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Cardiovascular Psychophysiology

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INTRODUCTION

The cardiovascular system is essential for life and has been a central focus of psychophysiological investigation for several reasons. First, at least some its parameters, like heart rate and blood pressure, are readily observed and quantified. Second, the cardiovascular system is a rich and intricate physiological system with multiple regulatory subsystems that are subject to central and peripheral autonomic controls and humoral influences. Consequently, it is highly sensitive to neurobehavioral processes. Finally, the complexity of the cardiovascular system renders it susceptible to a variety of disorders, many of which are impacted by psychological factors such as stress, and hence it assumes special significance in psychosomatic medicine.

The present chapter will provide an overview of the physiology of the cardiovascular system and its central and peripheral autonomic and neuroendocrine controls. It will then consider common psychophysiological measures from the methodological, analytic, and interpretative perspectives. Finally, we will highlight a few current issues and themes in the contemporary literature.

ANATOMY AND PHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

Overview

The cardiovascular system consists of the heart, a pump, and the vasculature, a distribution system, that together ensure that blood reaches all tissues of the body. The heart provides for a consistent flow of oxygenated blood by sending blood into the lungs (pulmonary circulation) and then to the rest of the body (systemic circulation). Figure 8.1 shows a schematized view of the heart and vasculature to emphasize connections among all the components. Deoxygenated blood from the venous side of the systemic circulation returns via the right atrium and then to the right ventricle of the heart from which it is pumped to the lungs for re-oxygenation. Blood returns from the lungs

by way of the left atrium, then enters the left ventricle from where it is pumped into the aorta, the large vessel from which all oxygenated blood is disseminated to the rest of the body. Blood leaving the aorta passes through ever smaller blood vessels, first entering the large arteries which later branch into smaller arterioles, metarterioles and finally into capillaries. Capillaries are small, thin-walled vessels from which oxygen and other nutrients diffuse into tissues, and into which the tissues release waste products such as carbon dioxide that must eventually be secreted or excreted from the body. After the capillary system, blood passes again into somewhat larger vessels, the venules and finally, the veins that carry blood from the systemic circulation back to the heart. The major veins that drain blood back into the heart, the inferior and superior vena cavae, return blood to the right atrium of the heart, from which blood passes to the right ventricle and again begins its journey through the pulmonary and systemic circulations.

The heart

The crucial pump of the cardiovascular system, the heart, consists of special cardiac muscle with properties different from that of skeletal muscle found elsewhere in the body. Cardiac muscle comes in three forms, atrial, ventricular, and specialized conducting fibers that serve as the electrical conducting system of the heart. The pumping action of the heart is primarily served by the atrial and ventricular muscle fibers. Cardiac muscle cells form a syncytium, so called because the tissue is electrically coupled to permit rapid spread of depolarization across the heart, particularly in a rostral to caudal direction. There are both atrial and ventricular syncytiums connected by an electrical conducting system. In the syncytiums, the boundaries of adjacent muscle cells along the longitudinal axis of the cardiac muscle consist of intercalated discs. These discs are specialized, highly permeable membranes capable of extremely fast spread of depolarization from one cardiac muscle cell to another. This is crucial to the pumping action of the heart where the rostral (atrial) and caudal

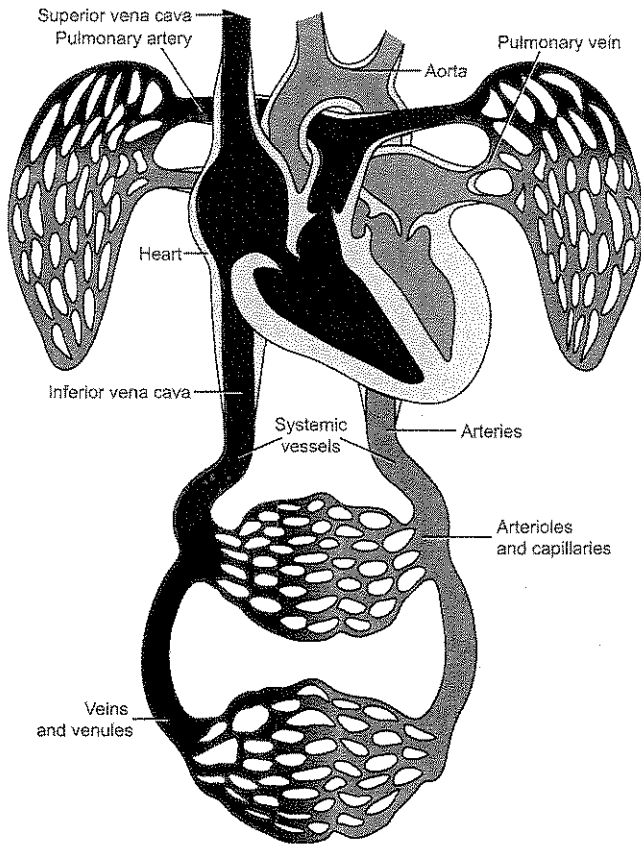


Figure 8.1. Systemic and pulmonary circulation. In keeping with usual depictions of the heart, the right side of the heart is on the left side of the picture. Lighter gray areas indicate oxygenated blood and darker gray areas indicate deoxygenated blood.

(ventricular) portions of the heart each must function as a single pumping unit, and where there must be coordinated action of each chamber.

The atrial and ventricular chambers are electrically connected by way of a conducting system that triggers ventricular contraction shortly after contraction of the atria. The specialized cardiac muscle fibers comprising the conducting system functionally couple the pumping actions of the atria and ventricles. Depolarization of two nodes of electrically active tissue, the sinoatrial (SA) and atrioventricular (AV) nodes, provides the electrical impetus that triggers contraction of the heart. The SA node in the wall of the right atrium just beneath the opening to the superior vena cava serves as the “pacemaker” of the heart. The SA node is the pacemaker because the speed of spontaneous depolarization of this node is typically faster than that of the AV node, and hence generally controls the rate of the beat. A system of internodal fibers forms a conducting system linking the SA and AV nodes. The depolarization wave is conducted away from the AV node and into the ventricles by way of the AV bundle (of His) which branches into the left and right bundles of Purkinje fibers that pass through the septum between the left and right ventricles. This system directs a wave of depolarization from the atria to the ventricles in a controlled

fashion that creates a highly coordinated pumping action with atrial contraction followed shortly by ventricular contraction.

The depolarization of cardiac muscle is different from skeletal muscle in that there is a depolarization spike followed by a sustained depolarization phase or plateau of about 0.2–0.3 seconds before the muscle repolarizes. The presence of the plateau provides a more sustained contraction in cardiac muscle than is typically observed in skeletal muscle. As a result, there is a more effective pumping action by the cardiac muscle because time is needed for blood to travel from the atria to the ventricles before the ventricles contract. The plateau in the depolarization wave of the cardiac muscle occurs because cardiac muscle depolarizes as a result of the opening of fast sodium (Na^+) channels (like those found in skeletal muscle), as well as slow calcium (Ca^{2+}) channels. The combined effect is a sustained depolarization. A similar plateau is seen in the depolarization curve of the Purkinje fibers of the conducting system. However, the velocity of conduction in atrial and ventricular muscle is on average slower (0.3–0.5 m/sec) than in the Purkinje fibers (which vary from 1.5–4.0 m/sec). This faster conduction in the Purkinje fibers permits the depolarization wave to reach all parts of the ventricular muscle quickly.

The cardiac cycle

The events that occur in the heart from one beat to the next beat are collectively referred to as the cardiac cycle (Figure 8.2). The cycle is composed of two main epochs: diastole, during which the heart does not pump and is filling with blood, and systole, during which the heart pumps. The cycle begins with depolarization of the SA node in the right atrium during the latter part of diastole. The wave of depolarization passing through the atrial muscle corresponds to the P wave in the electrical signal generated by the heart (i.e., the electrocardiogram or ECG) as recorded at the body surface (see Figure 8.3, panel A). The P wave is followed shortly thereafter by atrial contraction during which the QRS complex of the ECG appears, reflecting ventricular contraction and demarcating the onset of systole. During ventricular contraction, pressure in the ventricles is high enough to close the atrioventricular (AV) valves between the atria and ventricles. However, after ventricular contraction, as ventricular pressure falls below the atrial pressure, the AV valves open, and blood begins to rapidly fill the ventricles. Initiation of ventricular contraction leads to a large increase in ventricular pressure (more than 100 mmHg in a healthy heart). Once ventricular pressure is higher than the aortic pressure, the aortic valve opens, blood flows into the general circulation, and there is a rapid fall in ventricular volume. Late in the ventricular contraction phase, the ventricles repolarize, a phenomenon seen in the ECG as the T wave, and this initiates relaxation of the ventricles and the onset of diastole.

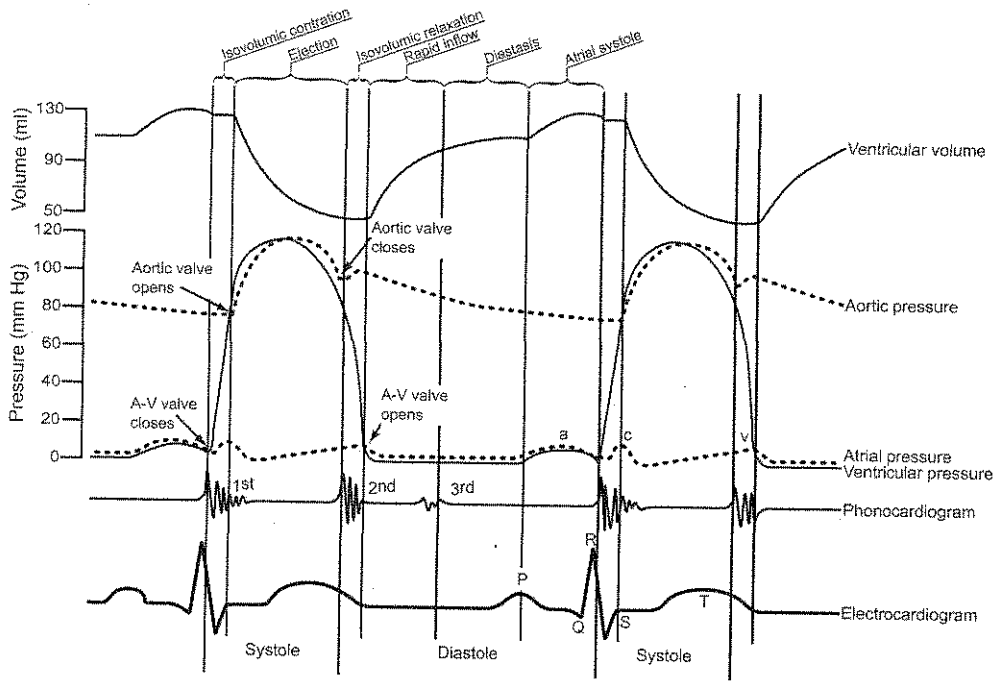


Figure 8.2. The cardiac cycle. Two cardiac cycles are shown for ventricular volume, aortic pressure, atrial pressure, ventricular pressure, the phonocardiogram, and the electrocardiogram (ECG). Phases of the cycle are indicated at the top of the figure above the brackets.

Blood flow, pressure, resistance, and cardiac output

Although Georg Ohm formulated his classic Ohm's law in the context of electrical circuits, the circulatory system adheres to the same basic relations as any other physical system where flow, pressure and resistance are operating. Ohm's Law applied to the circulation reflects the following basic relationships: (a) in order for flow in a vessel to occur, there must be a pressure gradient along the vessel (the homolog to electromotive force), and that (b) the resulting flow (the homolog of electrical current) is a function of the pressure gradient and an inverse function of the vascular resistance to that flow (the homolog of electrical resistance).

These relations are illustrated in Figure 8.4. Here, P_1 is the pressure at the initial portion of the vessel and P_2 is the pressure at the last portion of the vessel. Thus, the

gradient, or pressure differential along this vessel segment is $P_1 - P_2$. Note that as long as P_1 is larger than P_2 then blood will flow through the vessel in the direction indicated. Resistance (R), or the impediment to flow as a result of the vessel wall and the contents flowing in the vessel, occurs along the entire length of the vessel. Resistance can be increased by structural components of the vessel (e.g., bumps along the endothelial surface or bends in the vessel) or by increased viscosity (i.e., thickness) of the blood in the vessel. In this depiction, blood flow rate (Q ; usually expressed in liters/min) or the amount of blood that passes a particular point in the circulation in a given time is equal to $P_1 - P_2/R$. Thus, with a constant pressure gradient, when resistance increases, flow decreases. Alternatively, if the pressure gradient is larger, the flow increases (when resistance is the same). One commonly measured aspect of resistance is the total peripheral resistance (TPR) which

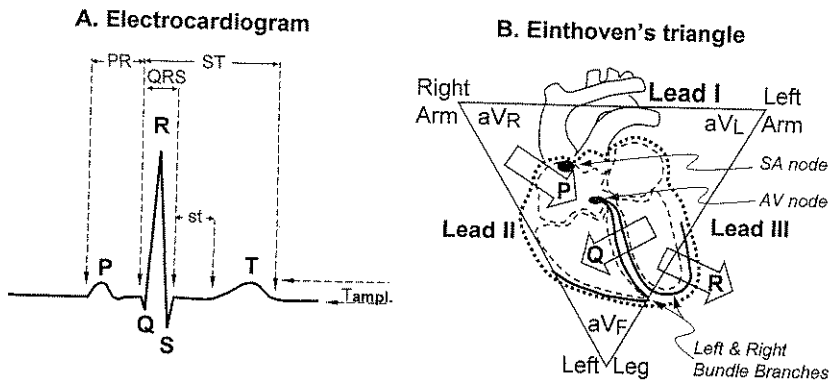


Figure 8.3. The heart and the electrocardiogram. (A) General morphology of the electrocardiographic (ECG) signal showing the P, Q, R, S, & T components, the PR, ST, and QRS intervals, the *st* segment, and the T wave amplitude. (B) The heart, conduction system, and Einthoven's triangle. Open arrow indicates the direction of propagation of electrical activation and the associated component of the ECG.

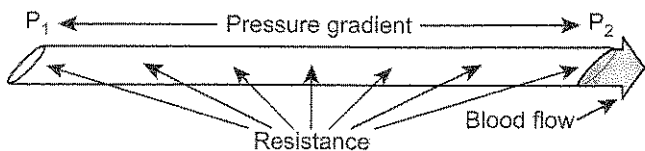


Figure 8.4. Ohm's Law applied to a blood vessel segment. This figure shows pressure differences along a vessel (difference in pressure between P_1 and P_2), resistance to flow in the vessel, and blood flow from the vessel segment. See text for relationships among these parameters.

is the resistance to flow over the entire systemic circulation (measured in dyne · seconds/centimeters⁵ or in peripheral resistance units; PRUs). This basic formulation relating resistance, pressure and flow underlies the movement of blood through the circulatory system.

