an additional note, the forward and back arrows located in the upper left corner are used to rotate the display among recently view panels.

Results and discussion of the exercise simulation. Theoretical and experimental evidence demonstrate the profound global physiological changes associated with exercise. For example, changes in arterial pressure, cardiac function, respiratory rate, and hormone secretion all occur in response to increased physical activity. In addition to simulating an exercise regimen and charting the responses, the following discussion will attempt to examine the mechanism(s) responsible for promoting these changes and ultimately demonstrate how one can effectively use QCP to communicate basic principles integral to exercise physiology.

As mentioned in the patient’s chart, our test subject’s name is Mr. Norm, a 37-yr-old healthy man with no prior history of major illness. The following values are based on the initial conditions that we used for the simulation. Changing the initial control period or exercise parameters will result in different values, all dependent on the physiological conditions. Upon standing for a period of 1 h, the monitor shows that Mr. Norm’s blood pressure (111/78 mmHg), respiration rate (14 breaths/min), and heart rate (93 beats/min) are all within normal limits. Selection of the blood flow button reveals that his cardiac output is 5,046 ml/min. Secretion of the pancreatic hormones glucagon and insulin are 57 ng/min and 12.5 mU/min, respectively. After 30 min of treadmill running at a speed of 2 miles/h and a grade of 2%, Mr. Norm’s physiological parameters change markedly. Significant increases in blood pressure (152/98 mmHg), respiration rate (21 breaths/min), heart rate (128 beats/min), cardiac output (11,417 ml/min), and glucagon secretion (79 ng/min) are all observed. Conversely, insulin secretion (8.1 mU/min) is decreased in response to increased physical activity. To facilitate comparison of the model results and real-life situations, we have included a brief overview of physiological changes seen in exercise and how they compare with those seen during the exercise simulation using QCP (Fig. 6).

CARDIOVASCULAR AND NEURAL CONTROL OF BLOOD FLOW DURING EXERCISE. The ability to increase muscle blood flow during exercise is of critical importance to ensure an adequate supply of oxygen and nutrients to meet the increased metabolic demands of the tissue. Skeletal muscle vasodilation is proportional to the skeletal muscle metabolic rate in exercise. This allows for increased blood flow to the tissue and facilitates proper functioning of the muscle during strenuous activity. To increase muscle blood flow in response to the elevated metabolic demand, the body must increase sympathetic activity, blood pressure, and cardiac output (6).

During the onset and continuation of exercise, signals from the brain as well as the exercising muscle and joints work in
concert to increase sympathetic output from the brain’s vaso-
motor center. A simple check of Mr. Norm’s general nerve
activity reveals that his sympathetic activity increases signifi-
cantly in response to treadmill exercise. This increased sym-
pathetic activity also plays a role in the acute rise in blood
pressure that we observe on Mr. Norm’s monitor panel. Es-
sentially, the increased sympathetic activity has an effect to
dramatically elevate the activity of his heart and promote
constriction of the peripheral circulatory arterioles. In addition,
the increased sympathetic activity has a profound effect to
increase venous constriction, resulting in a marked elevation of
venous return of 126%. Since within physiological limits the
heart pumps to the peripheral circulation (cardiac output) the
same amount of blood that it receives (venous return), we
would expect the elevated level of cardiac output that is
observed in the exercising subject.

Although sympathetic activity is increased and blood pres-
sure rises, the distinct differences in blood flow within the
exercising muscle and the peripheral circulation should be
noted. The blood flow in Mr. Norm’s skeletal muscle is
markedly increased, whereas blood flow to organs such as the
kidney and intestines are significantly decreased. While the
decreased flow to organs such as the intestines and kidneys
may be explained by increased sympathetic nervous system
activity, the effect of the sympathetic nervous system on
skeletal muscle appears to be a little more complex.

The observance of blood flow’s diametric responses between
Mr. Norm’s exercising tissue and various other organ systems
may be explained by a phenomenon known as sympatholysis.
Sympatholysis is a term coined by Remensnyder et al. (3) that
seeks to explain the decreased vasoconstriction of skeletal
muscle in the face of increased sympathetic activity. In concert
with sympatholysis, it may also be argued that increased blood
flow to muscle, as seen in our patient, may also be the result of
locally produced vasodilators, such as adenosine and nitric
oxide, within the exercising muscle.

