Dynamic Electrocardiography

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To Kate and Joy
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The mysteries of the electrocardiogram unfold in the encyclopaedic tome, *Dynamic Electrocardiography*, edited by Marek Malik and John Camm. Since the first published human electrocardiogram was recorded in 1887 by Augustus Waller (*Journal of Physiology* 1887; 8: 229–234), our understanding of cardiac arrhythmias and the electrical manifestations of cardiac diseases has burgeoned. Over the last several decades, advanced signal analysis and processing techniques have been applied to the electrocardiographic signal to extract increasingly important information regarding cardiac physiology. These techniques and their clinical importance are highlighted in *Dynamic Electrocardiography*.

The editors have been extensively involved in setting the standards in many of the areas discussed in the book. They fortunately provide their expertise as both authors and editors. Drs Malik and Camm have also assembled an outstanding group of contributors, many of whom are the leading experts in their field. As with all new developments, there are many applications and misapplications of these techniques. The editors have synthesized the topics so that the reader may focus on the technical details of how the techniques are performed, how they are properly applied, and what they might mean to the clinician. This compendium therefore serves as an important resource to the clinician and researcher. To our knowledge, there is no book that has the breadth of topics and the breadth of appeal.

The book opens with a section on heart rate variability. This section describes the multiple techniques that are used to measure heart rate variability and puts into context how these measurements are to be interpreted. The ability to extract information regarding autonomic modulation of the heart rate from detailed signal processing techniques focused on characterizing small changes in heart rhythm has opened up many areas of study. Because heart rate variability measurements can be made noninvasively, much effort has been expended to better understand what it means physiologically and prognostically. The ability of these measurements of heart rate variability to provide prognostic information regarding mortality, particularly in patients with cardiac disease, has been an important contribution. The role of the autonomic nervous system in modulating cardiac electrophysiology underlies its pathophysiologic link to sudden cardiac death. Further work in this area will better define this link. Ongoing and future studies will provide the information necessary on how to use these techniques to better treat patients and improve their survival.

Section II deals with measurement of baroreflex sensitivity and heart rate turbulence. These techniques are used to measure the responsiveness of the autonomic nervous system to a perturbation, via the arterial baroreflex. Once again, the physiology, techniques, and clinical utility of these tests are described in this section. These measurements have been shown to be independent powerful predictors of mortality, even when compared to standard heart rate variability measurements. Just as the exercise electrocardiogram is a more useful test for the detection of myocardial ischaemia than the resting electrocardiogram, so too these provocative manoeuvres may provide additional information not obtained by resting measurements of autonomic modulation.

Section III is devoted to evaluation of the ST segment for detection of myocardial ischaemia with review of the underlying basic electrophysiology and clinical methods. Though ST segment changes as a manifestation of myocardial ischaemia have long been recognized, this represents a crucial area of electrocardiography with important implications in patients with ischaemic heart disease.

Section IV highlights the developments made in understanding ventricular repolarization and their impact on patients with cardiac disease.
The complexities of ventricular repolarization become apparent with the multiple ways that exist to characterize it: the QT/RR relationship; circadian variation; QT dispersion; T wave morphology; and T wave alternans. The improved understanding from the cellular to the tissue level has led to the advanced application of these techniques. The chapters are very well organized to help guide the reader through the multidimensional approach to ventricular repolarization.

Sections V, VI, and VII deal with atrial fibrillation, ventricular arrhythmias, and recordings from implanted devices. These sections include selected topics regarding electrocardiographic techniques with a specific focus on newer techniques.

This book will serve the reader as an important reference for this broad array of topics. As the chapters are succinct and to the point, they will provide the reader the most readily accessible information in an easy to read format. Congratulations to Drs Malik and Camm on a superb effort.