Blood flow rate is also captured in Poiseuille's Law where:

$$Q = \frac{\Delta \text{ Pressure} \cdot \pi \cdot \text{Vessel radius}^4}{8 \cdot \text{Vessel length} \cdot \text{Blood viscosity}}$$

This formula illustrates an important aspect of the relationship between the factors that impact on blood flow, namely that changes in vessel diameter have a much greater influence on blood flow than any other factor. Indeed, conductance (or blood flow through a vessel for a given pressure gradient) is the reciprocal of resistance, and is proportional to the vessel diameter⁴. Thus, a very small change in vessel diameter by local, neural and hormonal control of the arterioles results in a relatively large change in blood flow.

Blood pressure is the force exerted by the blood against the vessel walls and is generally measured in units of millimeters of mercury (mmHg). Overall arterial pressure varies between the highest level of pressure seen at systole (systolic blood pressure or SBP) and the lowest level seen in diastole (the diastolic blood pressure or DBP). The difference between the systolic and diastolic pressures is called the pulse pressure (PP). Mean arterial pressure (MAP) is often calculated as: $DBP + 1/3 PP$ (or $2DBP/3 + 1SBP/3$) because diastole is about twice as long as systole.

Blood pressure varies across different parts of the circulatory system. When measuring blood pressure, it is important to report the body location from which the pressure is measured (e.g., at the brachial or femoral artery) and for the measurement site to be located at the vertical height of the heart in order to minimize the effects of hydrostatic pressure (the pressure exerted by the fluid in the circulatory system) on the blood pressure measurement. Figure 8.5 shows how blood pressures vary throughout the circulatory system. First note that pressures are high and pulsatile near the aorta where the heart continuously pumps blood into the systemic circulation. As the pressure pulse moves further from the heart, the elastic properties of the large arteries and the control of vessel diameter by smooth muscle in the arterioles damp out much of the pulse in the pressure wave. Because the diameter of the arteriolar vessels is controlled by both intrinsic (local) and extrinsic (autonomic and hormonal) factors, these vessels function essentially as valves controlling the flow of blood into the capillary system. Arterioles are strong walled vessels and their "valvular" function is important because it prevents excessive pressures from reaching the thin walled capillaries where the vessels could be damaged. Systemic pressure falls further as the blood returns from the capillaries, through the small venules and into ever larger veins that eventually return blood to the right atrium. In the normal heart, blood pressure will be at or near zero once blood returns from the largest veins, the inferior and superior vena cavae, to the right atrium. Pressures in the pulmonary circulation are not nearly as high as the systemic circulation, in part due to the short distances the blood must travel through the lungs, relative to the distance traveled in the systemic circulation.

Based on Ohm's Law it would appear that blood pressure would cause a proportional increase in blood flow throughout the body, however, vessels can distend, a fact that complicates the prediction of blood flow with increases in blood pressure. A bolus of blood entering a vessel distends it, and thus the diameter of the vessel does not remain constant. Distensibility is an important feature of veins in particular (which are on average about 8 times more distensible than arteries) because blood is stored in the veins

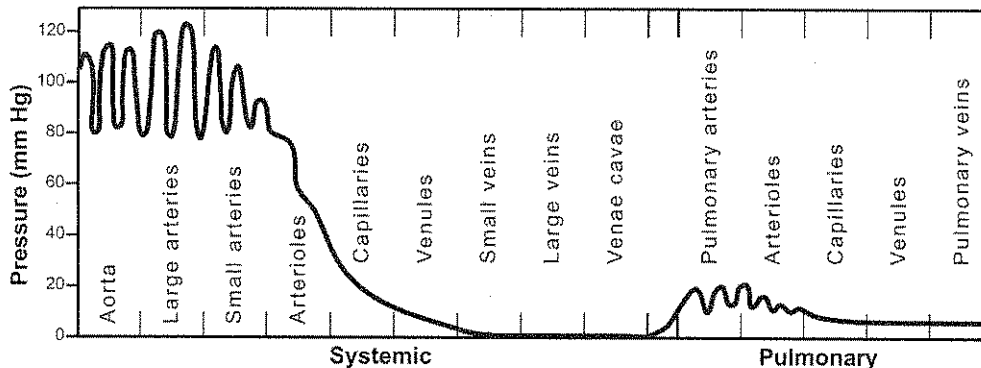


Figure 8.5. Blood pressure variations in the circulatory system. Blood pressure variations are shown for different types of vessels in the systemic and pulmonary circulation.

which form a reservoir from which blood can be marshaled when tissue needs increase. Distensibility of the vessels also helps to damp out pressure pulsations such that by the time blood reaches the capillary beds, the flow of blood is steady and provides a constant supply of nutrients and removal of wastes.

Cardiac output, another critical aspect of circulatory function, is the amount of blood pumped by the left ventricle into the aorta per unit of time (usually expressed as liters/min). Cardiac output can be expressed using another variant of Ohm's Law:

$$\text{CO} = \text{Mean arterial pressure} / \text{Total peripheral resistance.}$$

Cardiac output is directly controlled by the venous return, or the amount of blood that returns to the right atrium from the venous system each minute. Indeed the venous return and the cardiac output are usually equal (except when extra blood is stored in the heart or lungs for a few beats). Because the venous return is the sum of the local blood flows in all of the tissues of the body, the cardiac output is thus controlled by all of these local flows. Therefore, it is most appropriate to see the cardiac output as controlled by the local, neural, and hormonal controllers of these local blood flows, rather than as controlled by the heart.

Blood flow regulation

There are important local, intrinsic mechanisms for regulating blood flow to the heart and other tissues, the venous return and the cardiac output. These mechanisms work in concert with the extrinsic mechanisms (autonomic and hormonal) that are discussed in subsequent sections.

The primary intrinsic mechanism controlling blood flow to the heart is the Frank-Starling mechanism. It was observed that when there was greater venous return than was pumped out with the preceding beat, that the heart subsequently pumped more vigorously (i.e., greater contractility) and pumped a greater volume of blood (i.e., stroke volume, or the volume of blood pumped from the left ventricle with each beat of the heart). It was suggested that this phenomenon occurred due to the presence of stretch receptors in the cardiac tissue, which reacted to increased stretch by producing greater contraction of the ventricular muscle. Recent studies have suggested that a key molecular player in the Frank-Starling mechanism is a large, elastic molecule present in the sarcomeres of cardiac muscle, called titin or connectin (Fukuda, & Granzier, 2004). Not only does titin appear to have passive spring-like properties, but it may also be stretch-sensitive and thus play an active role in the Frank-Starling mechanism (Fukuda, Wu, Farman, Irving, & Granzier, 2003). Another intrinsic mechanism controlling the heart beat is that stretch of the right atrial wall produces an increase in the heart rate which in turn increases the stroke volume, although this effect plays a less important role than the Frank-Starling mechanism.

There are also local, tissue-based mechanisms that provide additional blood flow to tissues of the body when there is a local need for greater tissue oxygenation (Guyton and Hall, 2000). These mechanisms act both acutely (several seconds) and over longer periods (minutes to weeks). There are two primary theories about the acute mechanisms by which most initial changes in blood flow are locally regulated. The first is the vasodilator theory according to which blood flow is regulated by the release of vasodilator substances which increase in concentration when oxygen levels fall. Some of the possible vasodilator substances that have been proposed include adenosine (a strong contender), carbon dioxide, lactic acid, potassium ions, and hydrogen ions. The primary concern with this theory has been a problem in demonstrating that enough of these vasodilator substances are produced to account for the degree of vasodilation seen when vessels are deprived of oxygen. A second theory, called the oxygen (or nutrient) demand theory, suggests that the tissue responds to nutrient demand presumably by causing contraction of sphincters located at the entry of blood to capillary beds (i.e., precapillary sphincters) and in small arterioles (i.e., metarterioles). The theory holds that when these sphincters sense increased oxygen, they contract, thus limiting additional flow to those vascular beds with enough oxygen. This theory is based on observations of cyclical opening and closing of the precapillary and metarteriolar sphincters several times over a minute. These studies showed that the time that the sphincters are open is proportional to the amount of oxygen in the tissue. Evidence countering this theory also exists such that in some tissues, vascular smooth muscle will stay contracted even with only very small amounts of oxygen present. Guyton and Hall (2000) suggest that perhaps the mechanisms underlying acute local changes in blood flow are a combination of the mechanisms underlying these two theories.

Following acute changes in blood flow, flow tends to return to the original level through autoregulatory processes. Autoregulation is thought to occur via mechanisms that have been subsumed under one of two different theories: the metabolic theory, and the myogenic theory. The metabolic theory is based on the mechanisms just discussed (i.e., either release of vasodilator substances or smooth muscle constriction in response to excess oxygen), but now with the effect of resetting blood flow toward the previous level. The myogenic theory, in contrast, suggests that fast stretch of vessel walls leads to smooth muscle constriction. Although this mechanism has been demonstrated in isolated vessels, it is not clear that it would be generally useful throughout the body as any stretch of the vessel wall would lead to vasoconstriction, increased pressure in the vessel, and additional stretch. This vicious cycle would not be effective for the overall functioning of the vascular system.

In combination with these local mechanisms acting predominantly in the smaller vessels (i.e., capillaries and metarterioles), are mechanisms that alter flow in larger

vessels. When increased flow enhances shear stress in arterioles and small arteries, the endothelium lining these vessels releases nitric oxide which causes local vasodilation and a concomitant reduction in the shear stress. Thus, local mechanisms are available in most of the vessels that see relatively high pressures and those critical for oxygen delivery to tissues (all arteries except the very large arteries which have little smooth muscle and capillaries). These mechanisms prevent excess pressure in delicate capillaries while maintaining a sufficient supply of nutrient to the tissues.

On a longer time scale, blood flow can increase or decrease when there is a longer term change in need by altering the vascularity of tissue. Vascularity changes are structural resulting either from changing the size and/or number of vessels. A prime example of this mechanism is the increased number of vessels that infiltrate a cancerous tumor that has an ever increasing need for additional blood flow. Together, local mechanisms provide many ways that blood flow can change both acutely and over longer periods to adapt to changing tissue demands.

AUTONOMIC AND HORMONAL CONTROL

Beyond local intrinsic autoregulatory processes are extrinsic regulatory processes associated with autonomic and hormonal systems.

Autonomic nervous system

The cardiovascular system is under control of both the sympathetic and parasympathetic branches of the autonomic nervous system. A given organ system is often innervated by both autonomic branches, which typically exert opposing actions. Some organs are not dually innervated, however, and even for dually innervated organs, the autonomic branches may have synergistic rather than opposing effects or may otherwise be asymmetrical in their pattern of innervation or action. These patterns of innervation and effect are important in measuring, interpreting, and conceptualizing cardiovascular psychophysiological relations.

Historically, the peripheral components of the autonomic nervous system were the first to be described and studied, as they were the most distinct and accessible. Central neurons that give rise to the preganglionic axons of the autonomic nervous system are distributed across levels of the spinal cord and brainstem. The preganglionic fibers of the sympathetic system arise from the intermediolateral cell columns of the thoracic and upper lumbar spinal segments (thoracolumbar system). In contrast, the peripheral parasympathetic system arises from the nuclei within the brainstem, such as the dorsal motor nucleus and the nucleus ambiguus and from sacral cord segments (craniosacral system).

With few exceptions, preganglionic axons terminate in peripheral autonomic ganglia, where postganglionic neurons in turn issue projections to the target organs. For

the sympathetic system, these ganglia consist of the sympathetic chain ganglia that lie along the vertebrae (also termed paravertebral ganglia) and a few more remote ganglia (e.g., the celiac ganglion). In contrast, the ganglia of the parasympathetic system are more distributed, being located in or around the organ being innervated. Consequently, the postganglionic axons of the parasympathetic system are rather short and the preganglionic fibers are long, whereas the opposite relation holds for the sympathetic system. Because of the heavy interconnections within the sympathetic chain ganglia it was believed historically that the system discharges as a whole, whereas the distinct parasympathetic ganglia allowed for a more organ specific discharge. It is now clear that even the sympathetic system is capable of targeted actions, as microneurographic recordings in conscious subjects have demonstrated a striking specificity in the pattern of sympathetic discharge across organ systems (for review see Valbo, Hagbarth, & Wallin, 2004).

In comparison to the somatic motor system, an obvious question arises as to why the peripheral autonomic nerves are interrupted by a ganglionic synapse. Minimally, this synapse would delay transmission in autonomic efferents. Although conduction velocity is crucial in the somatic motor system, it is perhaps less so for the autonomic system. The emerging picture is that autonomic ganglia may not just passively relay incoming information from preganglionic axons. Rather, autonomic ganglia may represent a first level regulatory system. Parasympathetic cardiac ganglia, for example, have been termed a "heart brain" (Randall, Wurster, Randall, & Xi-Moy, 1996), which is characterized by anatomically and neurochemically distinct sets of interacting neurons that serve to regulate aspects of cardiac function (Gray et al., 2004 a,b; Randall, Wurster, Randall, & Xi-Moy, 1996; Richardson, Grkovic, & Anderson, 2003). The precise functions of these integrative networks within autonomic ganglia have not been fully elucidated and are beyond the scope of the present chapter.

Both sets of preganglionic neurons employ acetylcholine as the primary neurotransmitter, which binds to a nicotinic receptor subtype (N_N) and several muscarinic subtypes on the postganglionic neurons in the peripheral autonomic ganglia of both branches. Nicotinic receptors mediate a direct ion channel effect and muscarinic receptors can also promote activity via intracellular 2nd messenger pathways (for review and recent data see Beker, Weber, Fink, & Adams, 2003). Postganglionic parasympathetic fibers also employ acetylcholine as a primary neurotransmitter, although the receptor subtypes on the target organ are commonly muscarinic (M). In contrast, the postganglionic neurons of the sympathetic system employ norepinephrine as the primary neurotransmitter, which can act on alpha adrenergic (e.g., α_1 in arterioles) or beta adrenergic receptors (e.g., β_1 on the heart). As illustrated in Table 8.1, this pharmacological differentiation allows selective experimental manipulations of the autonomic branches. We will return to this issue later.

