LEARNING THE REGULATION
OF PERIPHERAL BLOOD FLOW

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Students can learn a great deal about the peripheral circulation when teaching is based on five building blocks: hemodynamic principles, neurohumoral control, and three elements of local control of blood flow (metabolic, myogenic, and paracrine). Study of a particular special circulation starts with the application of these building blocks in the context of the function of that tissue. For example, control of skin blood flow is largely concerned with regulation of body temperature (neurohumoral control) and the response to injury (paracrine control). Regulation of coronary blood flow is almost entirely a matter of meeting the metabolic needs of the myocardium (metabolic control). By mixing and matching the five building blocks and keeping in mind the special functions of a particular tissue, students can master the peripheral circulation efficiently.

Key words: skin blood flow; coronary blood flow; neurohumoral; metabolic; myogenic; paracrine; active hyperemia; reactive hyperemia; autoregulation

Basic science education of medical students is concerned with vocabulary and understanding. Students need a vocabulary that will be taken for granted in later courses; the survival value of simply knowing what words mean cannot be overestimated. In physiology this is not enough. Students need an understanding of at least a minimum number of phenomena. Underlying these phenomena are recurrent themes including homeostasis (together with negative feedback), the laws of mass and energy balance, and the many applications of Ohm’s Law. In addition, a basic science education should lead to a conviction that the grossly observable manifestations of health and disease can or will be understood at multiple levels from the function of organ systems to the structure of molecules. Students need enough concrete examples of this to make the generalization second nature.

As instructors, our criteria for selecting cardiovascular learning objectives for medical students are 1) importance in building a mental model of a functioning cardiovascular system and 2) relevance to clinical medicine. Our goal (perhaps never fully realized) is to help the students develop their own working model of the circulation that they can use to grasp the pathophysiology, pharmacology, and clinical medicine that will follow. It is not a catastrophe if a mental model is deficient in aspects of physiology that have little or no clinical application. It is not even a catastrophe if a mental model is not strictly correct, as long as it is based on sound fundamentals. There are plenty of opportunities to refine and expand the model later.

As they progress, medical students do not and should not retain what we teach them about cardiovascular physiology as a distinct body of information. Physiology is to medicine and surgery as physics is to physiology. A good background in classical physics is necessary if one is to understand physiology, but
being a practicing physiologist does not require that one remember everything learned in a physics course. Physics is the scaffolding needed to build an understanding of physiology, but the formal structure of course work in physics is already receding from active memory as it is applied to learning physiology. Perhaps this is because of Sherlock Holmes’s theory that the mind is like an attic in which extraneous things must be thrown out if what is needed is to be found (5).

Practitioners of medicine and surgery relate to physiology the way physiologists relate to physics.1 They remember certain facts and concepts that they find useful in everyday practice and forget the rest. However, the facts and concepts they remember would not have made sense at the time they were learned if they had been isolated from a coherent treatment of physiology. This is because a thorough understanding of the particular depends on its relationship to the whole.

This is not to say that physiology cannot be learned in the context of systems rather than as a freestanding course. Indeed, there is evidence that it can (see, for example, Ref. 1). When physiology is learned as part of a systems curriculum, either in problem-based learning or a lecture format, the physiologists involved should be sure that the major subtexts of a good physiology course are still there, including the importance of the laws of thermodynamics and homeostasis.

This paper concerns what we want our students to learn, not how they learn it. It is worth mentioning that in our course we only lecture on about one-half of the material we expect students to learn. For the rest, we send them to textbooks and other materials.

We teach physiology to first- and second-year medical students. In the first year, we require a mastery of fundamental concepts, with an emphasis on normal function. In the second-year, we ask students to learn pathophysiology in a systems context, either by means of a problem-based learning or a lecture-based curriculum.

REGULATION OF PERIPHERAL BLOOD FLOW

Prerequisites for learning about peripheral blood flow include some knowledge of the microanatomy of the vessel wall, autonomic nervous system, and vascular smooth muscle. Given these fundamentals, the regulation of peripheral blood flow can be taught efficiently by acquainting the students with a number of building blocks and then mixing and matching the blocks, depending on the particular organ or tissue under consideration.

Hemodynamic principles. In addition to understanding the relationships between pressure, flow, and resistance, students should know the resistance, exchange, and capacitance functions of the peripheral circulation. Finally, they will require an understanding of transmural pressure. We find that much of this material can be mastered through self study, if students are provided with an adequate text, learning objectives, and a number of study questions with annotated answers.