**Respiratory Control During Exercise.** While not as impor-
tant during bouts of acute exercise such as sprinting, increases
in respiratory rate play a significant role in one’s ability to
perform exercise regimens that call for sustained physical
activity (6). Respiration is controlled by central neurogenic
mechanisms located in the medulla oblongata and the pons of
the brain stem. The primary function of respiration is to ensure
that there is a proper balance between the levels of oxygen,
carbon dioxide, and hydrogen ions in the tissues (6).
Normally, a person at rest has a respiratory rate of \( \sim 12 \) breaths/min. Although Mr. Norm’s respiratory rate is 14 breaths/min, he is well within physiological limits of the norm. After 30 min of exercise, his minute ventilation, the volume of gas entering the lungs per minute, was markedly increased from 8.9 to 32.1 l/min. In addition, treadmill running increased his respiratory rate by 50%. The increase in respiration seen in Mr. Norm is primarily the result of the brain’s ability to transmit impulses, similar to those sent to exercising muscle, to the respiratory centers of the brain stem. These motor impulses have an effect to directly stimulate the respiratory center and result in an increased respiratory rate (6).

In addition to motor input nuclei, the respiratory center of the brain has chemosensitive areas that work directly (carbon dioxide and hydrogen ions) to stimulate respiration. With the increased metabolic demand placed on Mr. Norm, it is easy to see how one would think that increased carbon dioxide levels would be responsible for his increased ventilation. However, within the first minute of exercise, carbon dioxide levels actually decrease and revert toward normal after 1 min of exercise. This is due in large part to Mr. Norm’s ability to “match” his ventilation rate with that of increased carbon dioxide levels produced by exercising muscles (5).

Ultimately, the respiratory center is controlled through its ability to receive and integrate input from both motor neurons and chemoreceptors. However, in normal individuals, the neurological aspect of respiration predominates during exercise. The chemosensitive areas seem to be involved more in instances where there is neurological impairment, during which time they buffer extreme changes in respiratory gases (6).

**ENDOCRINE CHANGES DURING EXERCISE.** Endocrine factors also play an important role in facilitating efficient exercise performance. Upon examination of Mr. Norm, we find that glucagon secretion from pancreatic \( \alpha \)-cells increases from 57 to 79 ng/min in response to treadmill exercise. The simulated exercise regimen correlates well with what is seen in individuals subjected to increased physical activity (8). Glucagon is a pancreatic hormone that is secreted from \( \alpha \)-cells in response to reductions in blood glucose levels. Although the exact mechanism responsible for the increased secretion of glucagon remains unknown, increased circulating levels of amino acids and nerve activity are known to promote its release from the pancreas.
α-cells (6). The ability to elevate blood glucose during exercise is important because glucose ultimately serves as an energy source for muscle and nerve activity.

Opposing the effects of glucagon, insulin, secreted by pancreatic β-cells, functions to increase glucose uptake. Insulin is secreted in response to excess circulating glucose, such that the insulin secreted in large quantities after a meal promotes increased transport of glucose into muscle and adipose tissue. Blood glucose levels are also decreased by liver uptake, albeit in a non-insulin-dependent manner. Excess quantities of glucose in the muscle and liver are stored in the form of glycogen, which can be used as a source of energy in time of need.

During exercise, the need to store as well as increase the uptake of glucose, via activation of glucose transporters, is diminished (7). In fact, during increased strenuous activity, the muscle actually “becomes permeable to glucose even in the absence of insulin because of the contraction process itself” (6). In agreement with theoretical and experimental evidence, Mr. Norm’s level of insulin secretion decreased by ~50% in response to exercise.

Additional Simulations

The QCP software program can be used with a series of laboratory exercises and simulated patients provided as an on-line QCP laboratory manual (Tables 1 and 2). Laboratory guides for each exercise contain step-by-step instructions for loading patients or scenarios and running the simulations, along with tables students can use to record patient data. These exercises are valuable aids for teaching case studies and for small-group discussions.

To illustrate the use of these laboratory exercises and simulated patients as a teaching aid, the manual for the diabetes mellitus exercise is provided. This exercise can be studied alone or in conjunction with the simulated patient Ms. Thomas, who represents a case in which a patient has untreated Type I diabetes mellitus or insulin-dependent diabetes mellitus. The laboratory exercise focuses on the glucose and hormonal changes seen in such a case, whereas the patient case asks the students to analyze additional parameters including acid-base status and circulatory status. The diabetes mellitus laboratory manual begins with the following brief overview of the disease:

When glucose is being absorbed, increased blood levels of insulin are beneficial. This insulin facilitates glucose uptake by the tissues and helps to replenish the glycogen stores of liver and skeletal muscle.

In diabetes mellitus, the beta cells of the pancreas do not secrete adequate amounts of insulin when it is needed. Need is most evident following a carbohydrate-rich meal.

