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Research

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A Clinical Application of the "Brody Effect"

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ABSTRACT

Brody described the importance of differences in resistivity between blood in the left ventricular lumen and the myocardium, and the distance between the primary dipole in the myocardium and the image dipole in the lumen. The image dipole existing in the ventricular lumen influences the ECG voltages recorded from leads either radial or tangential to the left ventricular mass. The intensity of the image dipole and the magnitude of the effect on the body surface ECG are proportional to the differences in resistivity and the distance between primary and image dipoles. Tacrolimus, a commonly-used immunosuppressant, decreases left ventricular lumen and thickens the left ventricular free-wall tremendously; thus, although left ventricular myocardial mass does not change, ECG voltages in leads facing the left ventricular free-wall should decrease monumentally. The hypothesis of this study is that ECG voltages in lead aVF facing the left ventricular free-wall and oriented radially from its mass would decrease proportional with the decrease in luminal radius and thickening of the free-wall. ECG's and 2D-directed M-mode ECHO's of the left ventricle were recorded from dogs before and after receiving tacrolimus and developing drastic reductions in left ventricular luminal volumes. R waves in lead aVF determined by the radial spread of depolarization from subendocardium to subepicardium of the left ventricular free-wall decreased precipitously as the ratio of luminal radius to wall thickness decreased. The hypothesis that ECG voltages would decrease as luminal volume decreases and the wall thickens was accepted. This study demonstrates that factors other than wall mass must be considered in electrocardiology.

KEYWORDS: Brody Effect; ECG voltages; Echocardiography.

INTRODUCTION

The Electrocardiogram (ECG) is the best method for studying the rate and rhythm of the heart, it is also useful for detecting left ventricular hypertrophy in humans, and possibly so in dogs. In 1956, Brody described the effect of intracardiac blood volume on body surface potentials.[1] The powerful influence of the intracavitary blood mass on the heart-lead relationship increases the validity. The analysis of the inhomogenity problem leads to a theoretically correct but eliminating inhomogeneity effects need to be evaluated clinically for the use of the methods. The relationship between QRS amplitude and left ventricular mass was evaluated in early stages of left ventricular hypertrophy. A decrease in QRSmax and the specific potential of myocardium was observed in both models of experimental left ventricular hypertrophy. The changes in electrogenetic properties of myocardium have been shown in the early stage of developing left ventricular hypertrophy. The changes of nonspatial determinants influence the resultant QRS voltage in terms of the solid angle theory.[2] Tacrolimus (FK506) is an immunosuppressive macrolide antibiotic that is used to minimize transplant rejections having strong effects on the heart.[3,4] Tacrolimus leads an increase in end-diastolic wall thickness and a decrease in left ventricular end-diastolic volume in dogs.[3]

Pattern of left ventricular hypertrophy is an R wave – greater than normal in amplitude

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and longer than normal in duration – in a lead whose electrical axis (lead aVF) is normal to the epicardium of the hypertrophied left ventricular free-wall. The hypothesis of this study is that ECG voltages in lead aVF facing the left ventricular free-wall and oriented radially from its mass would decrease proportional with the decrease in luminal radius and thickening of the free-wall. ECG's and 2D-directed M-mode ECHO's of the left ventricle were recorded from dogs before and after receiving 0.1 mg/kg tacrolimus and developing drastic reductions in left ventricular luminal volumes.

MATERIALS AND METHODS

All animals received humane care in accordance with guidelines of the American Physiological Society and The Ohio State University. Ten, healthy dogs of either sex weighing between 10 and 14 kg were anesthetized with morphine-chloralose. Electrodes forming ECG lead aVF were placed, and lead aVF was recorded on a data acquisition system. Dimensions of the left ventricular and left atrial lumena were measured from two-dimension directed mode echocardiograms. After baseline measurements of echocardiograms and electrocardiograms were obtained, dogs were given IV 0.1 mg/kg tacrolimus, and recordings were obtained 15 minutes later. Peak voltages of P waves and R waves in lead aVF were measured, and left ventricular internal dimensions and free-wall thicknesses were measured from the M-mode obtained just below the position of the mitral valves. The ratios of left ventricular lumena, thicknesses of the left ventricular free-walls, and of P and R wave heights before and after tacrolimus were calculated. Ratios of values measured or calculated were compared by one-tailed Student's t requiring a $p<0.05$ for significance.