Neurohumoral control. The most important and most straightforward element of neural control is sympathetic adrenergic α-receptor-mediated vasoconstriction.2 Students should be convinced that although there are other neurohumoral mechanisms, this is the one to know if you know only one. It is reasonable for students to come away with the view that, with the exception of the external genitalia, this is the only significant innervation of blood vessels in the body. It is important to make this point because as they learn about other receptors for neurotransmitters in the vascular wall, they are tempted to believe that there are nerves to match. This raises the question of how to emphasize key points. I know that shooting off a cannon at the key moment does not work. Horace Davenport used to fire a toy cannon to emphasize a point, but all that students could remember was the cannon going off.

1 This paragraph and the one preceding represent an unsubstantiated belief, based on discussions with many physicians. However, for a more rigorous approach, which raises the possibility that the clinical practice of medicine does not yet rely enough on basic science to make use of a basic medical science education, see Sweeney (17).

2 Neurohumoral control of the human cardiovascular system is covered beautifully by Rowell (14).
Acetylcholine dilates blood vessels by causing the release of nitric oxide from endothelium (8). Here, it may be useful to take a cue from late night television. Nothing is as sure to keep the audience awake and appreciative as sex. The following approach allows one to make a number of important points regarding the peripheral circulation. The only significant instance of cholinergic innervation of blood vessels in humans is the external genitalia. There, parasympathetic nerves release nitric oxide and acetylcholine, which cause further release of nitric oxide. Nitric oxide activates guanylate cyclase and raises cGMP, which causes vascular smooth muscle relaxation. Sildenafil inhibits the breakdown of cGMP and is used for the treatment of erectile dysfunction. Most blood vessels of the body are not innervated by cholinergic nerves, but they do have the nitric oxide/cGMP system. In the presence of sildenafil, organic nitrates can produce inappropriately high levels of nitric oxide, causing vascular collapse (9).

Medical students should not be burdened with knowledge of sympathetic cholinergic vasodilator fibers in skeletal muscle or anywhere else. If they exist in humans, they are of little importance (14). Their presence and probable survival value in some mammals does not justify describing them in an introductory course. This is because of an important corollary to Vander’s Law (18): students have a hard time knowing what is important, so if you tell them every thing you know, they may learn the least important information best. This leads to statements like “stretch of the baroreceptors causes vasodilatation by activating sympathetic cholinergic fibers.” Still, I am assured that there is no evidence that students conclude that the baroreflex response to increased blood pressure includes an erection.

With the exception of the axon reflex in skin, we do not acquaint the students with the fact that blood vessels receive nonadrenergic, noncholinergic innervation (11). We think that students can build a reasonably accurate mental model of the circulation without knowing this fact. Of course, this view may change in the future, depending on new information about the functional importance of this innervation.

We tell the students about three vasoactive hormones. Angiotensin II and vasopressin may play a significant role in vasoconstriction related to volume loss, but probably not orthostasis, except under conditions of salt depletion (14). We resist the temptation to mention the vasodilatory effects of atrial natriuretic peptide (20) because we are not sure of its physiological importance.

Arteriolar smooth muscle of some vascular beds, especially skeletal muscle, has β-adrenergic receptors, which mediate relaxation. Once mentioned, placing these receptors in context requires care. Norepinephrine released from nerve endings does not reach these receptors, but circulating epinephrine does. I do not introduce the fact that at high concentrations epinephrine causes α-receptor-mediated constriction, although the students will learn this soon enough from the pharmacologists. In this practice I am following Vander’s Law, which states that it is not good to lie to students, but that does not mean you have to tell them everything you know (18).

**Local regulation of blood flow.** Local regulation of blood flow occurs by means of three basic mechanisms: metabolic, myogenic, and paracrine regulation. Metabolic regulation (10) occurs when vasodilator metabolites, which include adenosine, prostanoids, potassium ion, PCO₂, and hydrogen ions, are released from parenchymal and endothelial cells in response to increased metabolic activity or decreased O₂ supply and diffuse to nearby arteriolar smooth muscle cells, where they cause relaxation. Relaxation of arteriolar smooth muscle cells increases diameter and blood flow, supplying more O₂ and other nutrients. Tissue PO₂ decreases with increased use of O₂ relative to supply, and, under conditions when arteriolar wall PO₂ decreases as well, this contributes to vasodilatation. The relative importance of the various metabolic vasodilator mechanisms is not convincingly worked out, so it is best to simply lump all of the usual suspects together.

