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Appraisal of state-of-the-art

How many ECG leads are required for *in vivo* studies in safety pharmacology?

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ABSTRACT

This article explains the principles of electrocardiography, and explains how it is used by Safety Pharmacology, with a focus on the requirement for multiple leads in Safety Pharmacology assessment. Electrocardiography as used in different disciplines (e.g., medicine, anesthesiology, physiology, and pharmacology/toxicology/safety pharmacology) has different requirements for the number of electrodes applied. Electrodes may be placed at an infinite number of points on the body, and voltages (electrocardiograms) may be registered between/among them. However in safety pharmacology there is little evidence that more than 1—or at most 3—lead(s) is (are) required to provide all of the information that might be present using an infinite number. This is based upon (1) the biophysics of the heart as a generator of electrical potential/voltage, (2) the fact that most properties of electrophysiology affected adversely by drugs are expressed as changes in durations, and (3) experience. A single, unipolar lead (V_3) recorded from the left sternal border at the 5th intercostal space possesses minimal artifact and large, stable deflections. This lead allows for accurate measurement of heart rate and rhythm, durations of component deflections (e.g., PQ, QRS, QT), and J-point deviation. A greater number of leads seldom or never yield additional information that detects liabilities. Commonly voltages recorded between the right thoracic and left pelvic limbs (lead II) provides information similar to lead V_3, and lead II is easier to apply, and produces voltages with less artifact and similar to those in lead V_3. A lead measuring the voltage between the left and right thoracic limbs (lead I) along with lead II allows for estimating orientation of vectors in the frontal plane, but knowledge of these vectors seldom or never indicates liability of a test article.

1. Introduction

1.1. Why is electrocardiography used in safety pharmacology?

Electrocardiography is a method essential for studies in safety pharmacology, because it detects, simply, inexpensively, and non-invasively, many (most) drug-induced changes in electrophysiological properties of the heart (e.g., chronotropy, dromotropy, bathomotropy) that might translate to morbidity or mortality if expressed in man.

1.2. What is the electrocardiographic system?

There are 4 components to the electrocardiographic system (Fig. 1): (1) the heart as a generator of voltage, (2) the body volume which allows for transmission of those voltages to the torso surface, (3) the voltmeter (electrocardiograph) which detects, amplifies and records the voltages, (4) the electrocadiographer who interprets the electrocardiograms (the recordings of the voltages) to determine the state of electrophysiological health of the heart, and who often makes recommendations for treatment or identifies toxicity.

1.3. What are electrocardiographic leads?

Lead is used three times in electrocardiography. It stands for a position (e.g., V_3, rV_2) on the torso from which voltages are recorded. It stands for a wire extending from the patient to the electrocardiograph. It stands for a combination of electrodes between which voltages are measured. This discussion will be about points on the torso surface from which voltages should be registered.

1.4. What is an electrocardiograph and what are types of leads?

An electrocardiograph is a voltmeter which registers differences of electrical potential (the force that drives electrons from place to place). As such a voltmeter requires 2 inputs, termed positive (+) and negative (−). These inputs come from positions (leads) on the torso and/or limbs of the subject. The electrocardiograph measures voltage (potential to drive electrons) between these points, and of course there is an infinite number of points on the torso/limbs between which potential differences can be measured and might have meaning to the electrocardiographer. For example: (1) lead I measures the voltage difference between the left and right thoracic limbs, where the lead from the left thoracic limb goes to the positive pole of the electrocardiograph, and the lead from the right thoracic limb goes to the negative pole; (2) lead V_3 measures the voltage difference between an electrode on the left portion of the thorax and a

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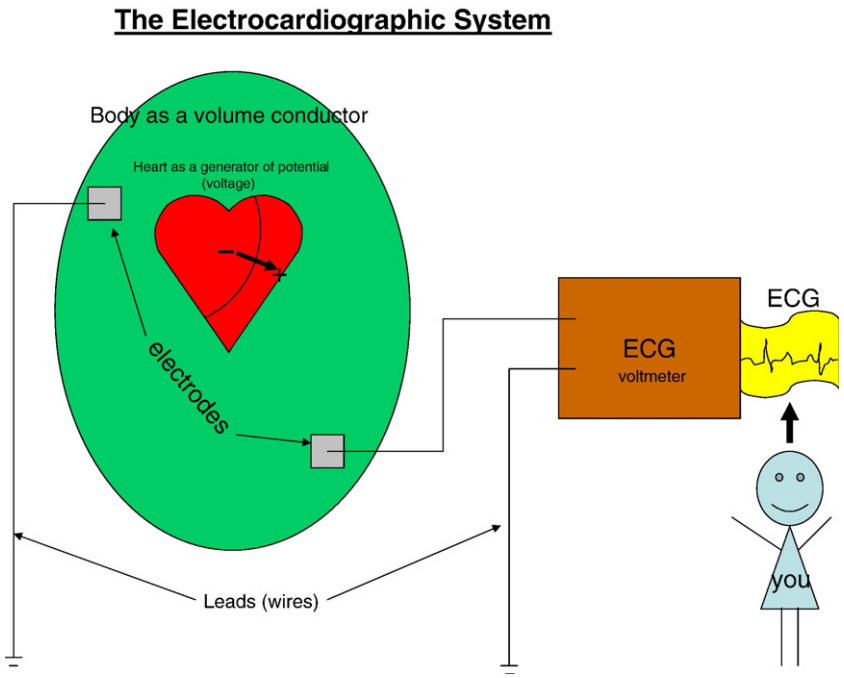