Table 8.1. Autonomic pharmacology

Synapse	Receptor	Agonist	Antagonist	Organ systems
<i>Acetylcholine</i>				
Autonomic Ganglia	Nicotinic (N_N)	Nicotine	Pentolinium/ Hexamethonium	broad autonomic
Postganglionic Parasympathetic	Muscarinic	Muscarine/ Pilocarpine	Atropine/ Scopolamine	heart/eccrine glands/sudomotor/ gastrointestinal/ciliary muscle
<i>Norepinephrine</i>				
Postganglionic Sympathetic	α_1	phenylephrine	prazosin	vascular vasoconstrictors
	α_2	clonidine	yohimbine	vascular vasoconstrictors (central antihypertensive actions)
	β_1	isoproterenol	atenolol	heart
	β_2	terbutaline	propranolol	bronchioles, vascular vasodilators, (nonselective) also in heart

There are additional complications and some exceptions to the above schema. Added complexity arises from the fact that many autonomic neurons, in addition to their primary neurotransmitter, express and release a variety of neuropeptides and neuromodulators such as neuropeptide Y, vasoactive intestinal peptide, enkephalins and substance P, which may impact transmitter release and/or receptor action (e.g., see Lindh & Hokfelt, 1990; Richardson, R. J., Grkovic, I., & Anderson, 2003). One rather fascinating exception to the pharmacological differentiation as summarized in Table 8.1 is the sympathetic innervation of eccrine sweat glands, which is cholinergic rather than adrenergic. The postganglionic sympathetic neurons that innervate eccrine glands initially appear to express norepinephrine but undergo a phenotypic switch to cholinergic production on interactions with the target tissue (see Landis, 1996). Subsequently, eccrine gland sweat production is controlled largely by muscarinic receptors, although other receptor types might also be involved (Kurzen, & Schallreuter, 2004; Longmore, Bradshaw, & Szabadi, 1985; see also Dawson, Chapter 7).

Another exception, more apparent than real, is the cholinergic sympathetic innervation of the adrenal medulla. In contrast to the postganglionic cholinergic innervation of eccrine glands, the cholinergic innervation of the adrenal medulla is by preganglionic fibers that bypass the ganglionic synapse. These neurons in fact show the typical cholinergic phenotype for sympathetic preganglionics. Furthermore, the direct innervation of the adrenal gland does not violate the general plan. In contrast to most visceral organs, the adrenal medulla derives embryologically from neural crest cells and is thus homologous with sympathetic ganglia. Also like ganglion cells, the adrenal medulla synthesizes and releases catecholamines – norepinephrine and epinephrine. The major difference is that

these adrenomedullary amines are released humorally into the general circulation where they can act at widespread sites. Epinephrine has a somewhat greater affinity than norepinephrine for α and β_2 receptors and an equal affinity for β_1 receptors. The effects of neural NE release and adrenomedullary NE and EPI release may be distinct, however, as diffusion barriers may reduce effects of circulating catecholamines on synaptic receptors. Of additional relevance are noninnervated α and β receptors on the heart and vasculature, which can only be activated by NE or EPI humorally or by norepinephrine spillover from adjacent synapses.

Heart. The general neuroarchitectural plan of the autonomic innervation of the heart is illustrated in Figure 8.6. Parasympathetic preganglionic projections arising from the nucleus ambiguus and the dorsal motor nucleus of the vagus project to the sinoatrial and posterior atrial ganglia, for the regulation of heart rate (chronotropic control), to the atrioventricular ganglia for the control of conduction (dromotropic control), and to the interventricular-septal-ganglia for the regulation of myocardial contractility (inotropic control, although this is minimal for the parasympathetic system) (Gray et al., 2004a,b; Johnson et al., 2004; Pirola, & Potter, 1990; Richardson et al., 2003; Sampaio, Mauad, Spyer, & Ford, 2003). The lower central motor neurons that give rise to preganglionic sympathetic cardiac projections reside in the intermediolateral cell columns, mostly in the upper thoracic segments (Ter Horst, Hautvast, De Jongste, & Korf, 1996). These preganglionic neurons project to the stellate and cervical sympathetic ganglia, which in turn issue postganglionic projections to the heart (Anderson, 1998).

The parasympathetic system has a much wider dynamic range of control over cardiac chronotropy than does

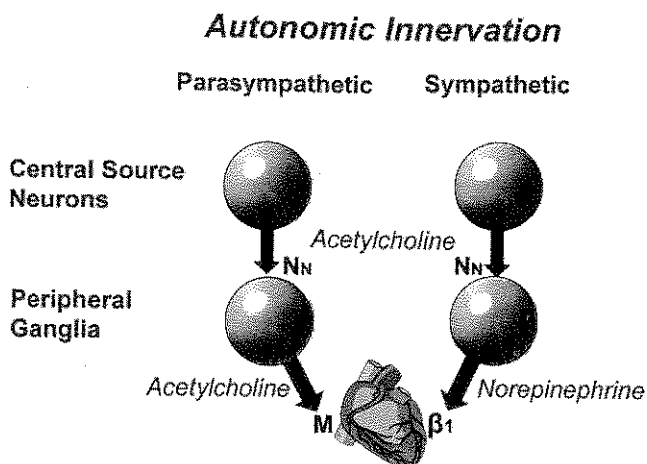


Figure 8.6. General pattern of pharmacology of the autonomic innervations. Abbreviations refer to the relevant postsynaptic receptor populations: NN – nicotinic cholinergic; M – muscarinic cholinergic; β_1 – beta1 adrenergic.

the sympathetic system, whereas the sympathetic system has a more predominant effect on the inotropic state. In humans, the dynamic range of sympathetic chronotropic control has been estimated to be about 230 msec, whereas that of the parasympathetic system is about 1710 msec (Berntson, Cacioppo, & Quigley, 1993a). Chronotropic control of heart period is rather linearly related to parasympathetic activity, whereas there is some nonlinearity in the sympathetic branch. When expressed as heart rate, the dynamic range is highly dependent on baseline heart rate, because heart rate is a nonlinear transform of heart period. The typical dynamic range of control of the sympathetic branch, in heart rate over a wide range of baseline values is ~ 3 –55 beats/min and that for the parasympathetic system is ~ 71 –125 beats/min). An additional complexity is that there are interactions between the branches at the level of the sinoatrial node, and these appear to be much greater when the chronotropic state is expressed in heart rate (Berntson, Cacioppo, & Quigley, 1995). Another difference between the sympathetic and parasympathetic innervations of cardiac pacemaker tissue lies in their temporal dynamics. The parasympathetic cholinergic receptor at the sinoatrial node is directly coupled by a G-protein link to a potassium channel through which a hyperpolarizing K^+ flux slows the spontaneous depolarization of the pacemaker potential. In contrast, sympathetic noradrenergic receptor action is mediated by a more indirect and slower 2nd messenger signaling pathway. Consequently, the parasympathetic system has a shorter latency of action, a more rapid rise time, and a higher frequency capacity – which is the basis for the selective contribution of vagal control to the high-frequency heart rate variability of respiratory sinus arrhythmia (Berntson, Cacioppo, & Quigley, 1993b; Somsen, Jennings, & Van der Molen, 2004). Vagal activation to a behaviorally relevant event, for example, can alter the

interbeat interval of the very beat within which the event occurs (see Somsen et al., 2004).

In contrast to parasympathetic dominance over heart rate, the sympathetic system dominates the control of cardiac contractility. Although there is parasympathetic innervation of the ventricles (Johnson et al., 2004), stimulation of the parasympathetic system in the absence of sympathetic activation may have relatively little direct effect on contractility beyond a secondary effect of heart rate slowing (Levy, 1984; Takahashi, 2003). Much of the parasympathetic innervation of the ventricles may represent presynaptic terminations on sympathetic synapses, which permits a vagal inhibition of sympathetic inotropic control (Levy, 1984; Takahashi, 2003). Interactions among the sympathetic and parasympathetic cardiac innervations are multiple and complex, and include a nitric oxide mediated parasympathetic inhibition of sympathetic control and neuropeptide Y-mediated sympathetic inhibition of parasympathetic control (Chowdhary, Marsh, Coote, & Townend, 2004; Ren, 1991).

Control of the vasculature. Although the heart is a crucial organ in generating the pressure differentials that contribute to circulation of the blood, the vasculature plays an essential part in the maintenance of blood pressure and the arterio-venous blood pressure difference that underlies the distribution of blood. This contribution is not merely as a passive conduit, but as an active regulator of the circulation and distribution of blood across organ systems. An important aspect of this regulation entails peripheral autoregulatory processes that are sensitive to local tissue conditions.

The autonomic nervous system, especially the sympathetic division, is also an important controller of the vascular smooth muscle. Adrenergic receptors on the smooth muscle serve as vasoconstrictors that regulate vascular tone, vascular resistance, and venous compliance. From the initial distinction between alpha and beta adrenergic receptors, an increasing array of receptor subtypes has been identified (α_1 , α_{2A} , α_{2B} , β_1) that have distinct functional roles in cardiovascular control (for review see Guimaraes & Moura, 2001). In the arterial system, the α_1 subtype of adrenoceptors mediates the classical vasoconstrictor actions of both sympathetic innervations and adrenomedullary catecholamines, whereas α_2 receptors are more prevalent in veins where they regulate venous tone and compliance. Several α_2 receptor subtypes are also present as autoreceptors on sympathetic terminals where they serve an inhibitory role in the regulation of NE release (Brede et al., 2004).

In contrast to α -adrenoceptors, the β class of adrenoceptors on smooth muscle mediates adrenergic vasodilation (Guimaraes & Moura, 2001). The β_2 subtype is most common in most vascular beds and mediates, for example, the muscle vasodilation during sympathetic activation associated with exercise. These β_2 adrenoceptors

may be particularly driven by humoral adrenomedullary catecholamines. β_2 receptors have also been described as autoreceptors on adrenergic presynaptic terminals. The β_1 subtype has been increasingly recognized as a mediator of vasodilation in certain vascular beds (e.g., the coronary and pulmonary arteries) and a novel β_3 receptor subtype appears to have vasodilatory functions in the mesenteric and other arterial beds.

Water balance. Additional hormonal and organ systems contribute to body water and electrolyte balance and thus play an important role in blood volume, blood pressure, water distribution, and hence cardiovascular regulation (Guthrie & Yucha, 2004). The kidney is the primary route by which fluids are eliminated in normal organisms. The renal tubular system receives a high volume of blood ultrafiltrate (at the renal glomerulus) including water and electrolytes such as sodium and potassium, most of which is ultimately reabsorbed by the renal tubules prior to passing to the urinary bladder for excretion. The hypothalamic-posterior pituitary hormone vasopressin has two important functions in circulation (Guthrie & Yucha, 2004). First it is a potent vasoconstrictor agent, hence its pressor effect, and secondly it promotes water resorption (antidiuretic effect) in the renal tubule system. Vasopressin stimulation is triggered by either osmotic or hypovolemic body water disturbances and its pressor effect serves to compensate for low blood volume, whereas its antidiuretic effect promotes water retention. The absence of vasopressin in *diabetes insipidus* results in a chronic condition of polyuria (frequent urination of large volumes) and polydipsia (frequent drinking).

Another important player in body water balance is the renin-angiotensin system (see Fitzsimons, 1998; Grisk & Rettig, 2004). Renin is a proteolytic enzyme secreted by *juxtaglomerular* cells of the kidney under conditions of low blood pressure and controlled in part by the sympathetic system. Renin converts a blood borne precursor (*angiotensinogen*) to angiotensin I, which is in turn converted to an active peptide hormone, *angiotensin II*, by the action of another enzyme *angiotensin converting enzyme* (ACE). Angiotensin II is notable for its wide range of actions, which include vasoconstriction, stimulation of thirst, and triggering of *aldosterone* release from the adrenal cortex. Aldosterone is an adrenocortical mineralocorticoid that promotes the resorption of sodium from the renal tubules and fosters salt appetite. Collectively, these actions compensate for the loss of body water and electrolytes and expand blood volume. In fact, they are so effective that overactivity in these systems may contribute to hypertension and ACE inhibitors are effective antihypertensive agents (Grisk & Rettig, 2004).

A final humoral system to be briefly mentioned here is the cardiac natriuretic system, which is implicated in water balance, blood volume, and blood pressure regulation (Luchner & Schunkert, 2004). Cardiac natriuretic fac-

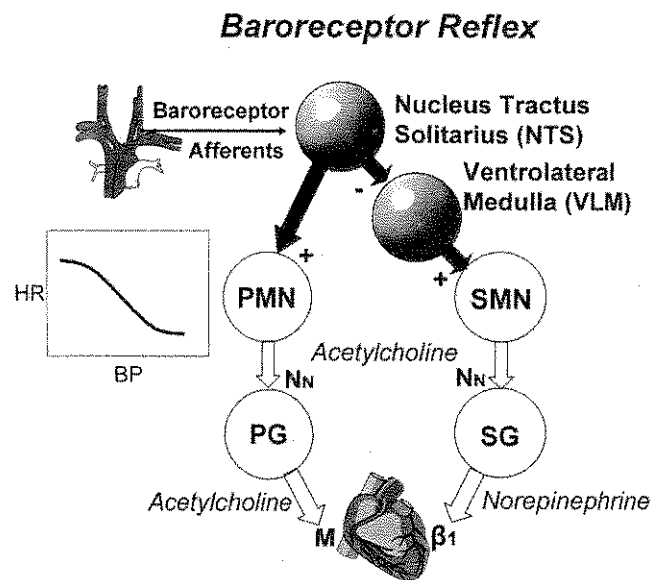


Figure 8.7. General organization of the baroreceptor heart rate reflex. Reflex originates in mechanoreceptors in the heart and the carotid and other great arteries. The NTS excites (+ symbol) the parasympathetic motor neurons (PMN) and inhibits (- symbol) relay neurons to the sympathetic motor neuron pool (SMN). Insert illustrates the relationship between blood pressure (BP) and heart rate (HR). PG and SG depict parasympathetic and sympathetic ganglia, respectively. Other abbreviations are as in Figure 8.6.

tors are released on myocardial stretch and trigger vasodilation, natriuresis (sodium excretion), and inhibition of the sympathetic nervous system and the renin-angiotensin system (Woods, 2004). This natriuretic system is suppressed by a β adrenergic mechanism and may promote vagal control, and illustrates some of the complexities in neural and humoral cardiovascular control.

Central neural control

The cardiovascular system is crucial for survival so it is not surprising that this system is regulated by complex central mechanisms, including lower-level reflex systems as well as higher neurobehavioral mechanisms.

Brainstem reflexes. Among the most well characterized of cardiovascular reflexes are the baroreceptor reflexes, including the baroreceptor heart rate reflex and the baroreceptor vascular reflex (Dampney, Polson, Potts, Hirooka, & Horiuchi, 2003; Ursino & Magosso, 2003; see also Chapter 19, this volume). The baroreceptor heart rate reflex circuit, depicted in Figure 8.7, is comprised of stretch receptor afferents from the carotid and other great arteries to the nucleus tractus solitarius (NTS), the major visceral receiving station in the brainstem. NTS projections can excite activity in parasympathetic source nuclei and via an indirect pathway can inhibit the rostral ventrolateral medulla (VLM) which is a major descending source of tonic drive on the sympathetic output neurons of the intermediolateral cell column. Through this circuit, for

example, increasing blood pressure and the associated increase in baroreceptor afferent traffic increases parasympathetic control and decreases sympathetic outflow. These reciprocal changes in the autonomic branches synergistically serve to oppose the pressure perturbation. The increase in parasympathetic and the decrease in sympathetic cardiac chronotropic control both lead to a slowing of heart rate. This, together with the reduced ventricular contractility due to withdrawal of sympathetic inotropic control, leads to a decrease in cardiac output. In addition, the withdrawal of sympathetic vasoconstrictor control results in vasodilation, which further diminishes blood pressure. Conversely, the unloading of baroreceptors during the assumption of an upright posture (orthostatic stress) yields the opposite pattern of autonomic control – an increase in sympathetic and a decrease in parasympathetic outflow, which compensates for the diminished blood pressure associated with the gravitational pooling of the blood in the lower body.