The feedback loop for metabolic regulation is shown in Fig. 1. In this feedback loop a decrease in arterial pressure reduces the delivery of oxygen, which ultimately causes release of metabolites, which raises flow toward normal. Alternatively, increased tissue metabolism leads to increased blood flow and a restoration of tissue PO₂. Tissue PO₂ is used as the error signal even though the real case is more complex; some vasodilator mechanisms do not rely on tissue PO₂.
and instead are related to metabolic activity in other ways. An example is potassium ion release. This simplification is complex enough for a medical physiology course. Some of our students have a problem with interpreting this type of simple feedback loop because they do not know when to stop following the arrows. For example, they might have trouble predicting whether a decrease in arterial pressure would lead to a rise or fall in blood flow and tissue Po2. Being careful to give the students the bottom line can counteract this problem. Decreased pressure decreases blood flow and tissue Po2, although not as much as would be the case if it were not for autoregulation.

We ask that the students know that myogenic regulation exists because we use it as a partial explanation for reactive hyperemia and autoregulation. The error signal for myogenic regulation is stretch of vascular smooth muscle cells (4). We do not present this as part of a negative feedback loop regulating flow because the complexity outweighs the net benefit to the student. Instead, we simply emphasize that the myogenic response counteracts the effects of increases or decreases in transmural pressure on arterial diameter (Fig. 2).

Figure 3 shows the minimum we want medical students to know about paracrine regulation. They should know about the influence of the endothelial cell on platelets and vascular smooth muscle (22). In the presence of endothelium, serotonin, ADP, and thrombin released from platelets cause vascular smooth muscle relaxation. However, the direct effect of these agents on vascular smooth muscle is contraction. Students should know the actions of thromboxane A2, if for no other reason than the fact that large numbers of Americans suppress their ability to synthesize thromboxane A2 with daily aspirin. We tell them about histamine but suppress the urge to ask them to learn about cytokines at this stage.

Figure 3 shows two other phenomena that are not paracrine related but that I think are worth mentioning. Flow-induced dilation (2) is an important part of producing high flows in the heart and skeletal muscle during metabolic hyperemia. The axon reflex is worth mentioning because students should know about the
response to injury of the skin. Although ATP and substance P have had their advocates, it appears that the mediator of the axon reflex is calcitonin gene-related peptide (CGRP) (15).

The building blocks described above can be used to explain four elements of local control of blood flow that recur as blood flow in each organ is discussed: active hyperemia (metabolic regulation), reactive hyperemia (metabolic and myogenic regulation), autoregulation (metabolic and myogenic regulation), and the vascular response to injury (paracrine regulation). Each of these elements can be fully discussed in the context of one of the special circulations and then recycled each time it is needed. For example, if skeletal muscle blood flow were discussed first, active hyperemia and perhaps reactive hyperemia would be discussed in this context. When the brain was then to be considered, it would only be necessary to point out that the brain also exhibits active hyperemia.

REGULATION OF BLOOD FLOW IN SPECIFIC TISSUES

The coronary and cutaneous circulations will be used to show how the building blocks described above can be used to provide a fairly sophisticated view of a special circulation.

Coronary blood flow. The importance of two interrelated physical factors (7), diastolic arterial pressure and myocardial compression, is especially important in learning about coronary blood flow. Because intramural vessels are compressed during cardiac contraction, perfusion of the myocardium is uniquely dependent on diastolic arterial pressure. It is useful to point out that aortic insufficiency can result in myocardial ischemia largely because of an abnormally low diastolic pressure. The gradient of the compressive pressure within the wall of the myocardium is such that perfusion of the subepicardium is not much affected by contraction, whereas the perfusion of the subendocardium stops. Over the complete cardiac cycle, average myocardial blood flow is as high as or higher than that in the subendocardium because the high flow during diastole balances the lack of flow during systole. The high flow during diastole is an example of reactive hyperemia occurring in the heart on a beat-to-beat basis. With stenosis of the distributing arteries on the surface of the heart, such as that which occurs in atherosclerosis, subendocardial flow is more threatened than subepicardial flow because more coronary reserve is in use to provide adequate perfusion under normal conditions (see below).

