Diabetes, a syndrome characterized by high plasma glucose and low plasma insulin concentrations, is associated with somatic and autonomic neuropathies as well as cardiac and vascular disorders. These consequences of diabetes significantly affect the organism's ability to maintain homeostasis. To understand the changes associated with diabetes, we developed a laboratory exercise that compares and contrasts the cardiovascular responses to exercise in an individual with diabetes and in an individual without diabetes. This exercise provides a unique opportunity to analyze, integrate, and interpret the changes associated with diabetes, since more is learned about how a system operates when the system is forced to perform than when it is idle. In this laboratory, anatomical and physiological data concerning diabetes are provided. Subsequently, a figure that illustrates the response of a specific cardiovascular variable during exercise (e.g., heart rate, cardiac output, blood pressure) is presented. Students are challenged to analyze and assimilate information from figures, answer questions, make calculations, fill in tables, and plot graphs. The laboratory does not require equipment or software, only rulers and pencils. The answers to the questions and tables are provided in the APPENDIX. Students obtain experience in evaluating and understanding diabetes as well as applying basic cardiovascular concepts. The emphasis is on the application of basic cardiovascular principles, interpretation of pictorial or tabular material, and problem-solving skills.

Key words: physiology education; teaching

Teachers are constantly searching for new and innovative methods of engaging students in interactive learning. One innovative method of teaching basic physiological concepts is to compare and contrast systems in physiological (nondisease states) and pathophysiological (special populations) conditions. This method is similar to that used by researchers when investigating physiological systems. Investigators perturb the system to understand its response and therefore its function. In this context, teachers can use special populations to teach function because disease states also perturb the system, which results in specific responses. This method utilizes a practical living process to dissect basic concepts while at the same time understanding a specific disease state.

Dynamic exercise can also be used as an educational tool, since more can be learned about how a system operates when the system is forced to perform than
when it is idle (1, 2). For example, significantly more can be learned about how the cardiovascular system functions during exercise than at rest. In this manuscript, we present a laboratory experience that utilizes a disease state (diabetes) and exercise to teach basic physiological concepts.

Individuals with diabetes mellitus, a syndrome characterized by high plasma glucose and low plasma insulin concentrations, are subject to anatomical and physiological changes that significantly affect the response to internal and external stimuli (homeostasis). Homeostasis is maintained, in part, by adjustments in the cardiovascular, endocrine, and nervous systems. However, individuals with diabetes have a reduced ability to compensate for changes in homeostasis due to significant changes in these systems. These reduced abilities to respond to changes in homeostasis are dramatically illustrated during the stress of exercise. In this context, we developed a laboratory exercise to assist students in understanding the cardiovascular adjustments made during a time when the regulatory components of the cardiovascular system are fully active, that is, during exercise, in individuals with and without diabetes.

The purpose of this laboratory exercise is to present an interactive teaching tool that helps students understand the anatomical and physiological limitations that exist in an individual with diabetes. In addition, students will learn basic cardiovascular principles. To this end, we developed a laboratory exercise to assist students in understanding the cardiovascular adjustments made during a time when the regulatory components of the cardiovascular system are fully active, that is, during exercise, in individuals with and without diabetes.

PEER EVALUATION

This laboratory exercise, along with two similar exercises examining the cardiopulmonary changes associated with aging and congestive heart failure, was presented at an Educational Materials Workshop at the annual meeting of the American College of Sports Medicine in Indianapolis, IN, in 1994. The Educational Materials Workshop presented a specific laboratory exercise each day for three consecutive days. The first-day workshop was entitled “The Cardiopulmonary Changes Associated with Aging,” the second-day workshop was entitled “The Cardiopulmonary Changes Associated with Congestive Heart Failure,” and the third-day workshop was entitled “The Cardiopulmonary Changes Associated with Diabetes.” Each workshop was conducted in a 3-h period. During the 3-h period, participants were introduced to the educational tool in a poster format. The poster consisted of a condensed version of the educational material. In addition, a slide presentation was available. During the slide presentation, participants could advance the slides at their own pace and experience how the tool could be used in the classroom. Finally, hard copies were available, along with paper and pencils, so that participants could sit down and experience how the tool could be used in a laboratory/interactive setting. The workshop was designed to be informal and interactive. There were no time restraints, and participants could avail themselves of any of the three presentation formats and come and go at their convenience. During the workshop, the poster, slides, and hard copies were offered simultaneously. The authors were readily accessible during each workshop to answer questions, share ideas on education, and encourage interaction.

Individuals who participated in the laboratory exercise included physicians, nurses, physical therapists, cardiac and pulmonary rehabilitators, educators, and scientists. Based on comments and interactions at the conference, as well as the communication with participants upon returning home (including requests for the materials), we believe that this format of presenting the information and materials was extremely well received. The following are excerpts from letters received after the meeting: “Your con-
cept is truly the direction that educators in our field should be striving to accomplish...Your material would be extremely useful for my Exercise Science students during their clinical rotations,” Joe Sagorsky, MS, Manager, Health Promotion Services; “Your education packets will provide exceptional learning experiences for our graduate students,” Shala Davis, PhD, College of Education, Virginia Polytechnic Institute and State University; “As I complete nearly 35 years of teaching in higher education, I’m still attracted to new and innovative ideas such as yours,” M. Thomas Woodall, PhD, Director of Adult Fitness/Cardiac Rehabilitation, Director of Human Performance Laboratory, Eastern Illinois University; “I will be offering a workshop on Exercise Physiology in Clinical Populations in the fall [1993]. This workshop is for exercise physiologists, nurses, and other rehab health professionals. I would like to incorporate some active learning activities in this workshop and was excited to see the work you had done in this area,” Karen Toft Dorn, Department of Nursing, Augustana College; “I was very impressed with this educational experience and think it would be very useful in the course I teach in cardiopulmonary physical therapy,” Tanya K. LaPier, Assistant Professor, Idaho State University; “Congratulations to you and your colleagues on a superb educational experience at the recent ACSM annual meeting in Indianapolis,” Chris Pamp, MEd, Providence General Medical Center, Cardiac and Pulmonary Rehabilitation; “I am organizing a journal club for summer research students here at the Mayo Clinic and I thought your ‘games’ might be a dynamic way to involve these students in discussions about cardiopulmonary physiology,” David N. Proctor, PhD, Mayo Clinic; “I teach Cardiovascular Physiology at the Master’s level and I believe your series will be a welcome addition to my course,” John P. Porcari, PhD, Executive Director, LaCrosse Exercise and Health Program, University of Wisconsin; “On behalf of the graduate students in Kinesiology, who attended the ACSM conference, I would like to tell you that we found your tutorial very informative,” M. T. Sharratt, PhD, Associate Dean for Graduate Studies and Research, University of Waterloo. We believe, as do others, that this interactive teaching format is an important component for innovative interactive learning.

SUMMARY

The purpose of this educational material was to provide an innovative and interactive teaching tool that helps students and researchers understand the cardiovascular changes during exercise in individuals with and without diabetes. The educational tool can be used in a classroom and/or in a laboratory setting for undergraduate, graduate, and nursing students as well as for professionals in cardiac and pulmonary rehabilitation. From the presentation experience and the comments received, the educational material proved to be a valuable teaching tool.

APPENDIX: THE LABORATORY EXERCISE

Subjects

The subjects presented in this laboratory exercise are hypothetical 30-yr-old individuals. One individual has diabetes, and the other individual does not. Basic anatomical and physiological data for these individuals are provided in BACKGROUND INFORMATION.

Time Required

Approximately 4.0-5.0 h are required for completion. If adequate laboratory time is not available, it may be necessary to complete this exercise during out-of-class time.

Level of Difficulty

Students attempting this laboratory exercise should have completed the cardiovascular section of an undergraduate physiology course. It would be suitable for undergraduate, graduate, premedical, medical, nursing, and allied health students. It requires that students be able to read data in graphical and tabular form, perform simple mathematical calculations, fill in tables, and plot data on graphs.

Equipment Required

A pen/pencil, ruler, paper, and calculator are needed.
**Special Skills/Background**

A basic understanding of cardiovascular regulation at rest and during exercise is required.

**Notes to the Instructor**

This laboratory exercise is very straightforward but does require a degree of independence and initiative on the part of the student. Depending on the nature of your student population, you may find it preferable to place your students in small groups. This may facilitate a general discussion of each mechanism and help any students who may experience difficulty with a specific section. The group dynamics may facilitate a more thorough understanding of each mechanism through the group discussions and attempts at answering the questions.

It is at your discretion whether or not this exercise is conducted in specified laboratory time or whether students should be allowed to conduct the exercise outside of the normal laboratory time. Some possible options you might want to consider are 1) conduct an in-class discussion of the basic anatomical and physiological concepts associated with diabetes, 2) help students work through the initial sections of the laboratory exercise, and encourage students to finish the exercise in small groups or individually, or 3) instruct the students on whether you prefer that they work in groups or individually and then have them complete the exercise on their own. If the students are instructed to work during their own time, you may wish to use your laboratory time to discuss their answers and any areas that prove problematic to them. The manner in which you conduct this exercise depends very much on the student’s background and level of understanding of physiology.

**Objectives**

The specific objective of this laboratory is to reinforce an understanding of the relationships between various cardiovascular variables and how they are altered in individuals with diabetes. This specific objective will be met once the following goals have been achieved.

**Goal 1.** The first goal is to acquire a better understanding and ability to integrate and apply various principles of cardiovascular physiology.

**Goal 2.** The second goal is to apply these principles of cardiovascular physiology at rest and during exercise in an individual with and without diabetes.

**Goal 3.** The third goal is to analyze and assimilate information from figures, answer questions, make calculations, fill in tables, and plot graphs.

**PRETEST QUESTIONS**

Pretest questions are designed to prepare students for the laboratory exercise. The questions should focus the student’s thinking and should prepare the student for the concepts that are developed in the exercise. The questions are not designed to determine or establish a knowledge base, rather the questions should prepare the student for the “brain strain” of the exercise.

1. List the anatomical (myocardial and vascular changes) and physiological [maximum oxygen consumption (VO₂max), resting heart rate (HR), and cardiac output (CO)] differences between individuals with and without diabetes.