In addition to arterial baroreceptors, there are a variety of cardiopulmonary mechanoreceptors that contribute to reflex regulation of the cardiovascular system. One such reflex, which is often capitalized on in psychophysiology, has its origin in lung stretch receptors (see Bertson, Cacioppo, & Quigley, 1993b). Inspiration results in the activation of these stretch receptors and their afferents, which project to the NTS. Input from stretch receptor afferents results in a reflexive inhibition of parasympathetic cardiac outflow and an excitation of the sympathetic system. As a result, there arise respiratory rhythms in both sympathetic and parasympathetic nerves, as well as in heart rate variability. Because the sympathetic cardiac synapses can not follow the typical respiratory frequencies, however, the respiratory rhythms in heart rate are driven by the parasympathetic system. Consequently, this respiratory sinus arrhythmia is commonly employed as an index of vagal control of the heart. We will return to this issue below.

An additional class of cardiovascular reflexes are the chemoreceptor reflexes (see Ursino & Magosso, 2003). Pure hypoxia (decreased arterial O₂ pressure), for example, triggers a local vasodilation in vital organs. Although this could be considered an adaptive local regulation, if widespread, it could result in a life-threatening hypotension. Chemoreceptors in the carotid bodies and aorta detect this low oxygen pressure and convey an afferent signal to the NTS which results in a reflexive increase in respiratory minute volume. Hypoxia also yields compensatory cardiovascular reflexes, including a sympathetic vasoconstriction of arterioles throughout many organ systems (except for coronary and brain arterioles), which serve to maintain blood pressure and circulation. A concurrent parasympathetic activation results in bradycardia, which may serve to minimize cardiac work in the face of hypoxia and may also enhance cardiac output (by increasing ventricular filling time). Pure hypoxia is rare, however, as hypoxia is generally associated with changes in partial

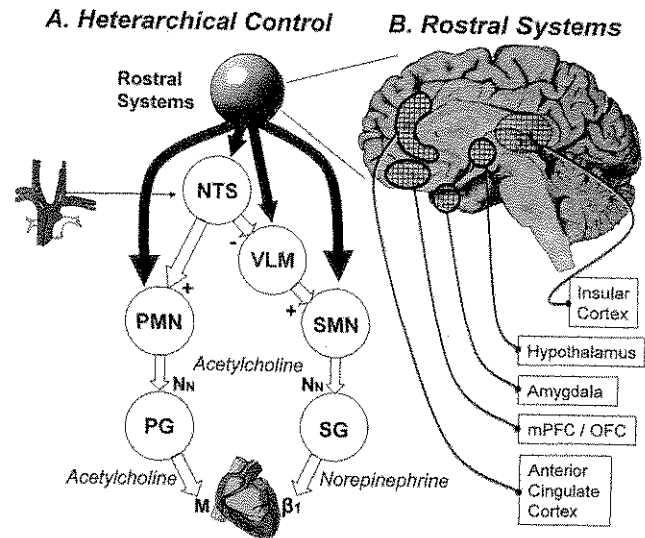


Figure 8.8. Rostral neural systems and heterarchical control. (A) Schematic representation of higher neural control of the autonomic nervous system. The figure illustrates the two general features of heterarchical control: a hierarchical structure together with long ascending (and descending) connections which bypass intermediate levels of organization. (B) Higher neural systems and areas that have been implicated in autonomic control. mPFC – medial prefrontal cortex; OFC – orbitofrontal cortex; other abbreviations are as in Figure 8.7.

pressure of CO₂, which can either increase (hypercapnia, e.g., during asphyxia) or decrease (hypocapnia, e.g., during increased respiration at high altitude). Chemoreceptors are also sensitive to CO₂ pressure (mediated by local pH), with higher levels of hypercapnia yielding progressively greater chemoreceptor activity. This signal has synergistic super-additive effects with hypoxia on chemoreceptor firing.

The cardiovascular reflexes outlined above are far from exhaustive. Rather, they are intended to be illustrative of the powerful reflex control over the cardiovascular system. In psychophysiological contexts, however, higher neuraxial levels may figure more prominently in autonomic regulation.

Higher neural controls. As illustrated in Figure 8.8, higher levels of the neuraxis, including neurobehavioral substrates of the limbic system and other forebrain areas can control, inhibit, or even bypass lower reflex mechanisms in the regulation of autonomic outflows. An example is the stress related suppression of the baroreflex which is mediated by rostral neurobehavioral systems (see Chapter 19, this volume). It is this reflex suppression that allows the concurrent increase in heart rate and blood pressure during stress, in direct conflict with baroreceptor reflexes. As is the case for the somatic nervous system, higher neural autonomic controls are far more flexible and variable than brainstem reflex substrates. Whereas brainstem reflex systems may display a rather fixed, reciprocal pattern of control over the autonomic branches, higher systems are

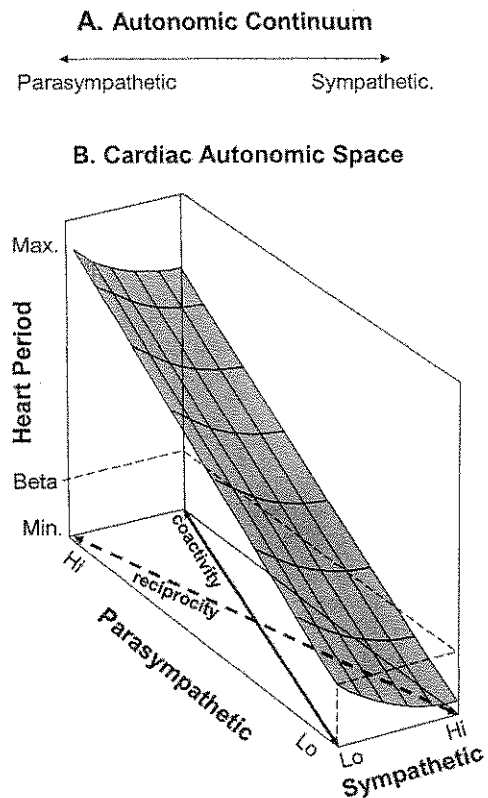


Figure 8.9. Autonomic space. (A) Continuum model of autonomic control, wherein the status of the system can be depicted along a single continuum extending from parasympathetic dominance to sympathetic dominance. (B) A more comprehensive model of autonomic control, characterized by an autonomic plane (representing the fact that parasympathetic and sympathetic systems can change reciprocally, coactively, or independently) and an overlying effector surface which illustrates the end organ state (heart period) for any location on the underlying autonomic plane. Beta illustrates the intrinsic heart period in the absence of autonomic control.

capable of reciprocal, coactive (coactivation or coinhibition) or independent changes in outflows of the two autonomic branches. This has required an expansion from the bipolar model of reciprocal autonomic control to a bivariate autonomic plane and overlying effector surface as depicted in Figure 8.9 (Berntson, Cacioppo, & Quigley, 1991, 1993a; see also Chapter 19, this volume).

There are ample routes by which higher behavioral substrates can impact autonomic cardiovascular regulation. Direct monosynaptic projections to brainstem reflex substrates and even to autonomic source nuclei have been described from rostral areas and structures that have been implicated in psychological and behavioral processes. These include the hypothalamus, amygdala, and prefrontal cortex (see Chapter 19, this volume).

A neuroanatomical tracing study illustrates the rich integration of higher neural systems in autonomic regulation. In this study, pseudorabies virus was injected into distinct areas in the rat heart (Ter Horst, Hautvast, Jongste, & Korf, 1996). Following such injections the viral infection spreads

transneuronally in autonomic nerves, in the retrograde direction back to the central nervous system, where viral labeling can reveal components of multisynaptic networks that regulate autonomic outflow. Among the areas labeled were the NTS and the ventrolateral medulla, as would be expected from Figure 8.8. Higher labeled structures included the raphe nuclei, which give rise to both ascending and descending serotonergic projections, and the A5 cell group, which gives rise to ascending and descending norepinephrine pathways. Additional structures that have been implicated in cognitive and affective processes were also labeled, including the midbrain periaqueductal gray, hypothalamus, amygdala, anterior cingulate gyrus, and the frontal and prefrontal cortex.

A combination of neuroimaging methods and autonomic measures is beginning to be applied to questions of rostral autonomic control. Although this integrative effort is in its infancy, initial findings suggest a close correspondence between neuroanatomical and neurophysiological studies on the one hand and functional neuroimaging studies of autonomic control on the other. PET and fMRI studies have reported that mental arithmetic, a Stroop-stress paradigm, or emotional contexts engage several forebrain areas that have been implicated in psychological processes and autonomic control, including the cingulate cortex, orbitofrontal cortex, insular cortex, and medial and dorsolateral prefrontal cortex, as well as related areas such as the hypothalamus, amygdala, and cerebellum (Critchley et al., 2005a; Gianaros, May, Siegle, & Jennings, 2005; Gianaros, Van Der Veen, & Jennings, 2004; Lane, Reiman, Ahern, & Thayer, 2001; Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004). Moreover, these studies found that the magnitude of cardiovascular responses (blood pressure, heart rate, and heart rate variability) was significantly related to the magnitude of activation in specific brain regions.

With the further development of imaging techniques, this approach will likely be of increasing importance in understanding neurobehavioral systems and their links to autonomic control. Studies using fMRI, for example, have already revealed functional subdivisions even within the anterior cingulate cortex, a complex structure that represents an important interface between cognition and emotion. These subdivisions differentially relate to behavioral inhibition (dorsal anterior cingulate) and vagal control (ventral anterior cingulate) in the Stroop task (Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004). Brain imaging methods not only hold considerable promise for the elucidation of central autonomic and neurobehavioral systems, but also for the clarification of the links between psychological states and processes and cardiovascular health outcomes (Critchley et al., 2005b).

Figure 8.8 illustrates some brain areas that have been implicated in both cognitive and affective processes as well as autonomic cardiovascular control. The extensive overlap of these rostral systems likely reflects the close

integration between behavioral and autonomic substrates that underlies the neurobiology of psychophysiological relations.

PSYCHOPHYSIOLOGICAL MEASURES: RATIONALE AND PHYSIOLOGICAL BASES

ECG

Electrocardiography (ECG or EKG) has been well developed by the field of medical cardiology (for reviews see Berne & Levy, 2001; Goldberger, 1998). The extremity (limb) leads in clinical electrocardiology can be represented by Einthoven's triangle, as illustrated in Figure 8.3B. These leads consist of the unipolar leads of the right arm (aV_R), left arm (aV_L), and left leg (aV_F) and the bipolar leads I (left arm – right arm), II (left leg – right arm), and III (left leg – left arm), with the right leg serving as ground. These leads are often approximated by electrodes placed on the torso, rather than the limbs. In addition, a series of unipolar precordial chest leads are commonly recognized that extend from the lower peristernal region (V_1) laterally to the left (V_1 through V_5) to the midaxial line on the lateral aspect of the chest (V_6). These multiple leads are important in clinical cardiology as they offer distinct electrical perspectives on the events of the cardiac cycle. For most psychophysiological applications, however, a lead II or comparable configuration (e.g., electrodes at V_6 and the right collar bone or aV_R) work well as they yield a relatively large R-wave.

As depicted in Figure 8.3B, the P wave represents the spread of excitation from the sinoatrial (pacemaker) node through the atria, the QRS complex corresponds to the invasion of the ventricular myocardium, and the T wave reflects the repolarization of the ventricles. The arrows in Figure 8.3B illustrate the electrical vectors during selected events within the cardiac cycle. The QRS complex may manifest in just QR or RS deflections depending on the selected lead and how it "views" the electrical events. For a standard lead II configuration, the Q wave reflects the initial depolarization of the ventricular septum, which is followed by the bulk of the ventricular myocardium (R wave). Although the T wave represents the repolarization phase, it generally has the same polarity as the R wave. This is attributable to regional differences (epicardium vs. endocardium) in electrical properties of the ventricular myocytes, which results in the repolarization wave proceeding in the opposite direction to the depolarization phase (the epicardium depolarizes last, but repolarizes first).

Figure 8.3A also illustrates some time/amplitude parameters that have been employed clinically or experimentally. The PR interval (actually the PQ interval if a Q wave is present) reflects the propagation time through the atria and the atrioventricular (AV) node, by way of the conduction system to the ventricles (dromotropic function).

A PR interval longer than 200 msec suggests a conduction impairment (heart block). Within-subjects variation in the PR interval has sometimes been taken to reflect variations in vagal control of the dromotropic state (it slows conduction), although it is not a reliable measure of vagal control as the sympathetic system also influences conduction time. The QRS interval is typically 100 msec, but a prolonged interval can be seen with a block in one of the bundle branches of the conduction system (see Figure 8.3B). The ST segment corresponds to the peak of the muscle action potential and ventricular ejection, the onset of which is also reflected in the first heart sound corresponding to the opening of the aortic valve. The QT interval represents the time from ventricular excitation to the return to the resting state, it can range from 250–500 msec or so and is dependent on the heart rate (shorter at higher heart rates).

The amplitude of the T wave (see Figure 8.3A) has been proposed as a measure of sympathetic control of the heart, as it is sensitive to sympathetic activation or beta adrenergic drugs, but less so to cholinergic drugs or markers of parasympathetic activity (see Contrada, 1992; Furedy, Heslegrave, & Scher, 1992; Kline, Ginsburg, & Johnston, 1998). This measure has not received general acceptance, however, as it does show some sensitivity to cholinergic manipulations (Annala, Yli-Hankala, & Lindgren, 1994), and shows inherent rate dependent changes (Contrada, 1992; Kline et al., 1998) that are independent of, and can be as large as, autonomic effects (Rashba et al., 2002).

Heart rate/heart period

Heart period, or the time in msec between adjacent heart beats is typically measured between successive R spikes in the ECG given the larger magnitude and sharper inflection of the R spike relative to other ECG components. Traditionally, heart period (in msec) was generally converted to heart rate (in beats/min or bpm), although now both measures are used commonly. Heart period and heart rate are simple reciprocals, and one can convert from one metric to the other by dividing 60000 by the heart rate or heart period value. Heart period values become heart rate (in bpm) and heart rate becomes heart period (in msec).