Active hyperemia (16) is the sine qua non of coronary blood flow. Because a substantial fraction of arterial $O_2$ is extracted under basal conditions, any increased requirement for $O_2$ must be met by increasing coronary blood flow. Acutely increased myocardial metabolism is almost always the result of increased sympathetic nerve activity to the heart. Depending on the circumstances, part of the increase in coronary blood flow may be provided by increased arterial (primarily diastolic) pressure. However, arteriolar vasodilatation resulting from release of vasoactive metabolites is usually essential to the adequate supply of $O_2$. In general, there is a linear relationship between coronary blood flow and myocardial metabolism. This is because 1) increased metabolism normally results in coronary dilatation and 2) if coronary stenosis prevents an increase in blood flow, metabolism does not increase because of lack of adequate oxygen. When teaching first-year students, we only mention the first of these reasons. When discussing pathophysiology with second-year students, we point out the second. Flow-induced dilatation (see below) of epicardial
distributing arteries is necessary to maintain the full pressure gradient across the wall of the heart.

We ask medical students to learn about the coronary stenosis and reserve (16) during the second year in the context of the study of the pathophysiology of the cardiovascular system. This can be done using a graph showing coronary blood flow as a function of pressure downstream from a stenosis (Fig. 4). It is important that the students understand that the pressure in such a graph is downstream from the stenosis. Furthermore, it is necessary to take the time to point out the hemodynamic implications of the stenosis. That is, as the stenosis increases, downstream pressure falls. It is dangerous to gloss over this seemingly obvious point. The region of the curve in which changes in pressure are accompanied by small changes in flow is the autoregulatory range. In this range the resistance of arterioles downstream from the stenosis is adjusted to compensate for changes in the poststenotic pressure. Hearts performing in this region show reactive hyperemia, and infusion of a vasodilator causes an increase in flow. This is because the downstream arterioles can dilate in response to either stimulus. The magnitude of the increase in flow is a measure of the size of the coronary reserve. When pressure distal to the stenosis drops below the autoregulatory range, reactive hyperemia and increased flow in response to a vasodilator...
are no longer observed. This is because the downstream arterioles are maximally dilated and cannot dilate more in response to any stimulus. Coronary reserve is zero.

This is the most elementary discussion of coronary stenosis and reserve that gives the student an appreciation of the topic. There are many issues that we do not raise with medical students. For example, coronary

FIG. 4.
Coronary reserve refers to the ability of vessels downstream from a stenosis to dilate and is manifested in the autoregulatory range by reactive hyperemia and/or increased flow in response to a vasodilator. Below the autoregulatory range, vessels downstream from a stenosis are completely dilated, so a vasodilator stimulus such as reactive hyperemia or a drug does not increase flow. Within the autoregulatory range, the magnitude of coronary reserve depends on how much downstream dilatation is necessary to compensate for an upstream stenosis. That is, there is more coronary reserve when the pressure distal to the stenosis is 100 mmHg than when it is 75 mmHg.
reserve can be estimated by measuring the pressure drop across the stenosis during infusion of a vasodilator (12). If increased flow occurs (because of down-stream arteriolar dilatation), the pressure drop across the stenosis increases. If no change in the drop occurs, coronary reserve is exhausted. Furthermore, we do not point out to the students that flow stops at a pressure well above zero. This is primarily because of the “waterfall” phenomenon (6). Medical students do not ask about the positive zero flow intercept; we do not invite trouble by pointing it out. In the context of an initial presentation of coronary stenosis and reserve, we do not confuse the issue by introducing the effects of reduced myocardial flow on myocardial performance, including myocardial stunning and hibernation (20). Although we are not explicit on the point, we are content to leave the impression that myocardial metabolism is unchanged as flow falls. Once students have absorbed this topic, we introduce the idea that low flow can cause reduced metabolism and other longer-term effects on the heart.

Coronary endothelial cells play two important roles in the regulation of coronary blood flow. The primary event in increasing coronary blood flow during active hyperemia is dilatation of arterioles by local metabolites. If distributing arteries did not participate in this dilatation, there would be an increased pressure drop along their length. This means that the pressure available to drive blood flow across the wall of the heart would be decreased. However, increased flow velocity in distributing arteries causes local release of nitric oxide and vascular smooth muscle relaxation. The resulting small increase in diameter of distributing arteries is sufficient to prevent the drop in pressure, which would ordinarily accompany the increased flow associated with active hyperemia (16).