In this exercise, we’ll first stop insulin production and then view the consequences of eating a meal in a repeat of the eating exercise presented in another lab.

Figure 7 and Table 3 show the protocol and results table provided with the laboratory exercise on diabetes mellitus, respectively.

The QCP laboratory manual and QCP 2005 user’s guide are available online at http://physiology.umc.edu/themodelingworkshop/integrative model/integrative model.html. In addition, a comprehensive list of individual simulation exercises and clinical patient scenarios with accompanying laboratory guides is available at http://physiology.umc.edu/themodelingworkshop/integrative model/simulations.html. The QCP 2005 user’s guide contains a section entitled “Patients,” which details the steps involved in creating a simulation patient and establishing initial conditions for the model.

Additional Information

The QCP model can be downloaded from the Department of Physiology and Biophysics at the University of Mississippi Medical Center’s Modeling Workshop website: http://physiology.umc.edu/themodelingworkshop/index.html. This website includes both online and downloadable versions of the QCP users and laboratory manuals as well as a forum for feedback and support.
In addition to QCP, this website includes the Model Builder and Model Solver software packages. These tools allow the user to create additional models using the Extensible Markup Language (XML). An extensive instructional section on using the XML schema is provided along with open-source models, both of which provide users with aid in creating their own models. The examples provided in the on-line library include renal and circulatory models along with models simulating basic physics problems such as projectile motion.

No model is perfect, and, as such, we welcome all suggestions and help in identifying problems in QCP. The model is based on over 4,000 simultaneous equations, and, in some instances, physiological relationships are unknown due to lack of scientific knowledge. A human readable XML source code has been made available on the webpage (as of May 2007). This allows users around the world to use and improve the software.

**Conclusions**

Mathematical simulations allow students as well as healthcare professionals to view and understand how mechanisms, concepts, and ideas taught in lecture are applicable to many of the pathophysiological states often observed in the clinical setting. A benefit of QCP is the ability to convey the response of several complex systems to physiological perturbations without incurring huge costs or harm to the patient. For example, Mr. Norm, in a virtual sense, revealed the marked physiological changes that occur in the neural, cardiovascular, respiratory, and endocrine systems in response to increased physical demands. Although not provided in this text, a comprehensive analysis of Mr. Norm’s response to exercise may be viewed using the toolbar buttons located just below the main menu.

**Table 3. Results table for the laboratory exercise on diabetes mellitus**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12:00</td>
</tr>
<tr>
<td>Glucose mass</td>
<td></td>
</tr>
<tr>
<td>Fat mass</td>
<td></td>
</tr>
<tr>
<td>Protein mass</td>
<td></td>
</tr>
<tr>
<td>Plasma [glucose]</td>
<td></td>
</tr>
<tr>
<td>Tissue glucose use</td>
<td></td>
</tr>
<tr>
<td>Brain glucose use</td>
<td></td>
</tr>
<tr>
<td>Fat glucose use</td>
<td></td>
</tr>
<tr>
<td>Muscle glucose use</td>
<td></td>
</tr>
<tr>
<td>Plasma [free fatty acids]</td>
<td></td>
</tr>
<tr>
<td>Tissue free fatty acid use</td>
<td></td>
</tr>
<tr>
<td>Muscle free fatty acid use</td>
<td></td>
</tr>
<tr>
<td>Plasma [triglycerides]</td>
<td></td>
</tr>
<tr>
<td>Fat triglyceride uptake</td>
<td></td>
</tr>
<tr>
<td>Liver glycogen</td>
<td></td>
</tr>
<tr>
<td>Plasma [insulin]</td>
<td></td>
</tr>
<tr>
<td>Plasma [glucagon]</td>
<td></td>
</tr>
</tbody>
</table>
Teaching With Technology

These toolbar buttons may be used to manipulate a variety of factors associated with Mr. Norm’s level of activity and overall physiological state. In essence, QCP allows one to examine, integrate, and understand a host of physiological factors without incurring great costs or causing harm to patients. First-year medical students at the University of Mississippi Medical Center have stated in their Medical Physiology student evaluations that QCP “... was a good way to apply/reinforce our knowledge.” Another student stated “I really like the program and the ‘hands on’ feel of the lab.” In short, most students seem to agree that QCP helped them to understand the integrative aspects of physiology. In conclusion, we believe that any tools that improve the ability to examine, integrate, and understand physiological responses are indispensable in conveying the critical concepts associated with the complex realities of modern medicine.

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REFERENCES