RESULTS

Table 1 shows values for all measures of ECG and echocardiography. All dogs given tacrolimus remained in sinus rhythm but all developed sinus tachycardia. Mean heart rate before tacrolimus was 78 (SEM 4.3) beats/minute and after tacrolimus was 158 (SEM 9.5) beats/minute ($p<0.0001$). The R wave decreased ($p<0.001$) from 2.29 (SEM 0.193) mV to 1.48 (SEM 0.163) mV, a difference of 0.81 mV. The height of the P wave increased ($p<0.001$) from 0.148 (SEM 0.024) mV to 0.392 (SEM 0.025) mV, a difference of 0.244 mV. The thickness of the left ventricular free-wall increased ($p<0.001$) from 0.655 cm to 0.92 cm, a difference of 0.265 cm. The original ECG recording has been shown in Figure 1. 2D echocardiography of the heart has been shown in Figure 2. A remarkable thickening of the myocardium was seen after tacrolimus administration. The calculation of the amplitudes for the clinical application of Brody Effect has been shown in Figure 3.

DISCUSSION

Conventional assessment of left ventricular hypertrophy using the electrocardiogram have relied on assessing

	Baseline	Tacrolimus	Difference	Ratio	T-test (P)
HR (bpm)	78.11±4.35	158.35±9.5	80.24	2.03	=0.021
P aVF (mV)	0.148±0.024	0.392±0.025	0.244	2.6	<0.001
R aVF (mV)	2.29±0.193	1.48±0.163	0.81	0.6	<0.001
LVEDDi (cm)	2.85±0.155	2.06±0.235	0.79	0.7	=0.032
LVEDWT(cm)	0.655±0.045	0.92±0.059	0.265	1.4	=0.012
LAA-d (cm^2)	7.18±0.67	4.17±0.286	3.01	0.6	=0.014
LAA-s (cm^2)	5.13±0.65	2.49±0.39	2.64	0.5	=0.024

±: SEM, HR: Heart rate, LVEDDi: Left ventricular end-diastolic diameter, LVEDWT: Left ventricular end-diastolic wall thickness, LAA-d: Left atrial area in diastole and LAA-s: Left atrial area in systole.

Table 1: Values for all measures of ECG and echocardiography.

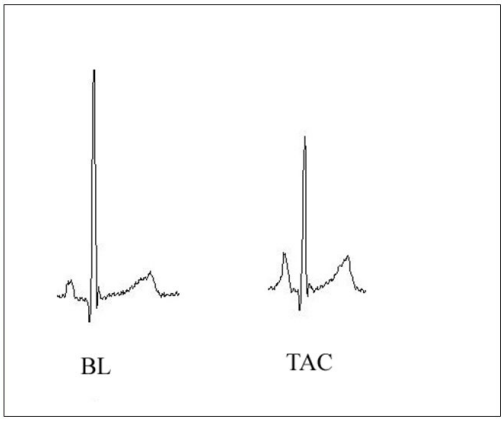

Figure 1: Electrocardiographic recordings before (BL) and after 1 mg/kg Tacrolimus (TAC). Note the decrease in R wave and the increase in P wave after tacrolimus administration.

