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,

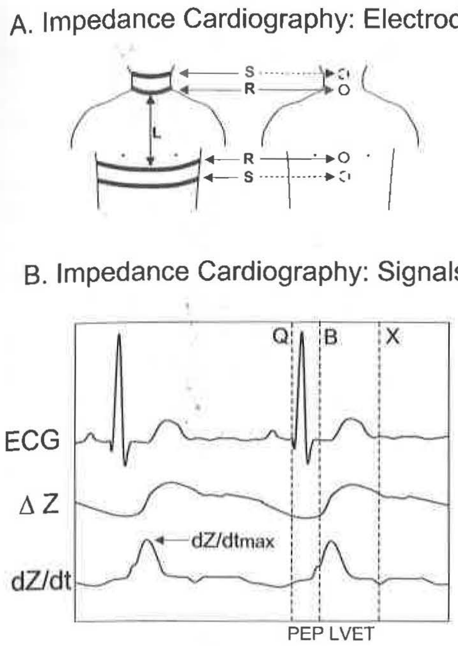

Figure 8.11. Impedance cardiography. (panel A) Typical electrode configurations. Left: standard mylar band electrodes, comprised of outer source (S) electrodes and inner recording (R) electrodes. Right: Qu et al. (1986) spot electrode configuration, consisting of two source electrodes on the dorsum (C4 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 Kirchov'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 signal 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 (Hawkley, Burleson, Berntson, & Cacioppo, 2003; Sherwood, McFetridge, & Hutcheson, 1998; Willemsen, 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, Hutcheson, & 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, Hutcheson, & 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; Berntson, 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):

$$SV = \rho_b\,(L/Z0)^2 \cdot LVET \cdot dZ/dt_{max}$$

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 noninvasive metrics of cardiac performance and autonomic control in psychophysiological contexts.

Cardiac imaging

Psychophysiologists 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 sounds 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