Previously it was assumed that the choice of cardiac metric or measure was not important, and depending on the experimental question and the nature of the results, that may indeed be true. However, there are times where the metric does matter because heart rate and heart period are not linearly related to each other (Berntson, Cacioppo, & Quigley, 1995). Berntson and colleagues (1995) reviewed literature across several mammalian species, including humans, showing that the relationship between changes in activity of the parasympathetic and sympathetic autonomic branches and heart period are more nearly linear than the relationship between activity in either branch and heart rate. Therefore, a given change in activation

of one of the autonomic branches will result in approximately the same change in heart period regardless of the baseline heart period, whereas the same is not true of heart rate. Using data from dogs as an example (from Parker, Celler, Potter, & McCloskey, 1984), an increase in stimulation frequency of 2 Hz of the vagal nerve results in a change of 70–72 msec in heart period regardless of whether the resting (baseline) heart period is 875 msec or 350 msec. However, when the dog's basal heart period is 875 msec (or 68.6 bpm) the change in heart rate with a 2 Hz increment in parasympathetic activation is 5.1 bpm, whereas at a basal heart period of 350 msec, the same 2 Hz change in autonomic input results in a heart rate change of 29.2 bpm. Therefore, the amount of cardiac change reported as a result of an experimental manipulation can differ considerably depending upon the metric chosen to represent change in cardiac function. This is particularly true if the baselines across individuals in a sample are quite different (or different as a function of an experimental factor), or if the amount of change is relatively large. Thus, Berntson and colleagues (1995) recommended that heart period be used as the metric of choice when (a) changes in cardiac function are likely to be a result of autonomic effects (e.g., for many of the short-term cardiac responses seen in the psychophysiology laboratory), and (b) when the changes in cardiac function vary widely as a result of an experimental manipulation or between groups because here the errors due to the nonlinear relationship between autonomic inputs and heart rate can be significant and result in misleading interpretations of the data. The nonlinearity of the effects of autonomic inputs on heart rate also may impact the apparent extent of interactive effects between the two autonomic branches on the heart. The idea that the two branches affect one another and thereby alter the net change in chronotropic control of the heart is termed *accentuated antagonism*. Although there is no doubt that there are mechanisms by which the two branches interact (see *Autonomic and Hormonal Control* section), the magnitude of the effects of these interactions may be smaller than has previously been suggested. Studies showing large *accentuated antagonism* effects have typically used heart rate as the chronotropic metric, whereas the few studies that have used heart period have not seen such large effects. Simulated data also revealed that using the same data to demonstrate interactions between the parasympathetic and sympathetic branches showed much larger apparent interaction effects with heart rate than heart period (Quigley, & Berntson, 1996).

Once the effect of an experimental manipulation is determined using the appropriate cardiac metric, one then can represent cardiac function over a number of beats where the unit of analysis is cardiac time, or over a period of time where the unit of analysis is real time. Heart period permits cardiac function to be reported in either cardiac time or real time, whereas heart rate is represented appropriately only in real time (Berntson et al., 1995; Graham, 1978). To derive heart period or rate in real time, it is important

to use a weighted averaging procedure so that the mean reflects the proportion of time that each beat contributes to the overall average.

Heart rate variability

Measures of heart rate variability (HRV) have figured prominently in cardiovascular psychophysiology and there is now an extensive literature on this topic, including two international committee reports on the origins and implications of heart rate variability and methods for quantification (Berntson et al., 1997; Task Force, 1996). Of particular relevance is the fact that high-frequency heart rate variability, in the respiratory frequency range, largely reflects variations in vagal sinoatrial control and has thus been applied as a selective index of parasympathetic cardiac control (see Figure 8.10A). A wide range of measures have been used to assess heart rate variability, including time domain and frequency domain metrics.

Time domain methods include measures of the variance among heart periods, the variance of the differences among heart periods, and geometric methods based on the shape characteristics of heart period distributions (see Task Force, 1996). The simplest of the time domain metrics is the SDNN, which is the standard deviation of the normal beat to normal beat intervals (normal-to-normal or NN). Because the variance of heart periods increases over time, the SDNN is generally derived over fixed time periods, such as 5 min or 24 h. The SDNN has not seen widespread application in the psychophysiological literature, although another time domain measure that is based on the variance of beat-to-beat heart period differences has been used more frequently. This is the square root of the mean squared successive heart period differences or the RMSSD (Root Mean Square Successive Difference) statistic. As this metric is based on the differences between adjacent heart periods it is nominally independent of basal heart period, although heart period level and heart period variability are themselves physiologically correlated. Because the differences between adjacent heart periods sample heart period variability over relatively short periods of time (the duration of a heart period), the RMSSD parses the total variance by filtering out lower frequency variability. Consequently, the RMSSD has been applied as a measure of high-frequency heart period variability and respiratory sinus arrhythmia. Although the RMSSD does effectively filter out low-frequency heart period variance, the properties of this filter, including its cutoff frequency and its frequency-dependent transfer function vary as a function of basal heart period (Berntson, Lozano, & Chen, 2005). A more systematic parsing of heart period variance into specific frequency components can be achieved by frequency domain methods.

Frequency domain (spectral) methods decompose the overall heart period variance into specifiable frequency bands (see Berntson et al., 1997; Task Force, 1996). A common approach is based on the Fourier theorem which

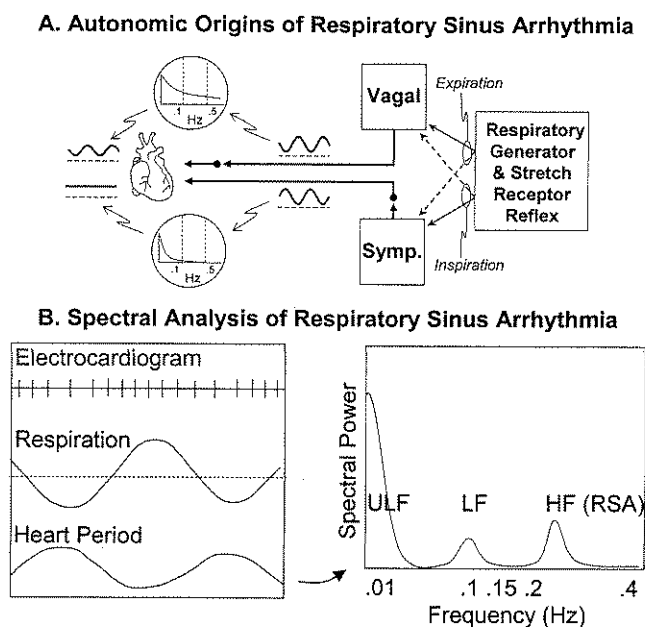


Figure 8.10. Respiratory sinus arrhythmia (RSA). (A) Neurophysiological generators of RSA. Respiratory rhythms are apparent in both sympathetic and parasympathetic nerves, but the different transfer functions (inserts) allow the parasympathetic but not the sympathetic innervations to impart a respiratory rhythm to the beat of the heart. (B) Illustrations of the relation between respiration and heart period, and its quantification by spectral analysis. ULF = ultra-low frequency; LF = low frequency, HF = high frequency.

asserts that any periodic time-varying waveform (in our case, the time varying fluctuations in heart period) can be decomposed into a set of pure sine wave components comprised of a fundamental frequency (f) and a set of harmonics ($2f, 3f, \dots, nf$). Stated conversely, any periodic time-varying waveform, however complex, can be approximated by the summation of a finite set of pure sinusoids of differing amplitudes.

Computationally, the Fourier transform decomposes the variance of a waveform into its frequency components, and “transforms” the time domain representation of the variance into a frequency domain representation or spectral density function (see Figure 8.10B for illustration). Importantly, the time and frequency domain representations are simply two complementary ways to characterize the same set of variances, with the time domain representation aggregating across frequencies and the frequency domain representation aggregating across time. The former preserves the temporal integrity of the signal at the expense of frequency resolution and the latter preserves the frequency composition of the signal at the expense of temporal resolution. If the spectral density function is integrated (summed) across frequencies, the result will equal the simple statistical variance of the signal in the time domain.

Origin and significance of heart period rhythms. As illustrated in Figure 8.10B, there are several peaks in the spec-

tral density function for heart rate variability, corresponding to one or more physiological processes (Berntson et al., 1997; Eckberg, 2000). Several general frequency bands of heart period variability have been defined in the literature. The high-frequency band (0.15 [or 0.12] to 0.4 Hz in the adult) generally corresponds to respiratory sinus arrhythmia (RSA), which reflects the respiratory gating of autonomic control by afferent input from lung stretch receptors (Berntson et al., 1993a; Eckberg, 2002). Although respiratory rhythms are apparent in the activities of both the sympathetic and parasympathetic cardiac nerves, the low-pass filter properties of the sympathetic sinoatrial synapses effectively smooth out these rhythmical fluctuations into a steady state influence on heart rate. For this reason, respiratory sinus arrhythmia is generally considered to index vagal cardiac control, although there are several caveats in its application (see Berntson et al., 1993a; Berntson et al., 1994, 1997; Cacioppo et al., 1994; Grossman, Karemaker, & Wieling, 1991; Grossman & Kollai, 1993).

Although the high-frequency band may be operationally set at 0.15 (or 0.12) to 0.4 Hz, the respiratory rate in some cases can extend below this band with slow breathing or above this band in infants or with rapid breathing in adults. For children, a commonly used respiratory band is 0.24–1.04 Hz (Quigley & Stifter, 2006). Measures of respiratory sinus arrhythmia will be biased if the breathing rate falls wholly or partially outside the selected band as the power in this frequency will not be captured within the high-frequency variability band. Consequently, it may be desirable to raise the upper band limit to 1.0 Hz with exercise, and to use a higher overall frequency band with infants (e.g., 0.20–1.20 Hz, see Bar-Haim, Marshall, & Fox, 2000). Even when respiration falls within the standard high-frequency band, the transfer function from vagal respiratory rhythms to cardiac respiratory rhythms is not flat, but decreases with increasing frequency. For these reasons it is optimal to obtain respiratory measures to insure that respiratory rates are within the high-frequency band and remain constant from condition to condition (e.g., baseline to task). If respiratory rates do change, this should be recognized and accounted for. The effects of a change in respiratory rate could be statistically controlled by adding respiratory rate as a covariate or by adjusting the estimate of vagal control by the known effects of respiratory frequency (see Berntson et al., 1997).

Respiratory depth can also alter RSA (e.g., see Grossman, Wilhelm, & Spoerle, 2004; Grossman, Karemaker, & Wieling, 1991; Grossman, & Kollai, 1993), although amplitude effects at moderate levels of variation are generally not as large as effects of rate. A paced breathing procedure could be implemented to experimentally control respiration (Grossman, Karemaker, & Wieling, 1991), although paced breathing itself may be stressful (Wilhelm, Grossman, & Coyle, 2004) and may interact with other experimental manipulations. Alternatively, if changes are observed in respiratory depth, this parameter could be entered as a covariate in statistical analyses. A more

comprehensive but more complex regression approach entails a transfer function analysis with paced breathing to define adjustment coefficients for respiratory parameters (Wilhelm, Grossman, & Coyle, 2004).

Lower frequency bands of heart period variability have also been defined in the literature. These include the low-frequency band (LF; sometimes termed the mid-frequency band) with a variable bandwidth (e.g., 0.05–0.15 or 0.8 to 0.12) centered around 0.1 Hz (sometimes referred to as the Mayer wave). Even lower frequency bands have been studied in the physiological literature (very-low .003–.05 Hz; ultra low < .003), but have not received much attention in psychophysiology. Variability within any of these bands represents a mixture of sympathetic and parasympathetic rhythms, as sympathetic rhythms can translate into cardiac rhythms at these frequencies. These lower frequency rhythms have received less attention in the psychophysiological literature, although the mid-frequency band has been of some interest and utility in the quantification of mental workload and baroreceptor function (see Boucsein & Backs, 2000; Van Roon, Mulder, Althaus, & Mulder, 2004).

An additional application of the 0.1 Hz rhythm has been in the development of an index of *autonomic balance*, which is said to characterize the relative functional point along a sympathetic-parasympathetic activation continuum (see Malliani, 1999). The index is the ratio of high-frequency variability to low-frequency variability. The general rationale is that variability in the lower band is driven by both branches of the autonomic nervous system so increases in sympathetic control will increase low-frequency variability but not high-frequency variability, and thus reduce the index value. This approach has been severely criticized on physiological grounds (Eckberg, 1997, 1998). One of the problems with this approach is that the low-frequency band is also determined by parasympathetic activity which can confound this index. In addition, the sympathovagal index assumes a reciprocally regulated autonomic continuum, wherein increases in one branch are coupled to decreases in the other. Although this may hold in some cases, such as with orthostatic stress, it does not in others, especially in psychological contexts (Berntson & Cacioppo, 1999).

Quantification. A common approach to quantification of heart period variability is by a Fast Fourier Transform (FFT), which represents a more computationally efficient approach than the full Fourier Transform. This efficiency comes with the restriction that the number of data points must be some power of 2 (e.g., 64, 128, 256, 512), but this does not generally pose a serious limitation. A more complete discussion of analytical approaches can be found in Berntson et al. (1997).

The FFT, as with other spectral methods, quantifies *periodic* components of variability and assumes at least weak stationarity of the signal (constant mean and variance over time). *Aperiodic* components or nonstationar-

ities can compromise analysis and interpretation of the data. Although moderate deviations from stationarity may not have large effects on spectral estimates, it is best to avoid these biases. One approach to enhance stationarity is to use short analytical epochs, as nonstationarities tend to increase over time. On the other hand, analytical epochs must be long enough to sample a sufficient number of respiratory cycles (a minimum of 10 cycles is recommended in the Society for Psychophysiological Research Committee Report, Berntson et al., 1997), although these could be aggregated over multiple shorter periods (e.g., 30–60 sec). A simple test is available to confirm stationarity of the data (Weber, Molenaar, & van der Molen, 1992).

Acquisition commonly entails digitization of the ECG signal at a minimum of 500–1000 Hz. Although some information may be derivable at lower frequencies, there is a progressive loss of information as digitization rate is further reduced (Riniolo & Porges, 1997). R waves must then be accurately detected, artifacts removed, and a heart period series derived. Because heart periods vary in duration, this beat series must be converted to a time series by an interpolation algorithm. The sample interval for the time series should provide 2–4 samples/beat (250 msec works with most subjects, although shorter sample times may be desirable with infants). The time series is then detrended with a first order polynomial to remove the mean and any linear trend in the data. The initial and terminal data points should be tapered by a standard hanning window, cosign window or similar function to eliminate starting and ending offsets which can introduce artifacts. The residual series is then submitted to a FFT, yielding an estimate of power (msec^2/Hz) distribution across frequencies (see Figure 8.10B) and the power within the frequency bands of interest can be summed (integrated) to yield an estimate of total power (msec^2) within those bands. Generally, these total power estimates are natural log transformed to normalize distributions. The power in the high-frequency band represents the quantitative estimate of vagal control of the heart.