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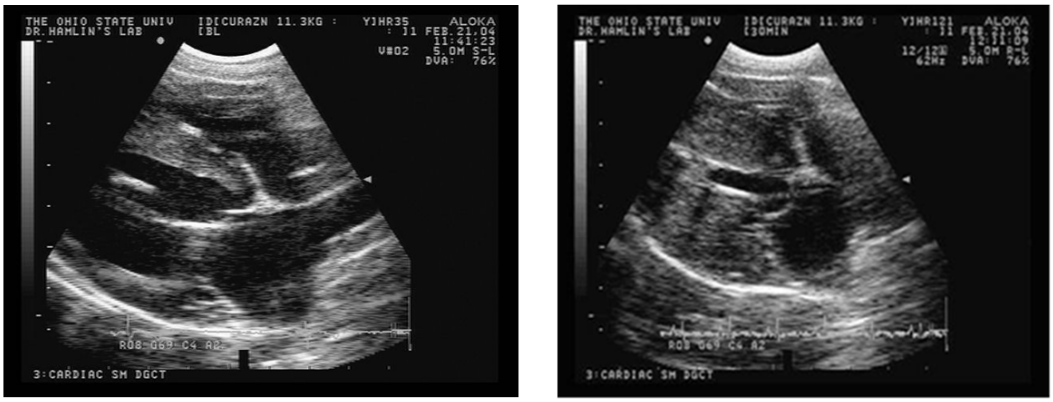

Figure 2: 2D echocardiography of the heart before (BL) and after 1 mg/kg Tacrolimus (TAC). Note the thickening of the myocardium after tacrolimus administration.

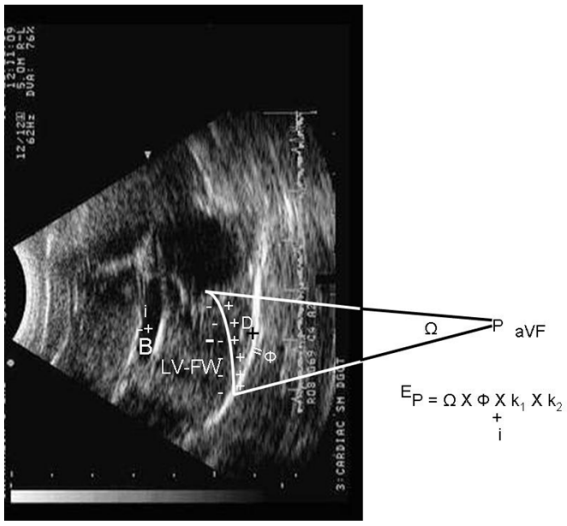

Figure 3: The calculation of the amplitudes for the clinical application of Brody Effect over lead aVF, ECG.

changes in the amplitude and/or duration of the QRS complex of the ECG to quantify LV mass. ECG measures of LV mass have typically been validated by imaging such as echocardiography.[5] Decreases in R-wave amplitude were evaluated in myocardial ischemic infarction in previous reports.[6] For further investigation of the effects on the amplitudes, this study evaluates amplitude and the blood volume of the heart when myocardial mass is stable. The amplitude of the R wave may be predicted by the solid angle concept (Figure 3). This necessitates constructing radii from the open ends of a boundary between resting (positive) and depolarized (negative) myocardium, to the electrodes on the body surface. The voltage generated at this electrode may be approximated by the solid angle (Ω) subtended, on a sphere of unit radius, by an infinite number of radii from the perimeter of the boundary between depolarized and resting myocardium to the point on the torso surface. The amplitude may be defined quantitatively as the magnitude of the solid angle, times the strength of the unit dipole (Φ), an infinite number of which produce the boundary, times a constant of resistivity of the medium between the heart and the electrodes, times a geometrical constant (for which there is no intuitive explanation).

In 1956 Brody described the effect of intracardiac blood volume on body surface potentials.[1] He demonstrated that a body surface potential, at point aVF produced by a wave of depolarization resolved to a single dipole (P) traversing the myocardium normal to its epicardial surface, would have a magnitude greater than might be expected from the single (primary) dipole, because an image (i) dipole exists in the volume of blood within the left ventricle. The magnitude of the image dipole and its contribution to the voltage on the body surface depends upon how large the primary dipole is, the distance (x) between the P and is, and the differences in resistivity between the myocardium (σ) and blood (σ) containing the two dipoles. When the wave of depolarization travels through the myocardium tangentially to the volume of blood (B), the image dipole actually detracts from the voltage recorded from a lead towards which the boundary is traveling.