Coronary endothelium also plays an important role in protecting vascular smooth muscle from the constrictor effects of a number of agonists in the blood. These include platelet-derived serotonin and thrombin (19).

The main point for students to carry away from a consideration of the effect of sympathetic nerves on coronary blood flow is that stimulation of sympathetic nerves to the heart increases coronary blood flow (7). It is fine to point out that the increase in flow is attenuated by α-adrenergic effects on coronary vessels as long as the main point that the β-adrenergic effects on the myocardium lead to active hyperemia is not lost.

Skin blood flow. Clinicians frequently use the cutaneous circulation as a guide to the overall status of the peripheral circulation. This is reason enough to ask that students learn something about skin blood flow. Furthermore, students can enhance their understanding of the peripheral circulation on the basis of their own direct experience of skin blood flow. For example, we point out that when they stand up after lecture, the skin that has been compressed between their ischial tuberosities and the chair will turn red and warm because of reactive hyperemia. They can also sit on one of their hands for a few minutes during lecture and then observe the reactive hyperemia. The low metabolism of skin is consistent with the idea that the myogenic response is responsible for reactive hyperemia in skin.

The amount and hue of blood contained in the subcutaneous venous plexus influences skin color in all but the most pigmented individuals. With the help of a blood pressure cuff, the students can observe the cyanosis of venous congestion, the redness of reactive hyperemia, and the cadaveric pallor of little or no blood at all.

Skin has a low metabolic rate, so its blood flow requirements are met, unless severe pathological reductions in blood flow occur. For the most part changes in skin blood flow are unrelated to changes in local metabolism. Skin temperature both influences and is influenced by blood flow. As core body temperature increases, cutaneous blood flow and temperature rise (13). This results from withdrawal of sympathetic tone and, at higher temperatures, release of bradykinin from active sweat glands. Local skin temperature also influences skin blood flow. At a given core temperature, placing skin in a warmer local temperature raises blood flow. This is because of reduced sensitivity of cutaneous vessels to norepinephrine. At extremely high or low temperatures, other mechanisms come into play. At local temperatures over 45°C, the vascular response to injury occurs. At local temperatures below 10°C, cold vasodilation is observed. At this temperature, vascular smooth muscle contraction fails and cutaneous vessels dilate.
ever, the increased blood flow warms the smooth muscle, which then contracts. This sets up periodic oscillations in skin blood flow.

A cutaneous vascular response injury (Fig. 5) is observed in response to many stimuli ranging from mechanical and thermal damage to insect bites to allergic reactions (see, for example, Ref. 3). With mechanical injury, a red line appears at the site of the insult. This is the result of local release of a number of vasodilators, including histamine, bradykinin, prostaglandins, and nitric oxide, all of which increase the filling of the subcutaneous venous plexus, causing a red line. The stimulus also activates pain fibers, which by means of an axon reflex release CGRP. CGRP causes dilatation in a wider region around the injury: a flare. Finally, the combination of increased capillary transport of plasma protein caused by histamine and bradykinin with the increased capillary hydrostatic pressure caused by arteriolar dilatation results in local edema formation: a wheal. Other types of injury elicit variations of this response. The list of vasoactive substances shown in Fig. 5 is a reasonable balance between oversimplification and overwhelming detail.

A final comment regarding audience may be in order. I have focused on the teaching of medical students because that is what I do. It seems logical that the general approach of building a simple but functional mental model could be applied to any introductory physiology course. Perhaps the main difference would be the selection of specific material relevant to the interests of the students.

In conclusion, the regulation of the peripheral circulation can be understood in terms of five building blocks: hemodynamic principles, neurohumoral control, and three elements of local control (metabolic,
myogenic, and paracrine). Comprehension of the regulation of circulation of specific organs is a matter of knowing the relative importance of each of the building blocks in a particular organ in a particular circumstance. The coronary and cutaneous circulations are contrasting examples in that regulation of coronary blood flow greatly influenced by local metabolic events and cutaneous blood flow is predominantly influenced by neural control related to central temperature regulation. However, in both organs other building blocks are needed to achieve a complete working model of the circulatory control.

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