Fig. 1. Overview of the electrocardiographic system, including: the heart as a generator of potential, the body as a volume conductor, electrodes placed on the limbs or torso surface, leads (wires) extending from the electrodes to the voltmeter (electrocardiograph), the electrocardiograph, the electrocardiogram, the interpreter.

combination of electrodes from the right and left thoracic and the left pelvic limbs. The electrode from the thorax goes to the positive pole of the electrocardiograph and the 3 electrodes (combined) from the limbs go to the negative pole; (3) lead aV_F measures the voltage difference between an electrode on the left pelvic limb and a combination of electrodes from the left and right thoracic limbs, where the lead from the left pelvic limb goes to the positive pole of the electrocardiograph and the 2 leads (combined and modified by high resistance) from the thoracic limbs go to the negative pole of the electrocardiograph.

Voltage differences between only 2 points form so-called bipolar leads; voltage differences between 1 point and the combination of the 3 limbs form so-called unipolar leads; voltage differences between 1 point and the combination of points from the 2 other limbs form so-called augmented unipolar leads.

1.5. What determines the numbers of leads and which one(s) is (are) required?

Of course the number of leads possible (permutations of inputs to the poles of the electrocardiograph) is infinite, therefore it is important to know how many, and which ones, are required to provide the information necessary for the mission of electrocardiography. That depends upon the mission. In clinical electrocardiography of humans (Morganroth & Gussak, 2004; Zipes & Jalife, 2004), to detect chamber enlargement, to localize myocardial ischemia and infarction, and to quantify dispersion of QTc among leads, 12 or more leads may be necessary. In conventional electrocardiography in veterinary clinical medicine (Detweiler, 1988; Tilley, 1993), 6 leads (of which only 2 or 3 of the 6 present information that is unique) are usually taken. But if the interest is only in determining heart rate, rhythm, durations of various electrophysiological processes (e.g., rate of discharge of the SA node, speed of conduction through the atria or ventricles or from atria to ventricles, durations of both ventricular depolarization and repolarization) or to search for abnormal discharge from within the atria or ventricles, then only 1 lead may be necessary (Malik & Batchvarov, 2000). But it better be a "good" lead, i.e., one from which deflections can be measured accurately (Horan, Flowers, & Brody, 1964)!

The decision on the numbers of leads is based upon experience. However the decision may be based upon theoretical, biophysical considerations as well; for example, how does the heart behave as an equivalent generator of potential? Of course the final decision on how many, and which, leads are necessary in studies on safety pharmacology may be answered only by the medical community and drug regulatory agencies who could state how often 1, 2, 3+….+*n* leads produced information that predicted safety with 100% sensitivity and 100% specificity. Since 100% sensitivity and specificity are impossible to achieve, rather we seek the fewest number of leads that produces results as good as the greatest number of leads ever used.

2. The heart as a generator of potential

The voltages are produced on the body surface by waves of depolarization (Durrer & Van der Tweel, 1965; Scher, 1964) and repolarization traversing the atria and ventricles (Fig. 2). These waves are in fact sheets of dipoles (positive and negative charges separated by a small distance) in which the face of the sheet in stimulated (depolarized) myocardium is comprised of negative charges, while the face of the sheet in the resting (repolarized) portion of the myocardium is comprised of positive charges (Wilson & Bayley, 1950; Bayley et al., 1954).

Fig. 3 shows a dog, its heart (albeit an abnormally large one) within the torso, and a single sheet of dipoles, frozen at an instant, traveling through the heart in a general direction from head to tail. The sheet of dipoles has negative signs in the region that is depolarized, and positive signs in the region that is yet to be depolarized. We may predict/estimate the magnitude and sign of the voltage produced by this wave at any point (P), say on left hind leg of the torso, using (1) the solid angle (Fig. 4) concept (Holland & Ornsdorf, 1977), (2) the vector (Fig. 5) concept (Frank, 1954; Grant & Estes, 1951), or (3) by gross approximation (Fig. 6) (Hamlin & Smith, 1960). Using the solid angle concept (Fig. 4), we construct radii from the open ends of the sheet to the point, measure the angle (Ω[1]) determined by the radii, and state that the sign will be positive because the point is in the general milieu of the positive face of the sheet, and that the voltage will be proportional to the magnitude of the angle. For mathematical correctness the magnitude of the angle should be multiplied by 2 constants, one dependent upon the resistive

[1] In this example the angle is in one plane, whereas the boundary is actually 3 dimensional, therefore the angle should be a solid angle.