Many other approaches to quantification have also been employed. A common alternative approach is autoregressive (AR) modeling, which is another spectral method. In contrast to the FFT, which is considered a descriptive statistic as it includes all data in the analysis, the AR approach views the signal as a combination of deterministic and stochastic components and attempts to model the salient deterministic components while eliminating “noise.” In practice, with the applications of filters and other refinements in FFT (see below) these approaches generally give highly similar results. A time domain approach that approximates spectral methods has been developed by Porges and colleagues (see Porges & Bohrer, 1990). After derivation of the time series as outlined above, this approach entails the application of a polynomial filter algorithm to remove frequencies outside the band of interest, and the statistical variance of the residuals is then calculated as an index of RSA. Another time

domain approach is the peak-valley method wherein an estimate of RSA is derived from the difference between the longest beats associated with expiration and the shortest beats associated with inspiration (Grossman, van Beek, & Wientjes, 1990). Both of these time domain methods yield values similar to spectral approaches, with each having its advantages and disadvantages. A myriad of additional methods are also available including cross spectral analysis, transfer function analysis, time frequency distributions (smoothed pseudo Wigner-Ville distribution and complex demodulation), and nonlinear dynamical methods to name a few. Space precludes a meaningful coverage of these approaches here, but the interested reader is referred to Monti, Medigue, & Mangin (2002), Pumpila, Howorka, Groves, Chester, & Nolan (2002), and Wilhelm, Grossman, & Roth (1999).

Summary. Patterns of heart rate variability offer important insights into cardiovascular dynamics and their central and peripheral autonomic control. High-frequency heart rate variability is largely attributable to variations in parasympathetic control associated with respiration and is widely used as an index of vagal control of the heart. There are several important caveats in these applications, however. There are many factors that can influence basal levels of RSA, including posture, age, activity, and aerobic fitness to name a few. Consequently, the differences in the magnitude of RSA across subjects or groups may not be a valid metric for differences in vagal control of the heart unless these variables are taken into account. Although within-subjects changes in RSA may be more valid as a marker of changes in vagal control, factors such as posture and activity still need to be considered. Moreover, RSA can be influenced by respiratory rate and to a somewhat lesser extent, respiratory depth, independent of the basal level of vagal control. This has raised a question as to whether the magnitude of RSA is a valid predictor of vagal "tone," or the average basal level of parasympathetic control. To the extent that vagal inhibition is not complete with inspiration, there may be some dissociation between respiratory vagal fluctuations and the basal level of vagal control. Minimally, respiratory parameters should be measured, and should be taken into account if they differ across critical experimental contrasts. The psychological significance of low-frequency heart rate variability is less clear, although as discussed above it may have some utility in assessment of cognitive workload. Although widely used, especially for estimating reflex regulation, the ratio of LF to HF variability as an index of autonomic balance may not have much meaning in psychological contexts unless the predominant mode of response can be shown to be reciprocal.

Blood pressure

Blood pressure can be measured in a number of ways, invasively, using intraarterial pressure transducers, or noninvasively, using auscultatory or oscillometric methods, arte-

rial tonometry, or the volume-clamp method (also called the Peñáz method). The latter two methods are especially useful when the research question calls for beat-to-beat blood pressure. The beat-to-beat methods are also more sensitive to movement, making them more difficult to record with fidelity. Because most psychophysiological laboratories are not equipped to perform invasive measures and provide the participant safeguards needed, we will focus here on the non-invasive measures. It is important to determine for any blood pressure monitoring device that it has met either or both of the Association for the Advancement of Medical Instrumentation (AAMI) or the British Hypertension Society (BHS) standards for accuracy and reproducibility (van Montfrans, 2001).

Auscultatory blood pressure measurement. The auscultatory method takes its name from the fact that auscultation or listening to bodily sounds is the basis of the technique. For arm blood pressure, a cuff is placed on the upper arm, with a stethoscope placed over the brachial artery (if done manually) or a microphone embedded in the cuff (if done with an automated device). When the cuff is inflated to a pressure sufficient to cut off all arterial blood flow (i.e., suprasystolic), no sound is heard. As the pressure in the cuff is slowly bled off, the so-called Korotkoff or K sounds appear. The cuff pressure at which the first sound is heard is taken as the systolic pressure and referred to as the start of phase I. As the pressure in the cuff decreases further, the sounds take on a murmuring quality (phase II) and then become clearer and louder (phase III). Following this, the Korotkoff sounds become muffled (phase IV) and eventually disappear altogether (phase V). In medical practice and typically in the psychophysiology laboratory, the pressure at phase V is considered the diastolic blood pressure, although sometimes Phase IV is used instead. Automated devices are particularly useful in the psychophysiological laboratory so that an experimenter need not be present in the room when a reading is taken, and also because this removes aspects of human error in reading the blood pressure (Shapiro et al., 1996).

Oscillometric blood pressure measurement. The oscillometric method utilizes oscillations in pressure in the cuff to determine systolic, diastolic and mean arterial pressure (Borow & Newberger, 1982; van Montfrans, 2001). With this method, following inflation of the cuff to a pressure above the systolic pressure where oscillations can be measured in the cuff, the cuff is slowly deflated. The systolic pressure is taken as the pressure when the oscillations in the cuff first begin to get larger, the mean arterial pressure is taken as the point when the cuff oscillations are maximal in size, and the diastolic pressure is taken as the point when the cuff pressure oscillations no longer get smaller in amplitude. As van Montfrans (2001) points out, there are issues still to be resolved with this technique, most notably, that specific algorithms used to determine systolic, diastolic, and mean arterial pressure are unlikely to

be equally accurate across all individuals thus leading to systematic errors. Especially problematic is the effect of increased arterial stiffness on oscillometric measurements which often is seen in elderly or diabetic subjects. Finally, the algorithms for each oscillometric device are different and proprietary, making it impossible for the researcher to document the algorithms used. Therefore, it is important to report the make and model of the oscillometric device used for any study.

Arterial tonometry. Blood pressure is measured using arterial tonometry (also called arterial applanation tonometry) by placing piezoelectric sensors over an artery that overlies bone (e.g., Colin 7000). Modest pressure is applied to the artery, partially flattening the artery. Multiple sensors are arrayed over the flattened artery and the device then records from the sensor reading the largest arterial pulse wave amplitude. This measure provides a pulse waveform that is calibrated against an oscillometrically derived blood pressure reading from the brachial artery. A common site for tonometric measurements is the radial artery at the wrist. Care must be taken that the sensor is placed correctly over the artery and the technique is sensitive to movement limiting the potential uses of the technique (Kemmons, Ueda, Otsuka, Yamamura, Winter, & Eckerle, 1991; Parati et al., 2003).

Volume-clamp or Peñaz method. The volume-clamp method typically uses a cuff on the finger to clamp the vascular volume of the finger at a specific level which is maintained from beat to beat (Parati, et al., 2003; Wesseling, 1990). A photoplethysmographic device (see section on plethysmography below) measures changes in blood volume beneath the sensor, and then using a pneumatic servo-control system, changes are made in the pressure within the finger cuff so that the artery returns to its previous volume. The amount of pressure change in the finger cuff needed to reestablish the volume in the artery is a function of the arterial pressure underlying the cuff. The device using this method that originally saw the widest use was the Finapres, which was withdrawn from the market, although it is still in use in many labs around the world. Newer devices using this technique are currently limited to the Portapres (an ambulatory monitor) and the Finometer (a stationary monitor; Parati et al., 2003).

General measurement issues for blood pressure. We outline here some general aspects of blood pressure measurement. First, because of the regional variations in blood flow, vessel diameter and blood pressure, it is important when measuring blood pressure to report the location from which pressure is measured (e.g., at the brachial or femoral artery). It's also important for the measurement site to be at the same vertical height as the heart to eliminate effects of hydrostatic pressure (i.e., the pressure exerted by the fluid in the circulatory system) on the blood pressure measurement. Another important feature is the size and placement

of the cuff. To determine the appropriate cuff size, the circumference of the upper arm is determined and the cuff width should be at least 40% of arm circumference, and the cuff length at least 80% of the circumference (Bailey & Bauer, 1993). In practice, this is usually accomplished by using standard, small, and large adult cuffs or a pediatric cuff (O'Brien, 1996). Partly because of the limitations of the instrumentation, it is uncommon for cuff occlusions to be made more frequently than once per minute. In addition, more frequent sampling than this may result in unpleasant side effects, and annoyance of the participant (Shapiro et al., 1996). Because of the variability in blood pressure that was noted previously, it is recommended that multiple blood pressure readings taken from a recording epoch be averaged to provide a more stable estimate of the blood pressure for that epoch. For specific recommendations, the reader is referred to Shapiro et al., 1996 and Llabre, Ironson, Spitzer, Gellman, Weidler, & Schneiderman, 1988.

Various participant or environmental factors can make it difficult to accurately interpret blood pressure results. These include recent eating, drinking, smoking, medications or exercise, and not controlling for phase of the menstrual cycle in women, or time of day. Blood pressure is affected by all of these factors and thus, when possible, they should be controlled within a study (Shapiro et al., 1996). Emotional factors also affect blood pressure. A well known example of this is so-called white-coat hypertension, which occurs when readings in a clinical or other evocative setting such as a lab are higher than those in a less evocative setting such as the individual's home.

Other vascular measures

Plethysmography, including venous occlusion plethysmography. Plethysmography is a technique whereby one determines the volume of a structure, either the entire structure (such as in whole body plethysmography) or part of a structure (such as determining blood volume in a body segment like the finger). Volume can be determined using a photoelectric sensor (photoplethysmography), changes in impedance (see section on impedance cardiography for a specific example of this method), or changes in circumference measured with a strain gauge.

The most common photoplethysmographic technique employs a photocell placed over an area of tissue perfused with blood. There are two variations of this method; energy emitted from an infrared source can be measured as it passes through the tissue segment (transillumined) or as it bounces off the tissue (back-scattered). Because electromagnetic radiation in this frequency is scattered by blood, the output of a photodetector is related to the amount of blood within the segment (Jennings, Tahmouh, & Redmond, 1980). In either case, the infrared energy is measured by a photoelectric transducer and recorded as a change in voltage or current. Currently, most photoplethysmographic devices utilize a light-emitting diode (LED) as an emitter and a phototransistor as a detector,

which do not alter the underlying skin and blood vessels. If the light is transmitted through the tissue to a photodetector on the other side, only a limited number of sites are convenient (e.g., earlobe, finger), and these are not necessarily sensitive to psychological changes. However, with the back-scattered photoplethysmographic technique, the light source and the photodetector are both located on the same side of the tissue and therefore can be placed almost anywhere on the body. The back-scattered photoplethysmograph is more sensitive to vascular fluctuations occurring close to the skin surface, whereas the transilluminated photoplethysmograph is sensitive to vascular changes in both the skin and deeper tissue. Blood flow also can be measured using a transcutaneous Doppler device which detects acoustic frequency shifts caused by moving red blood cells in underlying tissue (Rose, 2000). Doppler devices share many of the same issues and limitations as photoplethysmographic devices.

Using a strain gauge, one can also measure changes in blood volume of a body segment. The strain gauge is placed around the finger, or other body segment, and changes in resistance or voltage of the strain gauge provide an indirect measurement of blood volume changes. Venous occlusion plethysmography is a special example of the use of strain gauge plethysmography to measure blood volume in limb segments (Wilkinson & Webb, 2001). This technique requires two cuffs, one placed distal to the limb segment of interest, and one placed proximal to the limb segment. The distal cuff is inflated to a pressure above the systolic pressure to prevent blood flow into and out of the distal limb segment. The proximal cuff is inflated to a pressure sufficient to eliminate venous flow from the limb segment, but not preventing arterial flow into the segment. A strain gauge is placed around the limb segment, and the change in limb circumference per unit of time is used to infer the rate of arterial blood flow into the segment. The advantage of this method is that arterial blood flow into an isolated limb segment can be measured independent of other possible sources of blood flow (e.g., venous flow). An obvious limitation of the venous occlusion technique is that measurements cannot be taken continuously, and even at very short intervals, because numbness or pain in the limb can result. Measurements also can be altered by movement of the limb.

Jennings, Tahmoush, and Redmond (1980) reviewed many of the factors that influence vasomotor changes and discussed problems of interpretation using from the indirect measures described here. For example, changes in room temperature from one day to the next during a study alter the measures for reasons unrelated to the experimental situation. Another problem is the wide variation in skin and vessel anatomy (e.g., location of vessels) which make absolute comparisons between subjects impossible. Even within the same subject, difficulty in precise placement of the transducer makes comparisons only relative, especially if the transducer is removed and replaced. Because of differential distributions of muscles and blood vessels

in different body areas, it is difficult to compare results between studies when different recording sites are used. Finally, recall that blood flow is a complex function of pressure in the vasculature, the radius of the blood vessels, and the viscosity of the blood, and flow changes may occur via arterial and/or venous flow changes either into or out of the segment of interest. Thus, one must be careful when making interpretations from indirectly measured blood flow changes.

Because of the relative nature of the vasomotor measures described here, experimenters typically examine changes for each participant from a baseline period and compare this to the experimental or task period. The change between baseline and task is generally expressed as a percentage. The magnitude of an individual pulse can be determined by measuring the difference between the lowest point and the peak or an integrating coupler can be used to perform a similar function.

Other non-invasive vascular measures. Several other non-invasive measures of vascular function have been used particularly to assess cardiovascular disease risk. Considered here are only a few of those that do not require medical facilities for their application. Measures such as brachial artery ultrasonography have been used to assess flow-mediated dilation (Corretti et al., 2002). In this technique, suprasystolic cuff pressures are used to occlude all blood flow in the arm for several minutes. Upon release of the cuff pressure, blood flow increases to the occluded limb over and above flow before occlusion (a phenomenon called reactive hyperemia). A small flow-mediated dilation response during reactive hyperemia has been shown to be related to coronary artery disease (Kuvin et al., 2001) and cardiovascular disease risk (Kuvin et al., 2003), the latter case being documented with both brachial artery ultrasonography and peripheral arterial tonometry over a finger. The peripheral arterial tonometry technique is very similar to arterial applanation tonometry used to measure blood pressure, although with peripheral arterial tonometry, the goal is to use the arterial waveform to derive the pulse wave amplitude. This technique has been used to measure other features of vascular physiology including pulse wave velocity and a measure of arterial stiffness called the augmentation index (e.g., Davies & Struthers, 2003; Vuurmans, Boer, & Koomans, 2003).