2. An individual without diabetes can increase HR and, to a small extent, stroke volume (SV) due to circulating catecholamines released by sympathetic efferent nerve endings and the adrenal medulla. Can the individual with diabetes, working at the same percentage of VO₂max as the individual without diabetes, take advantage of this mechanism?

3. Consider the components of the autonomic nervous system that mediate the HR and contractility response to exercise. How might this response be altered in an individual with diabetes who has a decline in both parasympathetic withdrawal and β₁-adrenoreceptor responsiveness?

4. Predict which individual would have the higher resting HR? Which individual would have the lower maximum HR? Which individual would
have a lower HR at the same submaximal workload?

5. Consider the physical (muscle pump, ventricular compliance), neural (sympathetic and parasympathetic stimulation), and humoral (circulating catecholamines) factors that influence the SV response to exercise. How would these factors be affected by diabetes? How would the SV response differ from that of an individual without diabetes?

6. CO is the product of HR and SV. Would you expect CO at rest to be limited in the individual with diabetes? Would you expect CO during exercise to be limited in the individual with diabetes?

7. Mean arterial pressure (MAP) is a variable regulated during exercise. It is probably the most important variable for maintaining homeostasis. MAP is a function of CO and total peripheral resistance. How might each of these individuals regulate MAP at rest and during exercise?

8. Consider the factors that determine aerobic capacity as demonstrated by the following equation

$$\dot{V}O_{2,max} = CO \times (a - v)O_2 \text{ difference}$$

where $a - v$ is arteriovenous. Which of these variables do you think will play the greatest role in limiting $\dot{V}O_{2,max}$ in individuals with and without diabetes?

9. Based on your knowledge of diabetes and its effects on the cardiovascular system, do you think exercise should be recommended for the individual with diabetes? What would be the most likely benefits of an acute bout of aerobic exercise? What might be the contraindications for an individual with diabetes to be involved in strenuous exercise?

10. An individual with diabetes is associated with abnormal cardiovascular regulation due to the detrimental effects of chronic elevations of plasma glucose and triglycerides. As a result of abnormal cardiovascular regulation, exercise tolerance is low. Suppose this individual undergoes an exercise training program. Predict what would happen to this individual’s metabolic control and exercise tolerance.

ANSWERS TO THE PRETEST QUESTIONS

1. The anatomical changes associated with diabetes include an increase in myocardial and arterial stiffness due to the interstitial accumulation of connective tissue, a perivascular thickening of the basement membrane, abnormalities in vascular sensitivity, and altered cardiac autonomic function. The anatomical changes result in decreased vascular and cardiac compliances and increased peripheral resistance. The physiological changes associated with diabetes include impaired cardiovascular function (impaired handling of calcium that results in a decreased shortening velocity and slower relaxation of the cardiac muscle fibers, decreased CO, SV, maximal HR, exercise tolerance, and $V O_{2,max}$), compromised nervous function, metabolic changes (increased plasma glucose and free fatty acid concentrations, disturbances in plasma and cellular lipid and carbohydrate metabolism), and conversion of hemoglobin to hemoglobin A1c. Hemoglobin A1c binds to oxygen more tightly compared with the normal hemoglobin and is a direct result of glucose binding to the hemoglobin molecule.

2. Unfortunately, the individual with diabetes is not able to take full advantage of catecholamines released by the sympathetic nervous system and the adrenal medulla. Diabetes is often associated with autonomic neuropathies that delay and impair the release of norepinephrine from the sympathetic efferent nerve terminal and from the adrenal gland. In addition, a decreased number of cardiac $\beta_1$-adrenoreceptors, which reduces contractility, also contributes to a diminished SV response to increasing workloads.

3. At the onset of exercise, there is a centrally generated signal that simultaneously activates cardiovascular, respiratory, and motor centers (central command). Central command is responsible for the initial rapid rise in HR by the withdrawal of cardiac parasympathetic efferent activity. Above a HR of ~100 beats/min, there is a linear increase in HR with workloads up to ~75% $V O_{2,max}$ that results from cardiac sympathetic efferent activation of the sino-
atrial node. In addition, cardiac sympathetic efferent activity increases contractility. In the individual with diabetes, there is an attenuated withdrawal of parasympathetic activity that attenuates the initial rapid rise in HR. A decline in β₁-adrenoreceptor responsiveness results in an attenuated HR response to increasing workloads during exercise.

4. Resting HR is slightly elevated in the individual with diabetes. A decrease in parasympathetic tone mediates a higher resting HR. However, a lower intrinsic HR tends to result in a lower resting HR. Taken together, the individual with diabetes has a slightly elevated resting HR. The individual with diabetes also will have a lower maximal HR due to the diminished sympathetic outflow. A reduced number of β₁-adrenoreceptors results in a decreased maximal response to norepinephrine thus contributing to a lower maximal HR. Norepinephrine is released from both the cardiac sympathetic efferent nerves and the adrenal medulla. The individual with diabetes will also have a lower HR at the same submaximal workloads due to the reduced number of β₁-adrenoreceptors. Thus there is a diminished HR response to increasing workloads.

5. With diabetes, there is a slower HR response during exercise. The lower HR allows for an increased ventricular filling time. This results in part from the diminished vagal withdrawal and attenuated sympathetic outflow during exercise in the individual with diabetes. An increased ventricular filling time and muscle pump results in an increased end-diastolic volume (EDV), allowing for an increased SV. Despite an initial increase in SV, several factors limit its potential. An increase in afterload due to stiffening of the arterial vasculature that opposes the increase in SV, a diminished response to β₁-adrenoreceptor responsiveness that attenuates the increase in contractility, and a decreased ventricular compliance that limits the increase in EDV will all result in an attenuated SV response during exercise.

6. In the individual without diabetes, resting CO is ~5.6 l/min [SV (70 ml) × HR (80 beats/min)]. Although an individual with diabetes has a similar CO at rest (4.93 l/min), the diabetic myopathies and neuropathies elevate resting HR (90 beats/min) and reduce resting SV (55 ml). Thus CO is limited at rest due to a reduction in SV. During exercise, CO is limited in the individual with diabetes due to the attenuated HR and SV responses during exercise.

7. Diabetes is associated with an increased incidence of atherosclerotic and hypertensive diseases and cardiomyopathies. Unfortunately, these cardiac diseases are not clinically diagnosed until the pathological processes are far advanced. In spite of these changes in the heart and vasculature, resting MAP is similar between individuals with and without diabetes. The increase in MAP for individuals with and without diabetes is also similar through increasing workloads. However, the factors that contribute to the gradual increase in MAP are very different. In the individual without diabetes, MAP rises as a result of gradually increasing CO and decreasing total peripheral resistance. Systolic blood pressure (SBP) continues to rise as diastolic blood pressure (DBP) slowly decreases with increasing workloads. In contrast, the individual with diabetes increases MAP partially from an increase in CO but primarily from an attenuation of the decrease in total peripheral resistance. Initially, SBP accounts for the rise in MAP, and, once SBP levels off, DBP increases and maintains the gradual rise in MAP.

8. In both individuals, VO₂max is limited by a maximal CO. That is, the metabolic demands set by the active muscle during exercise cannot be met by the pumping capabilities of the heart. In the individual with diabetes, numerous hematological changes are evident. For example, erythrocytes deform less rapidly, which impedes their passage through arterioles into capillaries. Erythrocytes also spend a greater proportion of time in the arterial end of the capillary compared with the venous end, and hemoglobin A₁c is increased. Hemoglobin A₁c is a direct result of the hyperglycemia that increases the affinity of oxygen to the hemoglobin molecule. This results in a situation in which oxygen is not easily removed from the hemoglobin molecule. In addition to these hematological alterations, capillary basement thickening occurs, which increases the distance for the diffusion of oxygen. However, despite these changes, a-v oxygen difference between the two individuals differs very little at rest and with increasing workloads.
9. Yes, exercise should be recommended for the individual with diabetes. Cardiac problems such as a lower SV and ejection fraction and a higher left ventricular end-diastolic pressure are common in individuals with diabetes. Factors that appear to account for the increased incidence of these cardiac problems include atherosclerosis and autonomic neuropathies. However, there are a significant number of individuals with diabetes who do not develop atherosclerosis and autonomic neuropathy yet demonstrate the clinical signs of cardiomyopathies. This suggests that there exists a cardiomyopathy(ies), specific to diabetes, that may be due to the direct consequence of abnormal glucose/insulin concentrations on myocardial cell function. Exercise has been shown to normalize plasma glucose/insulin concentrations in individuals with diabetes. The normalized plasma glucose/insulin concentrations may in turn have a direct beneficial effect on myocardial cell function. Individuals with diabetes who demonstrate a greater incidence of cardiomyopathies also have higher triglyceride levels. Acute exercise in individuals with diabetes reduces the level of triglyceride by using more fat for energy than glucose at moderate levels of exercise. The lower triglyceride concentration will in turn reduce the production of atherosclerotic plaques within the coronary arteries. However, a strenuous exercise program that results in excessive cardiovascular stress may be detrimental in an individual with diabetes. For example, the distribution in blood flow is altered in the individual with diabetes because of the reduction in CO and impaired local vascular regulatory mechanisms. At any given workload, the viscera will receive less than their usual blood flow to facilitate the increase in blood flow to the active skeletal muscle. The individual with diabetes associated with advanced nephropathy may develop ischemia to the organs and possibly renal insufficiency. Individuals with diabetes demonstrate an augmented rise in DBP in response to exercise. The increased pressure may result in undue stress to the microvasculature of the eye and kidney and provoke hemorrhage. Finally, perceptions and pain thresholds in the lower extremities are often elevated in individuals with diabetes. Somatic neuropathy may result in severe foot damage due to the recurrent compression of the foot during prolonged walking or running. The damage will occur without recognition.

10. There are several advantages to an exercise training program. Exercise training in the individual with diabetes improves insulin sensitivity. In turn, insulin enhances glucose uptake and glucose metabolism by increasing the activity of glycogen synthetase (an enzyme responsible for the conversion of glucose to its storage form of glycogen). In addition, exercise training increases activity of lipoprotein lipase in the muscle and increases the ability of the muscle to take up and oxidize free fatty acids. Thus the plasma concentration of triglycerides is decreased. Cardiovascular fitness in individuals with diabetes is improved after an exercise training program. For example, \( V_{O_2 \text{max}} \) is significantly elevated. Resting SBP and HR are decreased after training. In addition, a lower HR at a constant workload is achieved. The lower HR at a constant workload is beneficial such that the HR reserve or the ability to further increase HR is increased. As a result of the cardiovascular adjustments to exercise training, exercise tolerance is enhanced. The enhancement is demonstrated by an increase in the maximal workload achieved and an increase in the time to reach fatigue.