Jeffrey Goldberger, MD
Melvin Scheinman, MD
Compared to many clinical methods and procedures, electrocardiography is not particularly new. The first human electrocardiogram was recorded by Dr Augustus Desiré Waller in 1887. Since that time, the development of electrocardiography was not uniform. Several waves of advancement of the physiologic understanding and clinical utility of the electrocardiogram can be traced throughout the past century. After the very first human recording, it took about 20 years for more precise equipment to be developed that allowed recordings to be made with sufficient fidelity for meaningful biological interpretation. Another two decades elapsed before the very core and principal rhythm abnormalities were appreciated and classified; it took some further decades to understand the ischaemic patterns in details; and so on.

The most recent wave of electrocardiographic advances resulted from the observations that not only the static snapshots of cardiac electrical activity but also their temporal development carry physiologically important and clinically useful information. In many aspects, the investigation of this dynamicity of electrocardiographic recordings was not only facilitated but directly allowed by modern electronic and computing technologies. Indeed, it is inconceivable to imagine a modern electrocardiograph without substantial electronic and computer components aimed not only at recording the tiny electrical potentials at the body surface but also at their processing and detailed elaboration. Meaningful and important electrocardiographic measurements and valuable clinical diagnoses reached in this way frequently go far beyond the ‘classical’ visual interpretation of the recorded images.

Because of the research and clinical importance of this new window of electrocardiography, we were very pleased when asked by Futura/Blackwell to edit a comprehensive book aimed at summarizing the most recent advances in electrocardiography, concentrating primarily but not exclusively on the dynamicity of the recordings. The field of modern dynamic electrocardiography is obviously rather broad. Therefore, we have divided the book into seven sections dealing with heart rate variability, baro-reflexes, dynamicity of ischaemic patterns, electrocardiography of ventricular repolarization, atrial fibrillation, ventricular arrhythmias, and finally the recordings made by an implanted device.

As with any other multi-author book, we faced the usual editorial dilemma between having the book tightly cross-referenced and having the individual chapters suitable for stand-alone reading. We eventually felt that a volume of this size should also serve as a reference textbook and that having individual chapters as stand-alone reviews is therefore preferable. Consequently, we are happy to recommend the reader to select separate chapters according to his/her particular needs. Needless to say, reading the book in its entirety will provide a more comprehensive insight into the recent advances in dynamic electrocardiography. In some areas of the field, the rapid development in dynamic electrocardiography leads to occasional controversies. In such cases, we tried to offer the reader the possibility of learning and comparing the different views.

With a book of this broad spectrum, we of course needed to rely on the help of others. Our sincere thanks therefore go to all the contributors who helped us by writing individual chapters. We truly appreciate their efforts – without their enthusiasms and kind involvement in the project, the book would never have been written. We are also grateful to the publisher for careful technical editing of the text and for their understanding and flexibility. Finally, our deep thanks go to Mrs Pam Fernandes who helped us with running the editorial office of the book. It would have been extremely difficult to organise the whole volume without her meticulous involvement.

Marek Malik
A. John Camm
October 2003
SECTION I
Heart Rate Variability
CHAPTER 1
Physiological Background of Heart Rate Variability

Roger Hainsworth

Introduction
Heart rate shows variations which are related, amongst other things to breathing, circadian rhythm and exercise. Resting heart rates can be very different in different subjects, with some having rates of 100 beats/min and others only 50 beats/min for no obvious reason. Highly trained endurance athletes may have resting rates of only 40–50 beats/min with very large stroke volumes to compensate. The maximum rate is partly age-dependent with older subjects achieving maxima during heavy exercise of 20–30 beats/min less than those achieved by younger individuals.

The rate of the heart and its beat-to-beat variations are dependent on the rate of discharge of the pacemaker, normally the sinu-atrial node. The sinu-atrial node in turn is influenced by activity in the two main divisions of autonomic nerves, which are controlled in a complex way by a variety of reflexes as well as by cortical factors.

This chapter will consider in turn the effects on the heart of the autonomic nerves, the control of autonomic activity by various reflexes, and the interaction of these reflexes during some more complex events.