Pulse transit time, used in calculating pulse wave velocity, was previously used to a considerable extent in psychophysiological assessments, predominantly because it was thought to relate to blood pressure. However, pulse transit time is a function of both cardiac changes (in pre-ejection period) and the stiffness of the peripheral arterial system (Steptoe, Godaert, Ross, & Schreurs, 1983). This means that psychological antecedents which alter pre-ejection period, vascular tone or both can contribute to changes in pulse transit time, and yet the physiological source(s) of these changes will be indeterminate (Shapiro

et al., 1996). One approach that may have promise in applying pulse transit time to the measurement of blood pressure, or blood pressure change, is the concurrent monitoring of (e.g., by impedance cardiography), and adjustment for, the cardiac determinants of PTT. A more recent use of pulse transit time has been to detect brief changes in respiratory effort and "microarousals" during sleep, although the physiological basis for these pulse transit time changes remains unclear (Smith, Argod, Pépin, & Lévy, 1999).

Baroreflex measures

The baroreceptor-heart period reflex is important in the short-term control of blood pressure. Estimates of baroreflex function have been proposed using relatively invasive procedures such as pharmacologically induced changes in blood pressure or neck suction to directly activate baroreceptors (for review see Parati, di Rienzo, & Mancia, 2000). However, the focus here will be on non-invasive estimates of baroreflex function derived from spontaneous changes in blood pressure and heart period. Baroreflex sensitivity or gain can be derived using either time domain (e.g., the spontaneous sequence method; Bertinieri, di Rienzo, Cavallazzi, Ferrari, Pedotti, & Mancia, 1985) or frequency domain methods (e.g., spectral methods; DeBoer, Karemaker, & Strackee, 1987). Baroreflex sensitivity estimated from these methods is defined either as the slope of the regression of heart period on systolic blood pressure (ms/mmHg; sequence method), or the gain of the transfer function relating variations in heart period and systolic blood pressure over the frequency range of 0.04 and 0.35 Hz (spectral methods). These estimates of baroreflex sensitivity do not represent identical estimates of sensitivity (Persson et al., 2001). For one, the sequence method utilizes shorter data epochs, namely sequences of 3–6 consecutive R-R intervals where systolic blood pressure increased by more than 1 mmHg over sequential beats and heart period progressively shortened, or where systolic pressure decreased and heart period progressively lengthened. Most sequences that meet these criteria are sequences of 3 interbeat intervals, with progressively fewer sequences observed as the number of interbeat intervals in the sequence increases. Moreover, the 3 interval sequences tend to provide higher estimates of baroreflex sensitivity than the longer sequences (Reyes del Paso, Hernández, & González, 2004), although in most studies, sequences of all lengths are averaged to provide a single baroreflex sensitivity estimate. This finding of differential sensitivity with differing sequence length may be related to the fact that vagal effects on heart period occur much more quickly in response to a pressure change than do sympathetic influences (DeBoer et al., 1987). The spectral methods (using Fast Fourier Transform or autoregressive modeling techniques) are also subject to specific biases. With spectral methods, one typically reports the gain of the transfer function or the square root of the ratio of the spectral powers for the heart period and systolic blood pressure signals,

called the α coefficient, over the entire frequency range noted above. However, it has been shown that the highest coherence between heart period and blood pressure occurs in two specific frequency regions, one around 0.1 Hz and the other in the respiratory frequency range (approx. 0.15–0.35 Hz), and there is greater baroreflex influence in the respiratory frequency range than in the lower frequency range (Parati et al., 2000). Also, spectral methods typically do not take into account the phase relationship between heart period and systolic blood pressure. Thus, the estimate is less than optimal because part of the measure is not due to the baroreflex (Parati et al., 2000). Finally, the spectral methods require the use of longer data epochs for calculation than does the sequence method which can be problematic for tracking short-term changes in baroreflex sensitivity. Short-term changes will lead to nonstationarity in the signals, thereby violating a primary assumption of spectral methods. Thus, these two estimates of baroreflex sensitivity derived from spontaneous sequences have different biases, neither being a perfect reflection of the true baroreflex sensitivity, but each of which provides a useful metric under certain circumstances (Persson et al., 2001).

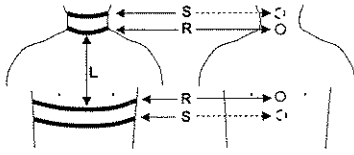
Several studies have demonstrated that psychological events can alter baroreflex sensitivity with mentally stressful events decreasing the gain of the baroreflex (e.g., Reyes del Paso, González, & Hernández, 2004; Steptoe & Sawada, 1989). In addition, respiratory biofeedback using slow paced breathing at approximately 0.1 Hz produced both within session and across session changes in baroreflex gain thereby revealing the influence of respiration on baroreflex sensitivity (Lehrer, et al., 2003).

A relatively new measure has been derived using the spontaneous sequence method called the baroreceptor effectiveness index (BEI; Di Rienzo, Parati, Castiglioni, Tordi, Mancia, & Pedotti, 2001). The BEI provides an estimate of how frequently (over a given period of time), the baroreflex is effective in altering the heart period. The data available to date on this measure show that the BEI is reflective of baroreflex function (the BEI dropped from 0.33 in intact cats to 0.04 after sino-aortic denervation), that the BEI is lower at night than during the day in humans (Di Rienzo et al., 2001), and that a visual attention task produced an increase in the BEI, whereas a mental arithmetic task did not alter BEI (Reyes del Paso, González, & Hernández, 2004). It seems clear that the BEI and baroreceptor sensitivity reflect different aspects of baroreflex function, but the usefulness of the BEI as a physiological indicator is not yet clear.

Impedance cardiography

Impedance cardiography is an important noninvasive method for obtaining more comprehensive information concerning cardiac function than can be derived from heart rate or heart rate variability alone. Impedance cardiography entails the application of a high-frequency,

A. Impedance Cardiography: Electrodes



B. Impedance Cardiography: Signals

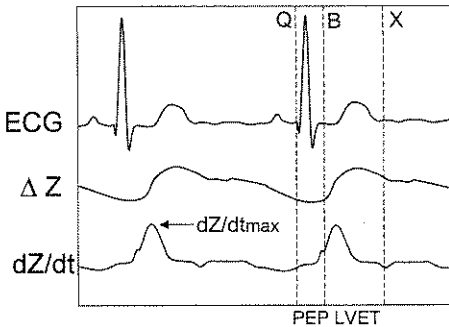


Figure 8.11. Impedance cardiography. (panel A) Typical electrode configurations. Left: standard mylar band electrodes, comprised of outer source (S) electrodes and inner recording (R) electrodes. Right: Qu et al. (1986) spot electrode configuration, consisting of two source electrodes on the dorsum (C4 and T9) and two recording electrodes on the ventrum. L = distance between the inner boundaries of the recording electrodes (for calculation of stroke volume and cardiac output). (panel B) Impedance signals, including the electrocardiogram (ECG) the basal impedance (Z) and the 1st derivative of Z. Q corresponds to the onset (or peak, see text) or the Q wave, B corresponds to the opening of the aortic valve (often indicated by a notch in the dZ/dt signal) and X (onset or peak, see text) corresponds to the closure of the aortic valve. PEP- pre-ejection period; LVET – left ventricular ejection time.

constant-current flow through a set of outer thoracic electrodes and recording of the associated voltage drop across another, inner set of electrodes. Because the current flow is held constant, based on Ohm's Law, the recorded voltage will vary inversely with the resistivity of the thoracic current path. Because the current is alternating, the resistivity to current flow is a function of both the DC resistance and the reactance of the circuit, collectively referred to as impedance. One of Kirchoff's Laws stipulates that the distribution of current through parallel resistive paths is inversely proportional to the resistances. The body components with the lowest resistivity are blood and plasma, so the measured thoracic impedance is highly sensitive to changes in the cardiac and aortic distribution and flow of blood during the cardiac cycle (Hoetink, Faes, Visser, & Heethaar, 2004). General methodological guidelines for impedance cardiography are available from a committee report of the Society for Psychophysiological Research (Sherwood et al., 1990).

Instrumentation. In measuring cardiac impedance, four electrodes are typically employed (see Figure 8.11). The outer (source) electrodes provide the constant current sig-

nal path to the subject (typically considered leads 1 and 4). Supply current parameters are not standardized across devices. Current levels generally range from 4 mA down to 0.1 mA, typically at 100 kHz, although lower frequencies have also been used. The inner two electrodes are used to measure voltage, which reflects the changes in impedance due to volumetric alterations in blood distribution and blood flow (recording electrodes, usually leads 2 and 3). The Minnesota Model 403B Impedance Cardiography device (Instrumentation for Medicine, Minneapolis) was one of the earliest and most widely used instrument, although it has now been replaced by the HIC 2000, & 3000 (Bio-Impedance Technology, Inc., Chapel Hill). More recently, impedance measures have been incorporated into ambulatory studies (Hawkey, Burleson, Berntson, & Cacioppo, 2003; Sherwood, McFetridge, & Hutcherson, 1998; Willemssen, De Geus, Klaver, Van Doornen, & Carroll, 1996). Several ambulatory units are now commercially available, including the VU-AMD (Vrije University, Vrije Netherlands), the AIM-8 (Bio-Impedance Technology, Chapel Hill, NC) and the recently introduced MW1000A (Mindware Technologies, Gahanna, OH) that includes a wireless network link.

There are two common electrode configurations used in recording thoracic impedance; band electrodes and spot electrodes. The band electrode consists of a thin, aluminum conductor secured to a Mylar adhesive tape that provides a means of attaching it to the subject. Spot electrodes are small, conductive disks (Ag/AgCl) with adhesive collars (same electrodes as typically used for measuring ECG). The conductive disk is generally covered with an electrode gel using a sponge-like material or imbedded in a conductive medium. Mylar band electrodes represent the standard and have been the most thoroughly validated. Spot electrodes, however, can also yield valid information and are considerably easier to use. The Qu et al. configuration entails two spot electrodes on the back and two on the front as illustrated in Figure 8.11 (Qu, Zhang, Webster, & Tompkins, 1986; see also Sherwood, Royal, Hutcherson, & Turner, 1992). Spot electrodes give generally comparable results to Mylar bands for systolic time intervals, but are less accurate for volumetric measures (stroke volume and cardiac output), especially for between-subject comparisons (Sherwood, Royal, Hutcherson, & Turner, 1992). A variety of other spot electrode placements have also been employed, which can give similar group values, but may yield variable results across individual subjects (Hoetink et al., 2002; Kauppinen, Hyttinen, & Malmivuo, 1998). A "whole-body" impedance approach has also been implemented with limb electrodes, which shows promising results, although it may be less sensitive to some cardiovascular parameters because a large proportion of the basal impedance arises from the limbs (Kauppinen, Koobi, Hyttinen, & Malmivuo, 2000).

The ECG is also required for impedance cardiography, as the Q wave serves as a landmark for the beginning of ventricular electrical activation and the R wave is employed as

the fiducial point of alignment for ensemble averaging of signals. Some devices extract the ECG from the impedance recording electrodes, although that does not always provide a very clear signal. Consequently, additional ECG electrodes are also often employed.

The primary dependent variables in impedance cardiography are ECG, Z0 (basal impedance) and dZ/dt (first derivative of Z0). Z0 is a measure of thoracic impedance, in ohms, and reflects the variation in blood volume and distribution over the cardiac cycle. The variations in Z0 over the cardiac cycle are small compared to the overall basal impedance (generally in the range of 10–40 ohms). Consequently, the dZ/dt is either derived electronically or calculated off-line to remove the baseline and to enhance the relevant components of the small variations in the signal. The recorded signal from which these parameters are extracted is a composite of the carrier frequency (100 kHz sine wave), basal impedance (Z0), and ECG. The circuitry in instruments varies from manufacturer to manufacturer, but generally the carrier frequency is demodulated and the Z0 and ECG are routed through low pass filters to remove any remaining high-frequency signals (> 50 Hz). To achieve optimal temporal sensitivity, these signals should be digitized at 1 kHz.

Scoring. Two sets of measures are generally derived from the impedance signal: (a) systolic time intervals such the pre-ejection period (PEP) and the left ventricular ejection time (LVET); and (b) volumetric measures such as stroke volume (SV) and cardiac output (CO). For the measurement of systolic time intervals, two landmarks are determined from dZ/dt, the B and X points. The B point is characterized by a notch or an inflection point near the onset of the rapid upstroke of the dZ/dt waveform, which serves as an index of the point in time when intraventricular pressure becomes higher than aortic pressure, the aortic valve opens, and ventricular ejection commences. The B point can be challenging to localize, especially when a distinct inflection point or notch is not apparent. It corresponds roughly with the peak of the first heart sound of the phonocardiogram, but this acoustic signal is complex and temporally distributed so that it does not serve as a viable marker of ventricular ejection time. Various methods have been used to estimate the B point from the impedance signal in the absence of a clear notch, including identification of the maximum slope or maximum slope change (2nd derivative), or the zero point crossing of the dZ/dt function (see Sherwood et al., 1990). An additional method that shows promise and may be superior to prior approaches is the use of a simple percentage or proportion (about 55%) of the time from the R peak to the peak of the dZ/dt wave (Lozano et al., in preparation).

The X wave peak is the lowest point on the dZ/dt waveform after the peak, and is taken as an index of the time when the aortic valve closes, marking the end of ventricular ejection. The peak (minimum) of the X wave is generally readily identified and has been recommended as the

X point (Sherwood et al., 1990). It has been suggested that more accurate volumetric estimates, however, may be obtained by using the X onset point which may more closely correspond to aortic valve closure (for discussion see Brownley, Hurwitz, & Schneiderman, 2000).

Four systolic time interval measures can be derived from these points and the ECG. LVET is the time from the B point to the X point. PEP is generally taken as the time between the Q wave onset and the B point inflection on the dZ/dt waveform, although the onset of the R wave (Q wave peak) has been recommended as a more consistent and identifiable fiducial point (this has been referred to as PEPr; Bertnison, Lozano, Chen, & Cacioppo, 2004). PEP and PEPr are measures of contractility that are used to index of sympathetic cardiac control. Additional indices of myocardial contractility include the Heather Index (HI) which is the ratio of the dZ/dt_{max} (ejection velocity) to the Q-dZ/dt peak interval, and the Acceleration Index (ACI) which is the dZ/dt_{max} divided by the B-dZ/dt peak interval. Additional inotropic and autonomic indices have also been derived from impedance signals (Thayer & Uijtdehaage, 2001).