**BACKGROUND INFORMATION**

Individuals with chronic exposure to elevated plasma glucose concentrations often develop peripheral neuropathies (affecting the autonomic and somatic nervous systems), cardiac myopathies, and alterations in vascular and myocardial compliances. Neuropathy occurs as a result of structural and biochemical changes within the nerves. Functionally, this results in abnormal neural regulation due to degeneration of neuronal tissue and decreases in neuronal enzyme activity that impair and delay the response of the autonomic nervous system. Cardiac myopathies are characterized by a decrease in cardiac contractility, rate of myocardial relaxation, SV, ejection fraction, and a higher left ventricular end-diastolic pressure. This is due to a decreased number of cardiac \( \beta_1 \)-adrenoreceptors, impaired myocardial calcium metabolism, and a decrease in myocardial compliance.

The elastic components (compliance) of the arteries and heart are decreased in the individual with diabetes. Vascular compliance is a measure of the expansion and recoil properties of the vessel during...
each cardiac cycle and provides the energy for a constant MAP and blood flow. An individual with diabetes has a decreased aortic compliance due to collagen infiltration into the vessel wall, interstitial accumulation of connective tissue, and a perivascular thickening of the basement membrane. Consequently, the aorta becomes less expandable. Under normoglycemic conditions, the aorta expands during the rapid ejection phase of the cardiac cycle. Expansion of the aorta simultaneously absorbs the energy imparted by the ejected blood. If the aorta fails to adequately expand (decreased compliance), the energy is not absorbed, and SBP increases. Functionally, this results in an increased SBP. However, individuals with diabetes also demonstrate a decrease in SV. Therefore, SBP is usually lower in individuals with diabetes. DBP is also affected by the decreased aortic compliance. DBP decreases due to the loss of the windkessel effect when the aorta fails to recoil adequately. However, diabetes is also associated with an increase in total peripheral resistance, which functions to increase DBP. Thus these individuals usually demonstrate an increase in DBP. An individual with diabetes also has a decreased myocardial compliance due to collagen infiltration into the myocardial tissue. Similarly, the heart is less distensible and does not expand well during diastole. The physiological consequence is a reduction in SV. Because SV is a component that determines CO, CO is, in turn, reduced.

Individuals with chronic exposure to elevated plasma glucose concentrations often develop increases in blood volume. The high plasma glucose concentration elevates plasma osmolality, which stimulates hypothalamic osmoreceptors to release arginine vasopressin. Arginine vasopressin functions to increase water reabsorption in the kidney. The increase in blood volume is an effort to decrease plasma osmolality. However simultaneously, the increase in blood volume is opposed by glucose-mediated osmotic diuresis and the inhibitory effects on renin and aldosterone.

Taken together, the individual with diabetes has specific limitations in the extent of the neural and humoral regulation of the heart and blood vessels. Therefore, the cardiovascular adjustments to exercise will be limited and can be directly contrasted and compared with an individual without diabetes.

Heart rate. At the onset of exercise, there is a centrally generated signal that simultaneously activates the cardiovascular and motor centers. This concept is referred to as central command. Central command results in the withdrawal of cardiac parasympathetic (vagal) efferent activity. The vagus nerve acts as a brake on HR. Vagal withdrawal, or releasing the brake, increases HR to ~100–120 beats/min. Beyond a HR of 100 beats/min, sympathetic efferent activity is activated to further increase HR up to the age-related maximum (220 beats/min – age in years). Cardiac sympathetic efferent fibers release norepinephrine activating cardiac β1-adrenoreceptors on the sinoatrial node, which functions as an accelerator on HR. Activation of sympathetic efferent nerves innervating the adrenal gland induce the release of catecholamines (epinephrine and norepinephrine) stored within the adrenal medulla. Circulating catecholamines released from the adrenal medulla also activate cardiac β1-adrenoreceptors. Cardiac sympathetic efferent nerve activity and circulating catecholamines increase HR in a linear fashion, with oxygen consumption up to ~75% VO2max.

The activation of sympathetic efferent activity is mediated by the muscle metaboreflex and the arterial baroreflex. The muscle metaboreflex is activated when there is a mismatch between muscle oxygen supply and demand. An increase in demand that is not adequately met by an increase in supply activates receptors located within the muscle to reflexly activate the sympathetic nervous system. The unloading of the arterial baroreflex reflexly increases sympathetic nerve activity. Unloading of the arterial baroreflex occurs when vascular resistance decreases more than CO increases.

Diabetes is associated with autonomic neuropathies, which result in a decline of parasympathetic and sympathetic influences on the heart. A reduction in parasympathetic tone to the heart results in an increase in the resting HR due to the lack of the braking effect on cardiac acceleration. The tachycardic response (increase in HR) at the onset of exercise is attenuated due to the delay in parasympathetic withdrawal. A reduction in the sympathetic
drive to the heart attenuates the HR response during exercise. In addition, a decreased number of cardiac β₁-adrenoreceptors also contributes to the attenuated HR response to increasing workloads.

The intrinsic HR is the heart's inherent ability to beat independently of neural innervation. Individuals with diabetes are often associated with a decreased intrinsic HR due to a decrease in the compliance of the myocardial wall and impaired myocardial calcium metabolism (Fig. 1).

Table 1 has been completed by considering the factors that influence HR, how the factors change with diabetes, and how the factors affect HR in the individual with diabetes (i.e., does this variable increase, decrease, or remain unchanged).

Complete Table 2 (as in Table 1) by considering the factors that influence HR and how they affect resting, maximal, and intrinsic HR in the individual with diabetes (i.e., does HR increase, decrease, or remain unchanged).

---

**Table 1**

<table>
<thead>
<tr>
<th>Factors Influencing HR</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on HR With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac sympathetic tone</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac parasympathetic tone</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Circulating catecholamines</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Responsiveness to sympathetic activity</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Responsiveness to parasympathetic activity</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

HR, heart rate; ↑, unchanged; ↑, increase; ↓, decrease.

1. From Fig. 1, determine the change in HR from rest (0% \(VO_2\) max) to ~0.75 L/min oxygen consumption in the individual without diabetes. Determine the change in HR from rest (0% \(VO_2\) max) to ~1.0 L/min oxygen consumption in the individual with diabetes. What mechanisms mediate these increases in HR? Why is the increase in HR attenuated in the individual with diabetes?

2. The individual with diabetes presents with a higher resting HR compared with the individual without diabetes. Calculate the percent difference in resting HR between the two individuals. What mechanisms are responsible for the higher resting HR?

3. What factors are responsible for the attenuated HR response, at rates >120 beats/min, during exercise in the individual with diabetes?

4. Calculate the percent difference in maximal HR between the two individuals. What limits the maximal HR in the individual with diabetes?

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**Table 2**

| Comparison of HR between an individual with diabetes and an individual without diabetes |
|----------------------------------------|-------------------------|-------------------------|
| Resting HR | Maximal HR | Intrinsic HR |
| Individual without diabetes | Normal | Normal | Normal |
| Individual with diabetes | | | |
**Stroke volume.** SV is the volume of blood ejected into the aorta with each contraction of the heart. It is a function of venous return or preload, contractility, and resistance to ejection or afterload. SV increases as a result of an increase in venous return and/or contractility. The increase in venous return lengthens the ventricular myocardial fiber and, in accordance with the Frank-Starling mechanism or length-tension relationship, the force of contraction increases, which results in an increase in SV. Increases in HR, cardiac sympathetic efferent activity, and catecholamines increase the influx of calcium into the myocardial cell. The increase of calcium influx contributes to an increase in contractility and thus SV. Catecholamines, in particular epinephrine released by the adrenal medulla, are of particular importance in maintaining SV during severe exercise.

An increase in afterload or aortic pressure decreases SV. Afterload is the pressure that the left ventricle must pump against during the rapid ejection phase of the cardiac cycle. In order for rapid ejection of blood to occur, the aortic semilunar valves open as a result of the pressure difference between the left ventricle and the aorta, that is, the generated pressure in the left ventricle must be greater than the pressure in the aorta. If the afterload is increased, then the generated pressure in the left ventricle must be greater to eject a given blood volume. In this situation, SV decreases.

During exercise, venous return is increased by means of the muscle pump compressing and expanding peripheral veins. Consequently, left ventricular EDV increases, the length of the cardiac muscle fiber is increased, and, in accordance with the Frank-Starling law of the heart, contractility increases. The increase in contractility ejects a greater quantity of blood out of the heart, and thus SV increases. In addition, the sudden and rapid increase in HR mediated by vagal withdrawal allows for more calcium to enter the myocardial cell, which in turn also increases contractility and consequently SV. The greatest increase in SV occurs up to 35–40% \( \dot{V}O_{2\text{max}} \). Beyond 35–40% \( \dot{V}O_{2\text{max}} \), SV changes very little. A small increase in afterload as a result of an increase in MAP may oppose the rise in SV.

With increasing workloads, ventricular filling times are significantly shortened (from a resting HR of ~80 beats/min to a maximal HR of 190 beats/min). Despite the reductions in ventricular filling time, SV is maintained as long as adjustments in cardiac performance are made (2). These adjustments include increases in cardiac sympathetic efferent activity and circulating epinephrine and decreases in resistance.

In individuals with diabetes, the attenuated HR response allows for a greater ventricular filling time, which increases left ventricular EDV. The increase in left ventricular EDV increases the length of the muscle fiber, and contractility is increased by the Frank-Starling mechanism. Despite the Frank-Starling mechanism, several factors in the individual with diabetes oppose the rise in SV. These factors include an increase in afterload due to a stiffening in the arterial vasculature, a diminution in cardiac sympathetic efferent outflow and sympathetic efferent outflow to the adrenal medulla, a decrease in the number of cardiac \( \beta_1 \)-adrenoreceptors, and a decrease in myocardial compliance (Fig. 2).