Effects of the autonomic nerves
In the absence of activity in sympathetic or parasympathetic nerves and with low levels of circulating hormones, particularly catecholamines, the heart will beat at its intrinsic rate of 100–120 beats/min. The rate at any particular time is determined by the balance between vagal activity, which slows it, and sympathetic activity, which accelerates it (Levy & Martin 1979). Generally, if the rate is lower than the intrinsic rate of the pacemaker, it implies predominant vagal activity, whereas high heart rates are achieved by increased sympathetic drive.

Vagal responses
The cell bodies of the vagal neurones lie in the dorsal motor nucleus and the nucleus ambiguus. The vagi run down the neck alongside the carotid arteries into the thorax. These nerves carry not only the nerve fibres which control heart rate but many other efferent nerves including those to the bronchi and the gastrointestinal tract. They also contain vast numbers of both myelinated and nonmyelinated afferent nerves innervating thoracic and abdominal viscera. Activity in the vagal branches innervating the sinu-atrial node determines heart rate. Activity in nerves to the conducting mechanism reduces its conduction velocity and high levels of vagal activity may completely block atrio-ventricular conduction. The question of vagal efferent activity on ventricular contractility remains controversial. Earlier work indicated that in mammalian hearts inotropic responses occurred only in atrial and not in ventricular muscle (Furnival et al. 1973). Confusion has arisen due to the depressed atrial contractility causing reduced ventricular filling. Recent work, however, does point to the existence of a small vagally mediated negative inotropic effect in the human ventricular myocardium (Casadei 2001).
Electrical stimulation of either vagus nerve results in slowing of the heart, and high frequencies of stimulation may result in asystole and this may last several seconds. Often during prolonged atrial asystole ‘escape’ beats may originate from other parts of the conducting mechanism. In animals at least, stimulation of the right vagus nerve seems to have a larger chronotropic effect than that from left vagal stimulation (Hamlin & Smith 1968). Stimulation of the left nerve has been reported to have a greater effect on A-V conduction and high frequencies cause A-V conduction block.

The relationship between vagal stimulation frequency and the resulting change in heart rate is hyperbolic, with changes in frequency at low heart rates having a much greater effect than when the rate is high. However, vagal activity does not directly control heart rate but rather it acts to regulate the interval between successive beats. If therefore, instead of plotting heart rate, we plot pulse interval against vagal stimulation, we see that the relationship becomes linear instead of hyperbolic (Fig. 1.2). The choice between pulse interval and heart rate is largely influenced by the interpretation that is required. If it is intended to be used to calculate cardiac output, then clearly heart rate is the appropriate variable. If, however, we wish to quantitate a vagal response, for example to a baroreceptor stimulus, then pulse interval should be used. The effect of this can be seen if, for example, a change in vagal activity induces a prolongation of pulse interval of 333 ms. At a heart rate of 90 beats/min this would correspond to a rate change of 30 beats/min, but at 180 beats/min the change in rate would be three times as much at 90 beats/min.

**Sympathetic responses**

The effect of vagal stimulation is very rapid. A single pulse has been reported to induce a maximal effect in only 400 ms (Levy et al. 1970). The significance of this is that heart rate can be controlled through changes in vagal activity, on a beat-to-beat basis. The effect of vagal stimulation is to release the neurotransmitter acetylcholine and this has two effects on the pacemaker potentials. Firstly, the cells become hyperpolarized and secondly, their rate of depolarization is decreased. Both effects prolong the interval before the critical depolarizing threshold is reached (Fig. 1.1)

Cardiac sympathetic preganglionic nerve fibres originate in the lateral grey horn of the upper thoracic region, synapse in the sympathetic ganglia, then form a plexus together with parasympathetic fibres over the mediastinum, before supplying all parts of the heart. Increasing the activity in cardiac sympathetic nerves is the principal way by which heart rate is
increased above its intrinsic level. This is achieved by causing an increase in the rate of depolarization of the pacemaker cells, causing the critical depolarization of the pacemaker cells to be reached more rapidly (Fig. 1.3). Sympathetic activity, therefore, acts in a similar way to vagal activity in that it directly regulates the pulse interval rather than the heart rate. The responses differ from those to vagal stimulation in that they develop much more slowly. Following the start of stimulation, there is a latency of up to 5s and then heart rate gradually increases to reach a new steady level in 20–30 s. This is clearly of significance when considering heart rate variability and reflex responses. If a change occurs in response to a stimulation within 5 s of its application the efferent mechanism can only be vagally mediated. Responses with longer latencies are likely to be mainly sympathetic.