The ejection velocity derived from the peak value of the dZ/dt waveform is used to calculate stroke volume (SV, in milliliters) according to the Kubicek equation (Kubicek et al., 1966):

$$SV = \rho_b (L/Z_0)^2 \cdot LVET \cdot dZ/dt_{max}$$

where ρ_b is the blood resistivity (often assigned a constant value of 135 ohms/cm, although more accurate estimates may be obtainable by direct measures of this parameter); L is the distance between the recording electrodes; Z0 is the mean thoracic impedance; LVET is as defined above; dZ/dt_{max} is the peak of the dZ/dt function (because it actually reflects a reduced impedance it is sometimes designated dZ/dt_{min}).

From stroke volume and heart rate (HR), cardiac output can be calculated as:

$$CO = SV \cdot HR$$

There have been a variety of alternative formulas offered for the calculation of impedance derived cardiac output estimates, including the Sramek equation, Bernstein's modification of this method, and a more recent proprietary modification of this method (Bernstein, 1986; see also Van De Water et al., 2003). Although some findings suggest that the latter methods may be somewhat superior to the Kubicek formula, the Kubicek equation remains the standard and is most widely used in psychophysiology.

Scoring of impedance cardiography can be accomplished on a beat by beat basis, although the method of ensemble averaging over longer epochs is more efficient and yields highly comparable results (Kelsey et al., 1998). This approach derives an average of both the ECG and dZ/dt waveforms. By ensemble averaging of the signals, random noise and movement artifact that is not synchronized with the R wave is effectively removed, which

provides for a more stable representation of cardiac activity. The ensemble method first determines the peak of the R wave of the ECG in the time series. From this point, a composite signal for both ECG and dZ/dt is calculated by averaging the signal from some fixed time before the R wave (typically 100ms) to 500–600 ms after the R peak. From these ensembled waveforms of ECG and dZ/dt , the landmarks for impedance scoring are identified as outlined above for individual cardiac cycles (see Figure 8.11). The duration of the epochs to be ensemble averaged generally ranges from 30 sec to 5 min, based in part on the experimental design and the questions to be addressed. Epochs should be short enough that cardiodynamics are relatively stable, as an average of changing values can be distorted. On the other hand, longer epochs are more efficient for scoring purposes. One minute epochs are satisfactory for most studies, and the results can be further aggregated over longer experimental periods (e.g., as five 1-min epochs over a 5-min stressor). Even longer periods extending over hours may be useable for assessing long term changes in impedance parameters (Riese et al., 2003).

Validity. Under rigorous experimental conditions, impedance-derived estimates of cardiovascular function have been reported to be highly reliable, and to correlate well with parameters determined by echocardiography or invasive techniques such as the Fick (dye dilution) method (Sherwood et al., 1990; Moshkovitz, Kaluski, Milo, Vered, & Cotter, 2004).

Generally, measures of systolic time intervals show greater correlations across methods than do the volumetric measures of stroke volume and cardiac output (Sherwood et al., 1990). Even for volumetric measures, however, a meta-analysis of three decades of validation studies revealed correlations of greater than 0.80 between impedance derived measures and those derived from reference standards, such as echocardiography and the Fick method (Raaijmakers, Faes, Scholten, Goovaerts, & Heethaar, 1999).

The accuracy of impedance estimates is enhanced by rigorous experimental control and the maintenance of constant conditions. Cardiac anomalies, for instance, may impact impedance measures of cardiovascular function. In addition, impedance-derived estimates of stroke volume and cardiac output can be biased by variations in preload or afterload associated with differences in posture or activity, and even vocalization may alter these parameters (Tomaka, Blascovich, & Swart, 1994). These considerations are especially critical for ambulatory studies. Improved volumetric estimates can also be obtained when blood resistivity is estimated from the hematocrit, rather than applying a generic constant (Demeter, Parr, Toth, & Woods, 1993).

With careful attention to experimental design and control, impedance cardiography can offer a range of non-invasive metrics of cardiac performance and autonomic control in psychophysiological contexts.

Cardiac imaging

Psychophysiologicals with access to medical facilities are using cardiac imaging techniques that typically fall within the purview of the cardiologist or radiologist. We focus here on techniques that provide non-invasive images, which include echocardiography (either with or without Doppler ultrasound) and magnetic resonance imaging (cardiac MRI). Other common imaging modalities include radionuclide single photon emission computed tomography (SPECT), electron beam computed tomography (CT), and positron emission tomography (PET), which require introducing radioisotopes (Gibbons, & Araoz, 2004). Although these methods will not be considered here, their further development may allow highly specific measures of neurotransmitter release, uptake and receptor action at the level of the heart (Carrio, 2001).

Echocardiography is an ultrasound-based technique that is very commonly available in hospitals, noninvasive, relatively inexpensive, portable, and safe for the subject or patient. Echocardiography is particularly useful in providing quantitative, anatomic information about the heart (Goldin, Ratib, & Aberle, 2000). The disadvantages of echocardiography are that it requires an experienced sonographer to record the images, considerable training to read them, and typically requires breath holding so images are not obscured by lung movements. Originally, echocardiographic images were taken in 2D, and simplifying assumptions were required for calculating measures such as left ventricular volume. Failure of these assumptions introduced large measurement errors across individuals. Echocardiography can also be combined with Doppler ultrasound to determine blood flow. Doppler ultrasound techniques rely on the fact that sound waves bounced off a moving target change their frequency in direct proportion to the speed of the moving material. From this, blood flow velocities can be calculated and together with echocardiography one can obtain functional and anatomic information about heart function (Fyfe & Parks, 2002). A more recent innovation in echocardiography, known as real-time 3-D echocardiography (RT3DE) appears promising because it requires shorter scanning times (about 4 cardiac cycles) that permit recording during a single breath hold (Weyman, 2005). This technique provides left ventricular volume, mass and ejection fractions that compare well with MRI, which is quickly becoming the gold standard for anatomic measurements (Weyman, 2005). The primary downside of RT3DE is the time required for analyzing the data to make volume calculations, although automated analyses should improve this.

The other primary noninvasive cardiac imaging technique is cardiac MRI. Cardiac MRI relies on the same physical principles as any other MRI used to image the body. In simplified terms, a magnetic field applied around a body part aligns some of the protons (positive charges) on hydrogen ions that are a large component of body tissues and water. When a radio frequency pulse is applied to

the magnetic field, these protons change their alignment, and after the pulse, fall back into alignment with the magnetic field. A radio wave produced when the proton falls back into alignment is detected by the MR scanner. The number of protons depends upon the constituents of the tissue, and these different proton densities are translated into different shades of gray or color. Images are acquired in 2-D slices through the tissue and multiple slices are stacked to create a 3-D image. Like echocardiography, MRI is thought to be safe. MRI also has the advantage of not being disrupted by air in the lungs and has a broader field of view than echocardiography (Fyfe & Parks, 2002). MRI has been shown to produce even more accurate estimates of left ventricular mass and volume than echocardiography (Higgins, 2000; Myerson, Bellenger, & Pennell, 2002). Multi-slice images can be presented sequentially in a movie or cine sequence that can show functional aspects of the heart (Goldin et al., 2000). Disadvantages of MRI are that some individuals cannot tolerate the close quarters and noise of an MRI scanner, and that some individuals have internal metallic devices or implants that preclude being able to place them in a strong magnetic field. Together these techniques provide important tools for non-invasive measurements of cardiac anatomy and function.

PSYCHOPHYSIOLOGICAL CONTEXT

A Medline search on the terms "cardiovascular AND psychophysiology" yielded 15,222 hits. Obviously, space precludes a comprehensive overview of the wide range of contemporary lines of investigation in cardiovascular psychophysiology. A few general themes, however, are worth brief mention.

Psychophysiological patterns

Much of the early work in psychophysiology focused on a single response dimension, such as ECG, EMG, or SCR. When more than one measure was taken, it was often to examine replicability across measures or to draw contrasts between the measures and their sensitivity to psychological states. Although there was some early interest in patterns of activity across response domains, it was not until the mid 1900s that the Lacey's (Lacey & Lacey, 1962) solidified the construct of autonomic response patterning. Since then, there has been a growing recognition that the psychological and health significance of psychophysiological states may derive more from the profile of activity across response domains, rather than from discrete responses or from simple threshold or sensitivity differences of distinct response domains.

Autonomic branches, psychological states, and cardiac risk stratification. As discussed earlier, the sympathetic and parasympathetic branches are often reciprocally controlled by reflex systems, but higher level neural systems can exert more flexible patterns of control that include

reciprocal, coactivational, or independent changes of the autonomic branches. These patterns of response may have distinct functional origins and differing consequences, but may not be apparent by measures of an end organ response (such as a change in heart rate) or by measures of either branch alone. An increase in heart rate, for example, could arise from an increase in sympathetic activity, a decrease in parasympathetic activity, a combination of both, a sympathetically dominated coactivation, or a parasympathetically dominated coinhibition.

These different patterns of autonomic response may arise from distinct neurobehavioral processes. In a conditioning study, Iwata and LeDoux (1988) found comparable heart rate increases to the conditioned stimulus in conditioned and pseudo conditioned groups. This finding raised the possibility that the psychophysiological states associated with these two conditions may not mirror the differences in the psychological significance of the CS. Selective blockades of the autonomic branches, however, revealed a distinct pattern of autonomic response despite the comparable end organ response. The pseudoconditioned CS yielded an independent sympathetic activation that drove the cardiac response. The conditioned CS, in fact, yielded a larger sympathetic activation accompanied by a parasympathetic coactivation, which yielded a comparable overall heart rate response despite different autonomic origins. This psychophysiological differentiation in the pattern of response across the autonomic branches would not have been apparent if only heart rate had been measured. A wide range of autonomic response patterns, including autonomic coactivation (e.g., Gianaros & Quigley, 2001; Bosch et al., 2001), are seen in psychological contexts in humans. An important area for future investigation is the elucidation of the specific determinants of these patterns of response.

Differential patterns of autonomic response may not only reflect distinct functional origins, they may have divergent consequences and health implications. RSA and heart rate variability have been effectively used for risk stratification in cardiac disorders, based on the fact that sympathetic activity can be deleterious, whereas parasympathetic activity may offset those deleterious effects in cardiomyopathies or myocardial infarcts (Gang & Malik, 2002; Schwartz, La Rovere, & Vanoli, 1992; Smith, Kukielka, & Billman, 2005). The importance of broader patterns of autonomic and physiological variables in health and disease is further illustrated by the ongoing development of more comprehensive cardiovascular risk factor profiles, which include multiple interacting dimensions including autonomic, neuroendocrine, and metabolic factors (Rosengren et al., 2004; Wood, 2001).

Loneliness and cardiovascular patterns. Autonomic patterns, rather than differences along single dimensions, also differentiate lonely from nonlonely individuals. Lonely individuals tend to display higher total peripheral resistance (TPR) and lower cardiac output (CO) than do

nonlonely people, and they show smaller changes in HR, cardiac contractility, and CO in response to laboratory stressors (Cacioppo et al., 2002; Hawkey, Burleson, Berntson, & Cacioppo, 2003). This pattern is reminiscent of individuals in passive coping contexts and/or making threat-related appraisals (Sherwood, Dolan, & Light, 1990; Tomaka, Blascovich, Kelsey, & Leitten, 1993). The higher TPR of the lonely likely reflect enhanced sympathetic vascular tone, whereas the lower cardiac output and smaller changes in HR and cardiac contractility suggest lower sympathetic cardiac control. These differences are not consistent with simply more or less sympathetic vs. parasympathetic activity, but with probable system-specific patterns of these activities.

The pattern of physiological states and reactivities of lonely individuals may not be limited to the autonomic domain, but may also manifest in neuroendocrine or immune processes as well. It is well established that stressors, such as medical school examinations, can compromise the immune system as evidenced by lower antibody titers to an influenza vaccination (Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998). This stress related deficit in vaccine-induced seroconversion, however, was positively modulated by social embeddedness, suggesting there also may be immunological correlates of loneliness. This possibility was further supported by the finding of diminished wound healing in lonely subjects (see, Cacioppo & Hawkey, 2003). Clearly, an understanding of the psychophysiology of loneliness would not be complete if attention were focused solely on the cardiovascular system or even the autonomic nervous system. Psychophysiological systems are quintessentially interacting systems. Although pragmatics may limit studies to a single or a small number of dimensions, the ultimate understanding of psychophysiological phenomena and their implications for health may require a broader perspective entailing the interactions among multiple psychophysiological systems.

Autonomic, endocrine, and immune interactions

Stressors, especially social stressors can impact immune functions, at least in part by modulating autonomic and/or neuroendocrine process. Social reorganization stress in mice, but not physical stressors such as restraint or shock, has been shown to trigger reactivation of Herpes Simplex virus (Padgett et al., 1998). In addition, introduction of an aggressive intruder, but not physical stressors, can result in notable hyper-inflammatory reactions to foreign antigens which can have lethal consequences (Sheridan, Stark, Avitsur, & Padgett, 2000). This appears to reflect alterations in glucocorticoid functions. Although social stress and physical stress yielded comparable increases in glucocorticoid levels, social stress resulted in the development of glucocorticoid resistance associated with alterations in post-receptor actions (Quan et al., 2003). This resulted in exaggerated immune responses, which were not adequately held in check by glucocorticoids. In this case, the

health consequences of social stress were related to altered immune functions, but these immune changes were secondary to an alteration in glucocorticoid processing.

In many cases, the health significance of psychophysiological states may relate to interactions among autonomic, neuroendocrine and immune systems. Exaggerated cardiovascular reactivity to stress has long been recognized as a predictor of atherosclerosis, hypertension and other cardiovascular disorders (Jennings et al., 2004; Matthews, Salomon, Brady, & Allen, 2003). More recent research suggests specific immune links in these relations. Atherosclerosis is now understood to be fundamentally an inflammatory disorder, in which exaggerated immune responses can promote plaque formation, restrict circulation, and foster emboli (see Libby, 2003; Strike & Steptoe, 2004). High heart rate reactions to stressors (especially those driven by sympathetic activation) predict greater immune consequences, and some immune responses to laboratory stressors can be reduced by sympathetic blockade (Bachen et al., 1995; Benschop et al., 1994; Bosch, Berntson, Cacioppo, Dhabhar, & Marucha, 2003; Cacioppo, 1994; Cacioppo et al., 1995). An explicit link between sympathetic reactivity to stress and cardiovascular disease is suggested by the finding that a laboratory speech stressor resulted in sympathetic activation and a correlated mobilization of a subset of T cells and monocytes that express specific cell surface markers (CXCR2, CXCR3, and CCR5; Bosch et al., 2003). The ligands for these markers are chemokines (chemical attractants) that are secreted by activated vascular endothelial cells. Consequently, stress would be expected to promote trafficking of these cells to these areas of activated endothelium and further exaggerate the inflammatory reactions associated with atherosclerosis.

This represents just one example of what are likely multiple and intricate interactions among autonomic, neuroendocrine and immune systems that contribute to health and disease. As the field of psychophysiology develops and becomes more interdisciplinary, it is likely these interactions will assume increasing importance.

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