![Figure 2](http://advan.physiology.org/)

**FIG. 2.**

Stroke volume (SV) at rest and during exercise on an absolute (L/min; A) and relative (% \( \dot{V}O_{2\text{max}} \); B) scale in an individual with (D) and without (ND) diabetes.
Complete Table 3 (as in Table 1) by considering the factors that influence SV, how they change with diabetes, and how they affect SV in the individual with diabetes (i.e., does this variable increase, decrease, or remain unchanged).

5. Calculate the percent difference in resting SV between the two individuals. What accounts for this difference in the individual with diabetes?

6. Calculate the change in SV (ml) from rest to 50% VO\textsubscript{2max} in both individuals. What factor is responsible for the initial SV response from rest to 50% VO\textsubscript{2max} in both individuals? What factors associated with diabetes account for the attenuated rise in SV?

7. Determine the percent VO\textsubscript{2max} at which SV begins to plateau in both individuals. Determine the SV that corresponds to this percent VO\textsubscript{2max}. How does the rise in SV in the individual with diabetes compare with the individual without diabetes? What mechanisms contribute to this difference?

8. Explain how an increase in afterload (aortic pressure) opposes myocardial function.

Cardiac output. CO is the product of HR and SV. It is the volume of blood pumped by the heart in 1 min and correlates well with oxygen consumption. Changes in HR and SV will influence CO. At the onset of exercise, the increase in CO is mediated by increases in SV (up to 35–40% of the individual’s VO\textsubscript{2max}) and HR. At higher workloads beyond 35–40% of the individual’s VO\textsubscript{2max}, increases in CO are mediated by increases in HR. In individuals with diabetes, the reduced SV and HR lowers resting CO and attenuates the CO response to exercise (Figs. 3 and 4; Table 4).

9. CO is the product of HR and SV. Using Figs. 1 and 2, calculate CO at rest and during exercise for both individuals. Plot the results in Fig. 3.

10. Determine CO at rest in the two individuals (Fig. 4). Subsequently, determine the components of CO at rest (Figs. 1 and 2). What accounts for this difference in resting CO between the two individuals?

11. Determine CO at an oxygen consumption of 1.5 l/min for both individuals. Determine the percent VO\textsubscript{2max} that corresponds to CO at an oxygen consumption of 1.5 l/min for both individuals. What do these data say concerning the individual with diabetes? What factors contribute to the reduced CO response during exercise in the individual with diabetes?

![Graph A](image1.png)

![Graph B](image2.png)

**TABLE 3**
Factors influencing SV in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing SV</th>
<th>How These Factors Change SV With Diabetes</th>
<th>Effect on SV With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous return (preload)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responsiveness to sympathetic activity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SV, stroke volume.
Innovations and Ideas

Oxygen Consumption (L/min)

Cardiac Output (L/min)

% Maximal Oxygen Consumption

**FIG. 4.**

CO at rest and during exercise on an absolute (L/min, A) and relative (% VO2 max; B) scale in an individual with (D) and without (ND) diabetes.

12. Calculate the percent difference in CO at 100% VO2 max, between the two individuals. What effect does a reduced CO have on exercise tolerance in the individual with diabetes?

**Systolic blood pressure.** SBP is the pressure exerted by the blood against the walls of the arteries when the heart is contracting (systole). SBP is a function of the volume of blood ejected into the aorta during ventricular systole or SV and compliance of the aorta. A greater SV increases the volume of blood within the arteries and thus increases SBP. When blood is ejected into the aorta, the vessel expands and absorbs the energy. If the aorta fails to adequately expand during systole (decreased compliance), the energy is not absorbed, and SBP increases.

At the onset of exercise, the initial increase in SBP is the result of an increase in SV (Fig. 2) up to 35–40% VO2 max. SV increases due to an increase in venous return and myocardial contractility. At workloads >55–40% VO2 max, SV levels off, yet SBP continues to increase gradually. Despite a leveling off of SV, the volume of blood ejected into the aorta per minute (i.e., CO) continues to rise due to an increase in HR. In addition, as CO increases, aortic compliance decreases. A decrease in aortic compliance will contribute to the elevation of SBP. The decrease in aortic compliance increases SBP because the energy generated during ventricular systole is not absorbed by the aorta.

In the individual with diabetes, there is a decrease in vascular compliance due to the proliferation of connective tissue into the vessel wall. Thus the vascular system fails to expand adequately during ventricular ejection, the energy of the ejected blood is not absorbed, and SBP increases. However, the increase in SBP is attenuated in the individual with diabetes due to the inability to substantially elevate SV. With increasing workloads, several factors oppose the rise in SBP. The levelling off of SV and the attenuated HR response are not sufficient to maintain CO. Even though individuals with diabetes are associated with a decrease in aortic compliance, SBP does not continue to rise because CO is not maintained (Fig. 5).

13. Determine resting SBP in both individuals (mmHg). How much lower is resting SBP in the individual with diabetes compared with the individual without diabetes? What factors account

**TABLE 4**

Comparison of HR, SV, and CO at rest and during maximal exercise in an individual with diabetes and in an individual without diabetes

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Maximal Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR, beats/min</td>
<td>SV, ml</td>
</tr>
<tr>
<td>Individual without diabetes</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Individual with diabetes</td>
<td>90</td>
<td>55</td>
</tr>
</tbody>
</table>

CO, cardiac output.
for the lower resting SBP in the individual with diabetes?

14. Is the increase in SBP from rest to 25% \( \text{VO}_2\max \) the same in both individuals? What is the major component responsible for the increase in SBP?

15. What other components are responsible for the initial increase in SBP?

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Factors influencing SBP in an individual with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors Influencing SBP</td>
<td>How These Factors Change With Diabetes</td>
</tr>
<tr>
<td>SV</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td></td>
</tr>
<tr>
<td>Arterial compliance</td>
<td></td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td></td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure.

16. At what percent \( \text{VO}_2\max \) does SBP plateau in the individual without diabetes? What accounts for the plateau of SBP?

17. What mechanisms mediate the SBP response at workloads between 25 and 75% \( \text{VO}_2\max \) in the individual without diabetes?

18. At what percent \( \text{VO}_2\max \) does SBP plateau in the individual with diabetes? What factors associated with diabetes account for the plateau of SBP?

**Diastolic blood pressure.** DBP is the pressure exerted by the volume of blood remaining in the arteries when the heart is at rest (diastole). It is a function of the length of time the heart is at rest or HR, compliance of the vasculature, and the outflow of blood into the periphery (resistance). An increase in HR reduces the length of time spent between each cardiac contraction. Consequently, the inflow of blood into the vasculature is increased. Thus blood volume in the vasculature increases during diastole, and DBP increases. Compliance also has an effect on DBP. A vessel with a high compliance expands during systole and rebounds during diastole. In turn, the rebound effect delivers energy into the vascular system. Consequently, DBP increases. If the vessel has a decreased compliance, the rebound effect is reduced, and DBP is lower. Peripheral resistance is regulated by sympathetic nerves (activating \( \alpha_1 \)-adrenoreceptors), hormones (arginine vasopressin and the renin-angiotensin system), and local metabolites (adenosine and nitric oxide) acting on the vasculature. Increases in peripheral resistance increase DBP by impeding the outflow of blood. Likewise, decreases in peripheral resistance decrease DBP by permitting the outflow of blood.

Figure 6 demonstrates that, during exercise, DBP decreases slightly in an individual without diabetes. Although HR increases in this individual (Fig. 1), vasodilator mechanisms, such as locally produced metabolites, autoregulation, and flow-mediated release of nitric oxide, decrease peripheral resistance. The balance between the increase in HR (increase DBP) and decrease in peripheral resistance (decrease DBP) results in a reduction in DBP.
During exercise, arterial pressure is monitored by the arterial baroreflex and the muscle metaboreflex. If cardiac performance of the heart is not adequate to elevate CO and maintain arterial pressure, the arterial baroreflex and muscle metaboreflex are activated to reflexly increase sympathetic outflow. As previously discussed, the individual with diabetes demonstrates a compromised CO response to exercise. Thus, to maintain MAP, the arterial baroreflex and muscle metaboreflex increase peripheral resistance. The increase in peripheral resistance is necessary to compensate for the attenuated CO response.

Complete Table 6 (as in Table 1) by considering the factors that influence DBP, how they change with diabetes, and how they affect DBP in the individual with diabetes (i.e., does this variable increase, decrease, or remain unchanged).

19. Calculate the difference in resting DBP (mmHg) between the two individuals. What mechanisms are responsible for the small difference in resting DBP?

20. DBP does not increase from rest to 25% VO\textsubscript{2} max in either individual. Why not?

21. In the individual without diabetes, calculate the change in DBP from rest to the cessation of exercise. What mechanisms are responsible for the change in DBP during exercise?

22. In the individual with diabetes, calculate the change in DBP from rest to the cessation of exercise. What mechanisms are responsible for the change in DBP during exercise?

Mean arterial pressure. MAP is the average pressure throughout the cardiac cycle. It is the pressure necessary to maintain adequate tissue blood flow. However, the duration of diastole is slightly longer than systole. The following equation is used to calculate MAP:

\[
MAP = \text{diastolic pressure} + \frac{1}{3} (\text{pulse pressure})
\]

\[
\text{pulse pressure} = \text{systolic pressure} - \text{diastolic pressure}
\]

MAP, determined by SBP and DBP, is the product of CO and total peripheral resistance. Factors influencing CO and total peripheral resistance will alter SBP and DBP. Ultimately, MAP will change. In the individual without diabetes, CO sharply increases (due to increases in SV and HR) at the onset of exercise. The rise in CO increases SBP and, therefore, MAP. At higher workloads when SV levels off, MAP is increased due to an increase in CO mediated by an elevated HR and contractility. Simultaneously, DBP decreases due to a reduction in total peripheral resistance. However, the increase in CO usually
exceeds the decrease in peripheral resistance, and thus MAP increases.

During exercise, arterial pressure is maintained and modulated by the arterial baroreflex and muscle metaboreflex. If CO is not adequate to maintain arterial pressure, the arterial baroreflex and muscle metaboreflex reflexly increase sympathetic efferent nerve activity. Recall Fig. 4, which demonstrates that, in an individual with diabetes, the CO response to exercise is attenuated. The attenuated CO unloads the arterial baroreceptors and activates the muscle metaboreflex. These reflexes activate the sympathetic nervous system, which constricts arterioles and attenuates the reduction in peripheral resistance to compensate for the reduction in cardiac performance (Figs. 7 and 8; Table 7).