In addition to its effect on the sinu-atrial node, sympathetic fibres also influence the conducting mechanism and the ventricular myocardium. The right sympathetic nerves, at least in dogs, have a greater effect on heart rate whereas the left nerves have a relatively greater inotropic effect (Fig. 1.4). It should be noted, however, that the high levels of heart rate reached through sympathetic activity can only be achieved because sympathetic activity also shortens the duration of ventricular systole. At rest, ventricular systole lasts about 300ms in a cardiac cycle of 800ms. At high heart rates, when the entire cardiac cycle shortens to 300ms, systolic time must be reduced to allow time for filling.

**Reflex control of heart rate**

The efferent activity in both vagal and sympathetic nerves is regulated by the central nervous system in response to excitatory and inhibitory reflex inputs. Table 1.1 lists some reflexes responsible for decreasing or increasing the heart rate. The body, however, is influenced by many diverse inputs and the overall effect is dependent on often complex interactions as well as cortical influences.

**Table 1.1 Reflex control of heart rate**

<table>
<thead>
<tr>
<th>Reflexes increasing heart rate</th>
<th>Reflexes decreasing heart rate</th>
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<tbody>
<tr>
<td>Atrial receptors</td>
<td>Baroreceptors</td>
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<tr>
<td>Pulmonary stretch receptors</td>
<td>Chemoreceptors</td>
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<tr>
<td>Muscle metaboceptors</td>
<td>Ventricular chemosensitive</td>
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<tr>
<td>Pain receptors</td>
<td>afferents</td>
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<td></td>
<td>Pulmonary 'J' receptors</td>
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<tr>
<td></td>
<td>Trigeminal afferents (diving)</td>
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</table>

**Baroreceptors**

Arterial baroreceptors exist in many regions of the body. Owing to their accessibility those in the carotid sinuses have been most extensively studied, and in humans these are the only receptors capable of being selectively stimulated. Animal studies, however, have established potentially important baroreceptors in the aortic arch.
Baroreceptors are stretch receptors which respond to changes in vessel transmural pressure. An important characteristic is their response to changes in pulsatility. This enables them to respond to changes in cardiac stroke volume caused by changes in venous return which may be too small to be detected as changes in pressure (Taylor et al. 1995). Baroreceptors are effective at ‘buffering’ short-term changes in blood pressure. They are less effective in long-term pressure control due to their property of resetting (Chapleau & Abboud, 1993).

Baroreceptors control blood pressure by their effects on the heart and blood vessels. The immediate cardiac response is vagally mediated and occurs very rapidly (Fig. 1.5). Eckberg (1978) applied brief stimuli to carotid baroreceptors by means of a neck suction device that increased carotid transmural pressure. He observed that maximal effects were obtained when a stimulus was applied 750 ms before a subsequent anticipated P wave. Baroreceptors, therefore, can control heart period on a beat-to-beat basis. Variations in heart rate mediated through the baroreflex can occur at relatively high frequencies. The actual frequency is dependent rather on the variations in the stimulus than on latency of the reflex.

Baroreceptor reflex stimulus–response relationships have a limited range of linearity. The nonlinearity may be a feature of the effector mechanism. For example in resting conditions where sympathetic activity is low baroreceptor stimulation has little effect on vascular resistance, whereas unloading can cause an increase in resistance (Vukasovic et al. 1990). Cardiac responses have different constraints. Stimulation at rest causes interval prolongation and unloading causes interval shortening. During exercise or orthostatic stress, if little vagal activity is present baroreceptor unloading would be expected to have a smaller effect.