23. Using Figs. 5 and 6, calculate the MAP response to exercise for the individuals with and without diabetes. Plot the results in Fig. 7.

Complete Table 8 (as in Table 1) by considering the factors that influence MAP, how they change with diabetes, and how they affect MAP in the individual with diabetes (i.e., does this variable increase, decrease, or remain unchanged).

24. Determine the change in MAP from rest (0% \( V_{O_2\max} \)) to 25% \( V_{O_2\max} \) in both individuals. What factors account for the rise in MAP?

25. Compare the MAP responses during exercise for both individuals. Although the responses are similar in the two individuals, the mechanisms contributing to these increases are different.

<p>| TABLE 7 |
|-------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Rest. mmHg</th>
<th>Maximal Exercise, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>DBP</td>
<td>MAP</td>
</tr>
<tr>
<td>Individual without diabetes</td>
<td>120 80 92</td>
<td>190 78 111</td>
</tr>
<tr>
<td>Individual with diabetes</td>
<td>110 85 91</td>
<td>155 90 109</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure.
TABLE 8
Factors influencing MAP in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing MAP</th>
<th>How These Factors Change With Diabetes</th>
<th>Effects on MAP in an Individual With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please describe the different mechanisms responsible.

26. In the individual with diabetes, CO begins to level off at 50% VO\textsubscript{2max} (Fig. 4). Yet, MAP continues to increase. What mechanisms mediate the increase in MAP?

27. In the individual with diabetes, an oxygen consumption of 2 L/min (Fig. 8A) corresponds to 100% VO\textsubscript{2max} (Fig. 8B). In the individual without diabetes, an oxygen consumption of 2 L/min corresponds to what percent VO\textsubscript{2max}?

Total peripheral resistance. Peripheral resistance reflects the state of vasoconstriction and/or vasodilation and measures the resistance to blood flow. Resistance is directly related to blood viscosity and vessel length and is inversely related to (vessel radius)\(^4\). Accordingly, the radius of the vessel is the single most important factor regulating total peripheral resistance since resistance varies inversely to the fourth power of the radius. Thus very small changes in arteriole radius have a significant effect on resistance. There are several factors that contribute to the radius of the arteriole. Recall from the discussion on DBP that the arteriole radius is regulated by both vasoconstrictor and vasodilatory influences. Vasoconstrictor influences are mediated by sympathetic efferent nerves activating \(\alpha\)\(_1\) adrenoceptors and hormones such as arginine vasopressin and the renin-angiotensin system. Vasodilatory influences are mediated by locally produced metabolites such as adenosine, flow-dependent endothelial-derived relaxing factor nitric oxide, and autoregulation. Autoregulation refers to the tissue’s ability to control its own blood flow.

Figure 9 illustrates that peripheral resistance decreases sharply at the onset of exercise, continues to decline with increasing workloads, and levels off at \(\sim 75\%\) VO\textsubscript{2max}. At the onset of exercise, the accumulation of local metabolites released by the exercising muscle elicits vasodilation, which decreases perfusion pressure. In turn, autoregulatory mechanisms cause the upstream vessel to dilate. Blood flow to this bed is now significantly increased. The shear stress acting on the vascular endothelium stimulates the release of flow-dependent endothelial-derived relaxing factor nitric oxide, which also contributes to vasodilatation. It appears that the intense vasodilatory stimulus should decrease MAP. However, the increase in CO usually exceeds the decrease in peripheral resistance, and thus blood pressure increases. If CO does not exceed the decrease in peripheral resistance, MAP will begin to decline. In response to the fall in blood pressure, arterial baroreceptors located in the carotid sinus and aortic arch are unloaded, which reflexly increases sympathetic efferent outflow. Sympathetic outflow to the vasculature functions to attenuate the fall in periph-

![Graph A](http://advan.physiology.org/)

![Graph B](http://advan.physiology.org/)
eral resistance and maintain MAP. In addition, if the perfusion pressure and/or blood flow is not ade-
quately to meet the metabolic demands of the exercising muscle during exercise, muscle metabore-
ceptors are also activated, which reflexly increase sympathetic efferent outflow.

The decrease in peripheral resistance compensates well for the increase in CO. That is, the higher the maximal CO in an individual (as in the individual without diabetes), the greater the decrease in peripheral resistance. There are two points to be made at this time. First, it is important that resistance decreases. If resistance increased or stayed the same in the presence of an increase in CO, MAP would increase to a phenomenally high value. For example, at rest in the individual without diabetes, MAP is 90 mmHg (5.6 l/min × 16 mmHg l⁻¹ min⁻¹). The calculated MAP would be 240 mmHg (15 l/min × 16 mmHg l⁻¹ min⁻¹) at 25% VO₂max if resistance STAYED THE SAME. At 100% VO₂max the calculated MAP would be 432 mmHg (271/min × 16 mmHg l⁻¹ min⁻¹). Clearly, peripheral resistance must decrease to prevent enormous increases in MAP. Second, if the rise in CO is limited, as in the individual with diabetes, peripheral resistance cannot decrease to the same extent as in the individual without diabetes. If resistance DID decrease to the same extent, MAP would decrease. For example, at rest in the individual without diabetes, MAP is 90 mmHg (5.6 l/min × 16 mmHg l⁻¹ min⁻¹). In the individual with diabetes, MAP is 88 mmHg (4.9 l/min × 18 mmHg l⁻¹ min⁻¹) at rest. At 25% VO₂max MAP would decrease to 30 mmHg (14 l/min × 2.1 mmHg l⁻¹ min⁻¹) IF resistance decreased the SAME percentage (26%) as in the individual without diabetes. Therefore, in the individual with diabetes who has a limited CO, resistance cannot decrease to the same extent or MAP would decrease to a dangerously low value. Individuals with diabetes also have impaired local vascular regulatory mechanisms (decreased response to metabolites and nitric oxide). The impaired local vascular regulatory mechanisms also contribute to the elevated peripheral resistance.

Complete Table 9 (as in Table 1) by considering the factors that influence total peripheral resistance, how they change with diabetes, and how they affect total peripheral resistance in the individual with diabetes (i.e., does this variable increase, decrease, or remain unchanged?).

28. Examine the peripheral resistance response at the onset of exercise in both individuals. What factors mediate the peripheral resistance response?

29. Calculate the change in peripheral resistance from rest (0% VO₂max) to 50% VO₂max in both individuals. Which individual demonstrates an attenuated peripheral resistance response? What accounts for the attenuation?

30. Determine the percent VO₂max at which peripheral resistance levels off. What prevents a further decrease in peripheral resistance beyond this point?

31. Determine the resistance unit at a HR of 100–120 beats/min for both individuals.

Muscle blood flow. Blood flow to any tissue bed is directly proportional to pressure and is inversely proportional to the resistance (flow = pressure/resistance). Muscle blood flow is regulated by local, humoral, and neural mechanisms. At rest, the nervous system and local metabolites are the primary regulators of muscle blood flow. During exercise, the nervous system, hormones, local metabolites, and flow-dependent endothelial-derived factors interact to regulate muscle blood flow.
At the onset of exercise, locally produced metabolites serve to increase muscle blood flow by decreasing resistance in the muscle vasculature. Autoregulation and the release of nitric oxide also contribute to the increase in muscle blood flow. Once HR reaches 100–120 beats/min, the activity of the sympathetic nervous system is increased. Sympathetic activation does several things. First, postganglionic sympathetic nerves release norepinephrine, which activates $\alpha_1$-adrenoreceptors located on the vascular smooth muscle. $\alpha_1$-Adrenoreceptor activation elicits constriction of the vessel. Second, sympathetic activation on the adrenal medulla causes the release of epinephrine and norepinephrine. Circulating epinephrine binds to $\beta_2$-adrenoreceptors located on the arteriole to elicit dilation and, with lesser affinity, $\alpha_2$-adrenoreceptors to elicit vasoconstriction. Circulating norepinephrine binds to $\alpha_1$-adrenoreceptors and elicits vasoconstriction. Because there are a greater number of $\alpha_1$-adrenoreceptors compared with $\beta_2$-adrenoreceptors, the vasoconstrictor effect dominates. Additionally, circulating epinephrine binds to $\beta_1$-adrenoreceptors on the myocardium to increase HR. Third, sympathetic activation to the kidney stimulates the release of renin, which is then quickly converted to the potent vasoconstrictor angiotensin II. Together, vasoconstrictor responses maintain MAP by matching CO with peripheral resistance. As the vasodilator stimulus becomes greater with increasing workloads, the vasoconstrictor response becomes enhanced such that the muscle bed becomes a major site of vasoconstriction to maintain blood pressure.

In an individual with diabetes, the chronic elevations of glucose induce endothelial cell dysfunction, which results in abnormal vasodilatation. In addition, CO fails to increase to a level adequate to meet the metabolic demands with increasing workloads. Despite endothelial cell dysfunction, vasodilatation in the muscle bed occurs at a faster rate than the increase in CO. Therefore, in the individual with diabetes who has a limited CO, resistance cannot decrease to the same extent or MAP would decrease. To oppose a decrease in MAP, aortic and carotid sinus baroreceptors reflexly increase sympathetic efferent activity. In addition, muscle metaborecep-

32. What mechanisms account for the initial increase in muscle blood flow in both individuals?

<table>
<thead>
<tr>
<th>Factors influencing Muscle Blood Flow</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on Muscle Blood Flow With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>Sympathetic nerve activity</td>
<td>Local metabolite production</td>
</tr>
</tbody>
</table>
33. Determine resting muscle blood flow for both individuals. Determine muscle blood flow at 25 and 100% \( \text{VO}_2 \text{max} \) for both individuals. What does one conclude about muscle blood flow in the individual with diabetes? What factors account for the difference in muscle blood flow between the two individuals?

34. What mechanisms influence muscle blood flow at higher workloads in the individual without diabetes?

35. Are these mechanisms working in the individual with diabetes?

Splanchnic and renal blood flow. As previously discussed, blood flow to any tissue bed is directly proportional to pressure and is inversely proportional to the resistance (flow = pressure/resistance). Splanchnic and renal blood flow is regulated by local, humoral, autoregulation, and neural mechanisms. At the onset of exercise, blood flow to the exercising muscle increases. Furthermore, muscle blood flow increases in proportion to the level of exercise intensity. Reductions in blood flow to the splanchnic and renal vasculature result in redistribution of \( \text{CO} \) to the active skeletal muscle.