It seems likely that the various baroreceptor groups operate over different ranges of pressures. Coronary artery baroreceptors have been shown in the dog to have very low operating ranges and therefore are suited to protect against hypotension. (McMahon et al. 1996). Carotid and aortic receptors have higher operating ranges and can, therefore, stabilize both increases and decreases in pressure.

Chemoreceptors

Peripheral chemoreceptors are situated in carotid and aortic bodies and are stimulated by asphyxia, i.e. hypoxia, hypercapnia and acidemia, as well as by severe hypotension. Under most conditions their level of stimulation is low and it is only during severe hypoxia or hypotension that they become strongly stimulated. The most obvious response to chemoreceptor stimulation is an increase in breathing. Their effects on the cardiovascular system are complicated by the effect on respiration. These effects are mediated mainly through pulmonary stretch receptors and, if this secondary modulation is prevented, carotid chemoreceptor stimulation leads to a cardiac slowing (Fig. 1.6).

Trigeminal afferents: the diving reflex

Immersion of the face or stimulation of trigeminal receptors by application of cold packs to the face elicits a diving reflex. This is very pronounced and of great importance to diving mammals. A response can also be seen in humans (Daly 1985). This comprises apnoea, hypertension and bradycardia. The respiratory arrest leads to asphyxial changes which stimulate chemoreceptors and further augments the bradycardia and vasoconstriction.

Cardiac and pulmonary nonmyelinated afferents

The various cardiac chambers are extensively innervated with nonmyelinated vagal afferents.
Physiological Background of Heart Rate Variability

(Hainsworth, 1991a). Similar innervation extends to the lungs, the so-called J receptors (Paintal 1995). The most effective stimuli to any of these nerves is injection of various noxious chemicals such as veratridine, capsaicin and phenyldiguanide. The most sensitive intrathoracic region for chemical stimulation is the left coronary artery and minute injections of stimulating chemicals there can lead to a profound bradycardia and hypotension (Fig. 1.7). Excitation of these cardiac and pulmonary reflexes may occur in humans following intravenous drug administration or injection of radio-opaque dyes (Perez-Gomez & Garcia-Aguado, 1977).

The normal physiological role of cardiac and pulmonary nonmyelinated afferents seems to be relatively minor. Large changes in ventricular pressure may cause a transient stimulation of ventricular afferents, but pressures need to be beyond those normally encountered (Drinkhill et al. 1993), and changes in coronary arterial pressure cause much larger responses. Similarly pulmonary nonmyelinated afferents are only excited by chemical stimulation, pulmonary congestion or gross overdistension (Coleridge & Coleridge 1991). It is hard to disagree with the proposition that, although cardiac and pulmonary nonmyelinated afferents may be involved in disease processes, they do not have an important regulatory role.

Atrial receptors

Complex unencapsulated nerve endings of myelinated nerve fibres are located mainly near the junctions between the venae cava and the pulmonary veins with the atria (Nonidez, 1937). They are responsible for what was originally known as the Bainbridge reflex. They are stretch receptors and their discharge is linearly related to atrial volume and pressure. Because atrial filling is dependent, amongst other things, on blood volume they are often thought of as volume receptors.

Stimulation of atrial receptors induces an unusual pattern of responses (Linden &
Kappagoda 1982; Hainsworth 1991b). Heart rate increases, but atrial receptors have little or no effect on vascular resistance in most regions. They do, however, target the kidney and increase salt and water excretion through a reduction in renal nerve activity and central inhibition of vasopressin. In this way an increase in cardiac filling leads to a diuresis and a natriuresis. Note that these responses are reflexly mediated in that nervous pathways are involved. They should not be confused with the diuresis and natriuresis resulting from the release of atrial natriuretic peptide. This occurs in response to stretching of cardiac myocytes and its physiological significance is uncertain.

Atrial receptors are likely to have an important role in circulatory control. However, the time course of any change needs to be considered in relation to its possible role in influencing heart rate variability. Because responses are mediated through sympathetic efferents, following stimulation a period of 20–30 s is required for a maximal response. Atrial receptors, therefore, are unlikely to be important in mediating or modulating high frequency heart rate oscillations.

Heart rate changes during complex events
The foregoing has considered the effects of changes in stimuli to single discrete reflexogenic areas. This is of importance in analysing the mechanisms which are involved but normal daily activities, including breathing, straining, changes in body position and various forms of physical exercise, result in changes in the stimulation of many diverse reflex mechanisms. This section is concerned with some of the more common activities which can affect the heart rate.

Sinus arrhythmia
Sinus arrhythmia is caused by variations in cardiac vagal efferent activity. Vagal activity occurs only during expiration, being inhibited during the inspiratory phase (Fig. 1.9). Several mechanisms seem to contribute. Reflexes from the low threshold pulmonary stretch receptors, which are also responsible for the Hering–Breuer reflex, almost certainly play a part (Hainsworth 1974). However, sinus arrhythmia can be seen to some extent in paralysed animals in absence of breathing movements and this has been attributed to central connections between the respiratory centres and the vagal nuclei (Anrep et al. 1936). Baroreceptors are also likely to be involved as the variations in heart rate are also associated with variations in blood pressure. It has been proposed that there is a central ‘gating’ mechanism whereby during inspiration the baroreflex is inhibited (Spyer & Jordan 1987). This concept is supported by the findings of Eckberg et al. (1980) who applied brief stimuli to the carotid baroreceptors in humans and observed maximal prolongation of pulse interval during expiration and almost complete inhibition of the reflex in early inspiration (Fig. 1.10).
Sinus arrhythmia occurs with a period of about 4 s which is too fast for variations in efferent vagal nerve activity during respiratory cycle and during changes in carotid sinus pressure. Note the cardiac acceleration during the phase of inspiration associated with cessation of vagal activity. Activity is also influenced by changes in carotid sinus pressure, but the inspiratory inhibition persists. (Reproduced from Neil 1979, with permission.)

Postural changes
In humans moving from supine to motionless standing results not only in displacement of blood into dependent capacitance vessels but also in a progressive transudation of plasma fluid across dependent capillaries (Hainsworth 1999). This inevitably results in decreases in venous return and in pulse pressure. This and the altered position of carotid baroreceptors leads to compensatory reflex vasoconstriction and tachycardia. Because of the exquisite sensitivity of baroreceptors to changes in pulsatility mean blood pressure in the upright position is maintained close to or even above that in the supine position. If the orthostatic stress becomes too great, and in susceptible individuals this can happen with relatively minor stresses, the vasoconstriction and tachycardia abruptly reverse to become vasodilatation and bradycardia (Fig. 1.11). This was described by Lewis (1932) as a vasovagal reaction indicating vasodilatation and a vagally mediated bradycardia. Occasionally, the bradycardia may extend to several seconds of asystole. The mechanism switching off the sympathetic activity and turning on vagal activity is unknown. It was formerly thought to be the result of a paradoxical stimulation of the ventricular receptor but this has now been shown not to be the case (see Hainsworth 2003).

Valsalva
The Valsalva manoeuvre involves straining against either a closed glottis or an external resistance. Pressures within the thorax and abdomen are greatly increased, impeding the inflow of
blood from outside these regions. It is important to note that, unlike positive pressure ventilation, blood does not pool in the abdomen. Fig. 1.12 shows effects of a controlled Valsalva and illustrates the various phases. Firstly, the raised intrathoracic and intra-abdominal pressures compress the major vessels causing an abrupt transient pressure rise. Secondly, the reduced venous return leads to a fall in cardiac output and blood pressure. The pressure fall is compensated by reflex vaso-constriction and tachycardia. On releasing the Valsalva, the intrathoracic and intraabdominal pressures fall again decompressing the vessels and causing a transient fall in arterial pressure. The previously impeded blood flows rapidly into the heart, and is pumped out into a constricted circulation resulting in an overshoot of blood pressure and, often, bradycardia.

The Valsalva manoeuvre provides a test of the integrity of the autonomic nerves and of the baroreceptor reflex. Deficient reflexes result in