When HR reaches 100–120 beats/min, sympathetic efferent nerves release norepinephrine onto the sinoatrial node to further increase HR and contractility, as previously discussed. Additionally, norepinephrine activates \( \alpha_1 \)-adrenoreceptors located on the splanchnic and renal vasculature eliciting vasoconstriction. Splanchnic and renal vasoconstriction serves two functions. First, it facilitates an increase in muscle blood flow (Fig. 11) by redirecting \( \text{CO} \) away from nonexercising beds. In the individual without diabetes, \( \approx 67\% \) of the maximal \( \text{CO} \) is directed to the active skeletal muscle during exercise compared with \( \approx 56\% \) in the individual with diabetes due to the limited availability of \( \text{CO} \). Second, splanchnic and renal vasoconstriction help to maintain adequate blood pressure. If splanchnic and renal vasoconstriction did not occur, total peripheral resistance would decrease, and thus blood pressure would decrease.

Complete Table 11 (as in Table 1) by considering the factors that affect splanchnic and renal blood flow, how they change with diabetes, and how they affect splanchnic and renal blood flow in the individual with diabetes (i.e., does this variable increase, decrease, or remain unchanged).

36. Calculate the percent decrease in splanchnic or renal blood flow from rest (0%) to 50% \( \text{VO}_2 \text{max} \) in the individual without diabetes. Why is this decrease necessary during exercise?

<table>
<thead>
<tr>
<th>Factors Influencing Splanchnic and Renal Blood Flow</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on Splanchnic and Renal Blood Flow With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CO} )</td>
<td>Sympathetic nerve activity</td>
<td></td>
</tr>
</tbody>
</table>

FIG. 11. Splanchnic or renal blood flow at rest and during exercise on an absolute (l/min; A) and relative (%\( \text{VO}_2 \text{max} \); B) scale in an individual with (D) and without (ND) diabetes.
37. Calculate the percent decrease in splanchnic or renal blood flow from rest (0%) to 50% VO2 max in the individual with diabetes.

**a-v oxygen difference.** The a-v oxygen difference refers to the ability of a vascular bed to extract oxygen. It is the difference in the oxygen content between the arterial and venous end of the capillary. The oxygen saturation of arterial blood is ~98% (arterial partial pressure of oxygen is 100 mmHg), whereas the oxygen saturation of venous blood is 75% (venous partial pressure of oxygen is 40 mmHg). Arterial oxygen content is the product of hemoglobin concentration (15 g Hg/100 ml blood) and oxygen-carrying capacity of hemoglobin (1.34 ml O2/100 ml blood). Thus the arterial oxygen content is ~20 ml O2/100 ml blood, and venous oxygen content is ~15 ml O2/100 ml blood. The a-v oxygen difference (20 ml O2/100 ml blood; 15 ml O2/100 ml blood) is the result of metabolizing tissues extracting ~5 ml O2/100 ml blood. This means, for every 100 ml blood that pass through the capillary bed, 5 ml oxygen diffuses into the tissue bed. During maximal exercise when the metabolism of the muscle substantially increases, the a-v oxygen difference can increase up to 15 ml O2/100 ml blood.

During exercise, the active muscle has a built-in mechanism for releasing more oxygen from the hemoglobin molecule. This mechanism is referred to as the Bohr effect. The Bohr effect is a principle that describes a rightward shift of the hemoglobin-oxygen dissociation curve in response to a decrease in pH. In addition, an increase in carbon dioxide or temperature induces a rightward shift. A rightward shift of the hemoglobin-oxygen dissociation curve results in a situation in which oxygen is released from the hemoglobin more readily and at a higher partial pressure. Thus the oxygen is available to diffuse into the muscle cell. As a result of the Bohr effect, the oxygen content of venous blood during exercise is ~2 ml O2/100 ml blood compared with 15 ml O2/100 ml blood at rest.

In the individual with diabetes, there is a reduction in CO (Fig. 4) and muscle blood flow (Fig. 10) during exercise. These limitations could potentially result in reduced transport of oxygen to the muscle. Despite these limitations, the a-v oxygen difference in this individual widens in a manner similar to that observed in the individual without diabetes. Furthermore, the a-v oxygen differences between the two individuals when expressed in relative units are virtually identical. Thus, when CO is limited and fails to meet the metabolic demands during exercise, the a-v oxygen difference increases even further to satisfy the oxygen demands of the exercising muscle.

To calculate the a-v oxygen difference, the Fick principle is used. Fick equation

\[ \dot{V}O_2 = CO \times a - v O_2 \]

where \( \dot{V}O_2 \) is the volume of oxygen consumed per minute.

Rearranging the equation to solve for a-v oxygen

\[ \frac{\dot{V}O_2}{CO} = a - v O_2 \]
Accordingly, the a–v oxygen difference can be calculated by knowing the volume of oxygen consumed per minute and the CO (Figs. 12 and 13).

38. Using the Fick principle and Fig. 3, calculate the a–v oxygen difference at rest and during exercise in the individuals with and without diabetes. Plot the results in Fig. 12.

Complete Table 12 (as in Table 1) by considering the factors that affect a–v oxygen difference, how they change with diabetes, and how they affect a–v oxygen difference in the individual with diabetes (i.e., does this variable increase, decrease, or remain unchanged).

39. Using Fig. 13, A and B, compare the a–v oxygen difference between the two individuals. What factors account for the difference?

40. Does this difference in the a–v oxygen difference play a significant role for exercise tolerance in the individual with diabetes?

ANSWERS TO TABLES

### TABLE 1
Factors Influencing HR in an Individual with Diabetes

<table>
<thead>
<tr>
<th>Factors Influencing HR</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on HR With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac sympathetic tone</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac parasympathetic tone</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Circulating catecholamines</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Responsiveness to sympathetic activity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Responsiveness to parasympathetic activity</td>
<td>↓</td>
<td>↓</td>
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</tbody>
</table>

### TABLE 2
Comparison of HR between an Individual with Diabetes and an Individual without Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Resting HR</th>
<th>Maximal HR</th>
<th>Intrinsic HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual without diabetes</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Individual with diabetes</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### TABLE 3
Factors influencing SV in an Individual with Diabetes

<table>
<thead>
<tr>
<th>Factors Influencing SV</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on SV With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous return (preload)</td>
<td>↑ At rest</td>
<td>↓</td>
</tr>
<tr>
<td>Arterial compliance</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ventricular compliance</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Responsiveness to sympathetic activity</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
### TABLE 5
Factors influencing SBP in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing SBP</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on SBP With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>CO</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Arterial compliance</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### TABLE 6
Factors influencing DBP in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing DBP</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on DBP With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular compliance</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Peripheral vascular resistance</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Ventricular filling time</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### TABLE 8
Factors influencing MAP in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing MAP</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on MAP in an Individual with Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Peripheral vascular resistance</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>SBP</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DRP</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### TABLE 9
Factors influencing total peripheral resistance in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing Peripheral Resistance</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on Peripheral Resistance in an Individual with Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural changes in resistance vessels, e.g., stiffening</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>CO</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### TABLE 10
Factors influencing muscle blood flow in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing Muscle Blood Flow</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on Muscle Blood Flow With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Local metabolite production</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### TABLE 11
Factors influencing splanchnic and renal blood flow in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing Splanchnic and Renal Blood Flow</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on Splanchnic and Renal Blood Flow With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### TABLE 12
Factors influencing a-v O2 difference in an individual with diabetes

<table>
<thead>
<tr>
<th>Factors Influencing a-v O2 Difference</th>
<th>How These Factors Change With Diabetes</th>
<th>Effect on a-v O2 Difference With Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Muscle blood flow</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Muscle oxidative capacity</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

### ANSWERS TO LABORATORY QUESTIONS

1. In the individual without diabetes, HR increased to ~45 beats/min from rest to 0.75 l/min oxygen consumption. In the individual with diabetes, HR increased to ~24 beats/min from rest to 1.0 l/min oxygen consumption. The initial rapid increase in HR, up to ~100–120 beats/min, is due to vagal withdrawal. Vagal efferent activity acts as a brake on cardioacceleration. Releasing the brake (vagal withdrawal) increases HR. In the individual without diabetes, the increase in HR to 120 beats/min occurs at ~25% of the \( \dot{V}O_2_{\text{max}} \) (0.75 l/min). However, the individual with diabetes must work at 50% \( \dot{V}O_2_{\text{max}} \) to achieve the identical HR response. Thus the slope of the line, or the rate of change in HR, is less in the individual with diabetes, demonstrating a
depressed HR response. This difference is due to a delayed vagal withdrawal caused by structural, biochemical, and functional impairment of cardiac parasympathetic efferent nerves in the individual with diabetes.

2. Resting HR is 20% higher in the individual with diabetes. The autonomic nervous system functions to modulate HR. Parasympathetic activity functions to decrease HR, whereas sympathetic activity increases HR. At rest, parasympathetic activity dominates. Therefore, an elevated resting HR may indicate a reduced parasympathetic activity or an enhanced sympathetic activity to the heart. However, because individuals with diabetes have autonomic neuropathies and a reduced number of β₁-adrenergoreceptors, the likely explanation for the elevated resting HR is an attenuated parasympathetic inhibitory influence.

3. Once again, the individual with diabetes demonstrates a depressed HR response at a given workload (Fig. 1B). This individual must work at a greater percent of the VO₂max to achieve the same increase in HR, that is, the increase in HR is less than that achieved in the individual without diabetes at any given percent of the VO₂max. Thus the slope of the line is decreased from workloads of 1.3 to 1.7 l/min in the individual with diabetes. However, this is a result of structural, biochemical, and functional impairment of cardiac sympathetic efferent nerves (autonomic neuropathies) and a reduction in the number of cardiac β₁-adrenergoreceptors.

4. Maximal HR is ~27% lower in the individual with diabetes. Maximum HR is achieved by cardiac sympathetic efferent nerves activating cardiac β₁-adrenergoreceptors on the sinoatrial node and to a lesser extent by circulating epinephrine and norepinephrine released from the adrenal medulla. Because the individual with diabetes has an impairment of the autonomic nervous system and a decrease in β₁-adrenergoreceptor numbers as previously described, this individual does not have the mechanisms required to reach an age-related maximum HR. In addition, changes in the peripheral circulation (blood flow to the working muscles is reduced, which is mediated in part by an increased peripheral resistance) result in local muscle fatigue, which significantly limits exercise tolerance.

5. The resting SV is ~21% lower in the individual with diabetes. SV is a function of preload, afterload, and contractility. In individuals with diabetes, afterload (MAP, see Fig. 8) is the same at rest. However, contractility is reduced due to diabetic myopathies and a decrease in the number of cardiac β₁-adrenergoreceptors. Additionally, preload is reduced due to a decrease in myocardial compliance. Thus a reduced preload and contractility account for the lower resting SV in the individual with diabetes. In addition, the slightly higher HR at rest in the individual with diabetes slightly reduces ventricular filling time, which may also contribute to the reduction in SV.

6. From rest to 50% VO₂max, SV increased 70 ml in the individual without diabetes and 59 ml in the individual with diabetes. In both individuals, the initial increase in SV (Fig. 2A) is due to an increase in venous return mediated by the action of the muscle pump. However, the individual with diabetes has a reduced myocardial compliance, and thus the heart does not expand to sufficiently increase EDV. Therefore, at the same percentage of VO₂max (Fig. 2B), the individual with diabetes has a significantly reduced SV response. Interestingly, the reduced HR allows for an increased ventricular filling time. However, because the myocardium is less compliant, the individual with diabetes cannot take full advantage of the reduced IHR (increase ventricular filling time). This concept may best be explained by relating what happens to SV when an individual is taking a β₁-adrenergoreceptor blocker. The β₁-adrenergoreceptor blocker reduces HR at rest and during exercise. The reduced HR increases ventricular filling time so that these individuals have an increased SV.

7. The plateau in SV occurred at ~40–50% VO₂max in both individuals. At 50% VO₂max, SV in the individual without diabetes is 140 ml. At 50% VO₂max, SV in the individual without diabetes is 114 ml. Thus, at 50% VO₂max, SV does not rise to the same level as in the individual without diabetes. Furthermore, Fig. 2 demonstrates that the rise in SV is attenuated at all workloads in the individual with diabetes. SV is a function of preload, afterload, and contractility.
decrease in contractility accounts for the decreased SV response during exercise. This is due to cardiac myopathy caused by an alteration in autonomic function, decreased myocardial compliance, decreased myocardial β₁-adrenoreceptor number, and changes in subcellular organelles that control the movement of intracellular calcium. The decrease in myocardial compliance limits the distensibility of the heart during diastole. Thus preload is also decreased. Taken together, these factors attenuate pressure developed by the left ventricle and decreases the SV response during exercise in the individual with diabetes.

8. During ejection, the aortic semilunar valve opens, and blood is rapidly ejected into the aorta. For this to occur, the pressure in the left ventricle must be greater than the pressure in the aorta. Therefore, afterload is the aortic pressure that the heart must pump against during ejection. However, if the aortic pressure is increased, the heart must generate a greater pressure to eject a given blood volume.

9. Complete the CO graph.

10. CO is the product of HR and SV. In the individual without diabetes, resting CO is 5.6 l/min [SV (70 ml) x HR (80 beats/min)]. Although an individual with diabetes has a similar CO at rest (4.93 l/min), the diabetic myopathies and neuropathies elevate resting HR (90 beats/min) and reduce resting SV (55 ml). Thus the reduced CO is due to a reduced SV.

11. CO at an oxygen consumption of 1.5 l/min is 23 l/min for the individual without diabetes and 16 l/min for the individual with diabetes. At a CO of 23 l/min, the individual without diabetes is working at 50% V̇O₂max. At a CO of 16 l/min, the individual with diabetes is working at 64% V̇O₂max. These data demonstrate that, at a given oxygen consumption (i.e., 1.5 l/min), CO in the individual with diabetes does not rise to the same level as in the individual without diabetes. An increase in CO is due to an increase in SV and HR. However, the individual with diabetes is not able to increase CO to the same level for a given workload as the individual without diabetes due to the depressed HR (Fig. 1) and SV (Fig. 2) responses to exercise.

12. The individual with diabetes has a 30% lower CO than the individual without diabetes at 100% V̇O₂max. This indicates, in part, that the individual with diabetes has a limited left ventricular function. CO is the volume of blood that the heart pumps per minute. In situations that demand an increased blood flow for the delivery of oxygen and rapid removal of metabolites, such as exercise, CO is increased. Because individuals with diabetes have a limited CO, oxygen delivery and metabolite removal do not occur at levels required to meet the demands of higher workloads. Thus individuals with diabetes experience muscle fatigue easily and have a reduced exercise tolerance. These data illustrate that CO is the limiting factor for exercise tolerance.

13. Resting SBP is 120 mmHg in the individual without diabetes and 110 mmHg in the individual with diabetes. Resting SBP is 10 mmHg lower in the individual with diabetes because resting SV (Fig. 2) is lower. The reasons for the lower SV are due to cardiac myopathies, which reduce left ventricular function, and a decreased myocardial compliance, which limits the increase in left ventricular EDV. The reduced aortic compliance associated with diabetes tends to increase SBP. It is important to note that the reduction in SV is greater than the decreased compliance at rest.

14. Both individuals demonstrate a rapid increase in SBP of 40 mmHg (nondiabetics: 120–160 mmHg; diabetics: 110–150 mmHg). Figure 5 (SBP) looks almost exactly like Fig. 2 (SV). This is because SV is the major component contributing to SBP at the onset of exercise.

15. SBP is a function of SV and vasculature compliance. SV, mediated by an increase in venous return via the muscle pump, is the major component responsible for SBP. Vascular compliance also contributes to SBP. In individuals with diabetes, collagen infiltrates into the vascular wall and results in a thickening of the aorta and the arteries. This decreases the overall vascular compliance. The decrease in vascular compliance increases SBP because the vessel does not expand adequately and the energy during systole is not absorbed. Conversely, individuals without diabetes have a greater vascular compliance compared with individuals with diabetes.
INNOVATIONS AND IDEAS

diabetes. Thus compliance does not contribute significantly to the increase in SBP in the individual without diabetes.

16. In the individual without diabetes, SBP plateaus at 75% \( \dot{V}O_{2\text{max}} \). The plateau in CO (Fig. 4) is responsible for the plateau in SBP.

17. At workloads between 25 and 75% \( \dot{V}O_{2\text{max}} \), SBP continues to increase although not as rapidly as the increase that occurs at the onset of exercise. SBP gradually increases as a result of increases in contractility and HR (Fig. 1), increasing CO. The gradual increase in SBP is mediated by cardiac sympathetic efferent nerves activating cardiac \( \beta_1 \)-adrenoreceptors and, to a lesser degree, circulating catecholamines released by the adrenal medulla.

18. In the individual with diabetes, SBP plateaus at 50% \( \dot{V}O_{2\text{max}} \). The plateau occurs for several reasons. The plateau in SV and CO prevents a further increase in SBP beyond 50% \( \dot{V}O_{2\text{max}} \). In addition, cardiac myopathies, decreased myocardial compliance, and reduced number of cardiac \( \beta_1 \)-adrenoreceptors prevent further increases in SBP in the individual with diabetes.

19. Resting DBP is 80 mmHg in the individual without diabetes and 83 mmHg in the individual with diabetes. DBP is the pressure exerted by the volume of blood remaining in the arteries when the heart is at rest. DBP is dependent on HR and the outflow of blood into the periphery (resistance). The elevated resting HR (Fig. 1) decreases the time when the heart is at rest, and thus more blood remains in the arteries during diastole. The elevated resting HR (Fig. 1) decreases the time when the heart is at rest, and thus more blood remains in the arteries during diastole. The increased blood volume contributes to the elevated DBP. Total peripheral resistance is slightly higher (see Fig. 9) and also contributes to the elevated DBP. However, the decrease in aortic compliance lowers DBP. Taken together, the individual with diabetes has an elevated DBP at rest and during exercise.

20. From rest to the first workload, HR and SV increase. From the equation \( CO = HR \times SV \), it is clear that CO substantially increases. The increase in CO is sufficient to raise MAP without an increase in peripheral resistance (MAP = CO × total peripheral resistance). Therefore, DBP is unaltered.

21. From rest to the cessation of exercise, DBP decreased 5 mmHg. DBP decreases in the individual without diabetes because peripheral resistance decreases. During exercise, local metabolites released by the exercising muscle, autoregulation, and endothelial-released nitric oxide provide a strong vasodilator stimulus. The lower resistance facilitates the runoff of blood into the periphery during diastole. The elevated CO is opposed by an adequate reduction in peripheral resistance. Thus DBP decreases.

22. From rest to the cessation of exercise, DBP increased 7 mmHg. DBP increases in the individual with diabetes because of an inability of CO to maintain adequate tissue blood flow. The plateau in CO and tissue blood flow unloads the arterial baroreflex and activates the muscle metaboreflex. These reflexes activate the sympathetic nervous system, which constricts arterioles and attenuates the reduction in peripheral resistance. The elevated HR is not opposed by an adequate reduction in peripheral resistance, and thus DBP increases. At this point, it may be important to state that elevations in DBP are reasons to terminate exercise. Elevations in DBP indicate reductions in cardiac performance. To compensate for reductions in cardiac performance, the sympathetic nervous system is activated.

23. Complete the MAP graph.

24. In the individual without diabetes, resting MAP is 92 mmHg. At 25% \( \dot{V}O_{2\text{max}} \), MAP increased to 104 mmHg for an increase of 12 mmHg. In the individual with diabetes, resting MAP is 91 mmHg. At 25% \( \dot{V}O_{2\text{max}} \), MAP increased to 97 mmHg for an increase of 6 mmHg. The initial increase in MAP in both individuals is due to a sharp increase in CO mediated by an increase in HR and SV.

25. In both individuals, there is a steep increase in MAP at the onset of exercise. With increasing workloads, there is a further gradual increase in MAP. Although the responses are similar in the two individuals, the mechanisms contributing to these increases are different. In the individual without
diabetes, MAP sharply increases at the onset of exercise due to an abrupt rise in CO and decrease in total peripheral resistance. With increasing workloads, CO gradually increases due to sympathetically mediated increases in contractility and HR. Thus MAP is maintained by an increase in CO. In the individual with diabetes, MAP also increases due to an abrupt rise in CO (although smaller than in the individual without diabetes) and decrease in total peripheral resistance. However, total peripheral resistance does not decrease to the same degree. In this individual, the CO response is attenuated due to the reduced SV. With increasing workloads, the reduced CO reduces blood pressure and tissue blood flow. Consequently, the reduced blood pressure and blood flow unloads the arterial baroreflex and activates the muscle metaboreflex, which function to activate the sympathetic nervous system. Sympathetic efferent nerves constrict arterioles and attenuate the reduction in peripheral resistance. With increasing workloads, a decrease in vascular compliance and augmented vasoconstrictor response, mediated by the arterial baroreflex and muscle metaboreflex, maintain MAP. Thus MAP is maintained by an increase in peripheral resistance. Taken together, it is clear that, in the individual without diabetes, MAP is elevated due to an increase in CO, whereas, in the individual with diabetes, MAP is elevated due to an attenuation in the decrease in peripheral resistance.

26. At higher workloads, MAP continues to increase in spite of a reduced cardiac pump function (CO). The reduced CO unloads the arterial baroreceptors and activates muscle metaboreceptors, which reflexly activate sympathetic efferent nerve activity. Thus DBP increases. As demonstrated previously, MAP = DBP + 1/3 pulse pressure. An increase in DBP can increase MAP. The increase in DBP is a compensatory mechanism to increase MAP during exercise when CO is limited and is indicative of impaired cardiac pump function.

27. In the individual with diabetes, an oxygen consumption of 2 l/min corresponds to 65% \( \dot{V}O_{2\text{max}} \).

28. At the onset of exercise, peripheral resistance dramatically decreases in both individuals although the response is attenuated in the individual with diabetes. At the onset of exercise, local metabolites released by the exercising muscle, autoregulation, and endothelial-released nitric oxide provide a stimulus for vasodilatation, and peripheral resistance decreases. The individual with diabetes has impaired local vascular regulatory mechanisms. Therefore, the vascular response to metabolites and nitric oxide are attenuated.

29. In the individual without diabetes, resting peripheral resistance is 16 mmHg \( \cdot l^{-1} \cdot min^{-1} \). At 50% \( \dot{V}O_{2\text{max}} \), peripheral resistance decreased to 4.8 mmHg \( \cdot l^{-1} \cdot min^{-1} \) for a decrease of 11.2 mmHg \( \cdot l^{-1} \cdot min^{-1} \). In the individual with diabetes, resting peripheral resistance is 18 mmHg \( \cdot l^{-1} \cdot min^{-1} \). At 50% \( \dot{V}O_{2\text{max}} \), peripheral resistance decreased to 7.5 mmHg \( \cdot l^{-1} \cdot min^{-1} \) for a decrease of 10.5 mmHg \( \cdot l^{-1} \cdot min^{-1} \). Thus, in the individual with diabetes, peripheral resistance does not decrease to the same level as in the individual without diabetes. The peripheral resistance response is attenuated in the individual with diabetes because of an inability of CO to further elevate SBP and maintain adequate tissue blood flow. The plateau in CO and tissue blood flow unloads the arterial baroreflex and activates the muscle metaboreflex. These reflexes activate the sympathetic nervous system, which constricts arterioles and attenuates the reduction in peripheral resistance. In addition, the individual with diabetes has impaired local vascular regulatory mechanisms. Therefore, the vascular response to metabolites and nitric oxide is attenuated.

30. The peripheral resistance response to exercise levels off at 50% \( \dot{V}O_{2\text{max}} \). This is observed in both individuals. As previously discussed, increases in HR beyond 100–120 beats/min are mediated by the sympathetic nervous system, which functions to further elevate HR and contractility. Simultaneously, sympathetic efferent nerves activate \( \alpha \)-adrenoreceptors located on the arterioles causing vasoconstriction. Arteriole vasoconstriction, mediated by the arterial baroreflex and muscle metaboreflex, attenuates the metabolite, autoregulatory, and nitric oxide vasodilatory stimulus, thus opposing further decreases in peripheral resistance at the higher workloads. The individual with diabetes takes advantage of the reflex-mediated vasoconstriction to compensate for the reduced CO in order to maintain blood.
pressure. The individual without diabetes utilizes the reflex-mediated vasoconstriction to oppose a decrease in peripheral resistance.

31. For the individual with diabetes, the resistance unit at a HR of ~100–120 beats/min is 12 mmHg l⁻¹ min⁻¹. For the individual without diabetes, the resistance unit at a HR of ~100–120 beats/min is 10 mmHg l⁻¹ min⁻¹. This value is obtained from Figs. 1 and 9. This is the point at which peripheral resistance begins to level off due to sympathetic efferent activity causing vasoconstriction.

32. In both individuals, the initial increase in muscle blood flow is mediated by a simultaneous increase in CO (Fig. 4) and decrease in peripheral resistance (Fig. 9). The increase in CO is mediated by an increase in SV (Fig. 2). The decrease in peripheral resistance is mediated by the accumulation of vasoactive metabolites, autoregulation, and endothelial-released nitric oxide. Local vascular regulation (responses to metabolites and nitric oxide) is impaired in individuals with diabetes.

33. Resting muscle blood flow is 1.0 l/min in the individual without diabetes and 0.75 l/min in the individual with diabetes. At 25% VO₂max, muscle blood flow increases to 8.2 l/min in the individual without diabetes. This is ~30% of CO. At 25% VO₂max, muscle blood flow increases to 2.6 l/min in the individual with diabetes. This is ~14% of CO. At 100% VO₂max, muscle blood flow increases to 18 l/min (~67% of CO) in the individual without diabetes and to 10.7 l/min (~56% of CO) in the individual with diabetes. Both individuals demonstrate an increase in muscle blood flow at the onset of exercise, although the response is attenuated in the individual with diabetes. The response is attenuated due to a reduced CO (lower SV). In turn, the reduced CO prevents further increases in blood pressure and adequate tissue blood flow. The reduction in blood pressure and tissue blood flow unloads the arterial baroreflex and activates the muscle metaboreflex, which activates the sympathetic nervous system. Constriction of the arterioles attenuates the increase in muscle blood flow. Thus the reduced blood flow (CO) and compensatory vasoconstriction attenuate the muscle blood flow response. In addition, the impaired local vascular regulation (reduced response to metabolites and nitric oxide) attenuates muscle blood flow in the individual with diabetes.

34. At higher workloads, the metabolic demand far exceeds the supply. This results in a rapid accumulation of exercise-induced metabolites providing an intense vasodilator stimulus. At this point, the vasoconstrictor effect, mediated by the arterial baroreflex and muscle metaboreflex, becomes an important modulator of dilation. Vasoconstriction serves to control the level of dilation and maintain blood pressure. At very high workloads (75% VO₂max), the skeletal muscle receives a large portion of CO due to the intense vasodilator stimulus. At this point, the sympathetic nerves exert a powerful vasoconstrictor effect on the skeletal muscle vasculature despite the signal to vasodilate.

35. These mechanisms are working in the individual with diabetes. In fact the sympathetic-mediated vasoconstriction is augmented to compensate for the reduced CO and maintain blood pressure. This is demonstrated by the attenuated muscle blood flow response. These data suggest that blood pressure is the variable that the system regulates and does so at the expense of blood flow. It is important to reiterate that, in addition to these mechanisms, local vascular regulatory mechanisms are attenuated in individuals with diabetes.

36. In the individual without diabetes, splanchnic or renal blood flow decreased 21% from rest to 50% VO₂max. This decrease in splanchnic or renal blood flow is necessary for the following reasons. In the individual without diabetes, resting muscle blood flow (Fig. 10) is 1.0 l/min. At 50% VO₂max, muscle blood flow is 9.0 l/min (41% of CO). At 100% VO₂max, muscle blood flow is 18 l/min (67% of CO). That is, 67% of maximal CO is shifted to the active muscle. Splanchnic and renal blood flow must decrease to redirect CO away from nonexercising beds to the active skeletal muscle. Also, splanchnic and renal vasoconstriction attenuate the decrease in peripheral resistance, which also helps to maintain blood pressure.
37. In the individual with diabetes, splanchnic and renal blood flow decreased 13% from rest to 50% \( \dot{V}O_{2\text{max}} \). In the individual with diabetes, resting muscle blood flow (Fig. 10) is 0.75 l/min. At 50% \( \dot{V}O_{2\text{max}} \), muscle blood flow is 5.3 l/min (24% of CO). At 100% \( \dot{V}O_{2\text{max}} \), muscle blood flow is 10.7 l/min (56% of CO). Note that 56% of CO is shifted to the active muscle at \( \dot{V}O_{2\text{max}} \). This is due, in part, to splanchnic and renal vascular vasoconstriction.

38. Complete the a-v oxygen difference graph.

39. The a-v oxygen difference is significantly enhanced in the individual with diabetes (Fig. 13A). However, at the same percent of oxygen consumption, the a-v oxygen difference is similar (Fig. 13B) despite a reduced CO (Fig. 4). This suggests that the ability of a vascular bed to extract oxygen compensates for the reduced CO. Furthermore, the Fick equation (\( \dot{V}O_2 = CO \times a-v O_2 \)) demonstrates mathematically that the a-v oxygen difference must increase to compensate for a reduced CO to maintain oxygen consumption.

40. The increase in the a-v oxygen difference at absolute workloads (Fig. 13A) does not contribute significantly to exercise tolerance. This is demonstrated in Fig. 13B in which the a-v oxygen difference is similar at the same percentage of the \( \dot{V}O_{2\text{max}} \) for both individuals. Additionally, the a-v oxygen difference continues to increase with increasing workloads and does not level off as seen with SV, CO, and SBP. From the Fick equation, \( \dot{V}O_2 = CO \times a-v O_2 \), it is clear that CO is the limiting factor in oxygen consumption, not the a-v oxygen difference.

This project was made possible by the generous support of the Porter Physiology Development Program, APS.

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Received 29 June 1994; accepted in final form 15 September 1995.

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SUGGESTED READINGS