Since the R-wave of lead aVF ECG is produced by radial spread in an endocardial to epicardial direction through the left ventricle, and the P wave is produced by tangential spread through the atria, if both ventricle and atria become smaller and

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therefore have thicker walls, the voltages of the R wave should be decreased and that of the P wave should be increased due to a decreased image dipole.

As will be demonstrated by the experiments reported here, despite the fact that the mass of the left ventricle does not change in response to the immunophylline, tacrolimus, the height of the R wave in lead aVF decreases and the height of the P wave increases dramatically. It will be shown by echocardiography, that the left ventricular and atrial lumena become small, the left ventricular free-wall and atrial walls thick (pseudohypertrophy), and that the alterations in amplitudes can be explained by application of the Brody effect. This may limit the ability to identify hypertrophy of the left ventricular free-wall, and may falsely suggest enlargement of the atria.

The P waves increased in amplitude and the R waves decreased in amplitude, acutely, in response to tacrolimus. Obviously in the 15 minutes between baseline and the administration of tacrolimus neither change could reflect a change in muscle mass, the depolarization of which produces the ECG deflections; thus an alternative explanation must be offered. It is reasonable to assume that the topographical relationship between the electrodes on the torso surface and the heart did not change enough to account for altered voltages. Similarly it is reasonable to assume that the unit dipole (Φ in Figure 3) – sheets of which constitute the waves of depolarization – did not change substantially. Since the amplitude of the P wave increased while the amplitude of the R wave decreased, and both dipole sources are nearly equidistant from the electrodes on the torso surface, the differences between baseline and tacrolimus cannot be explained by altered resistivity (k_1 in Figure 3) of the body as a volume conductor. Thus, there are only 2 possibilities to explain the divergent effects of tacrolimus on the amplitudes. First an increased amplitude of the P wave and a decreased amplitude of the R wave could be explained by changes in the magnitude of the solid angle formed by the radii from the boundary between depolarized and resting myocardium (Ω in Figure 3); i.e, the sheet representing atrial depolarization became larger and that representing ventricular depolarization – actually depolarization of the left ventricular free-wall which generates the R wave in lead aVF – became smaller. However, observation of the atria and ventricles on the echocardiograms show that both became smaller after tacrolimus. Furthermore, although we could not observe the entire left ventricular geometry on the echocardiogram, it is clear that both atria and ventricles became smaller. Thus, it would be inconsistent to explain an increase in P wave amplitude and a decrease in R wave amplitude on the decrease in magnitude of the sheets of dipoles producing the respective deflections. Thus, the only explanation to account for the increase in amplitude of the P wave and decrease in amplitude of R wave is the Brody effect.

Both atria and ventricles became smaller; i.e., their epicardial perimeters decreased. Since the muscle mass could not have changed, it follows that both must have become thicker, which was observed unequivocally on the echocardiograms. Thus the image dipole in the left ventricular volume would be reduced in magnitude, since the primary dipole in the free-all of the left ventricle would be more distant from the ventricular cavity. This occurs because the spread of depolarization through the left ventricular free-wall is radial through the wall. Thus, the sum of the primary and image dipoles would be reduced (the primary being normal but the image reduced), and the height of the R wave would be reduced. But because the spread of activity through the atrial wall is tangential to the volumes of blood within the atria, the thickening of the atrial walls would increase the image dipole, thus making the sum of the primary and image dipoles greater after tacrolimus than during baseline. Further studies may evaluate the effect of phi change differently for atria versus ventricles and resistivity of myocardium change differently for atria and ventricles.

The severe tachycardia caused by tacrolimus may be related with binding to the 12-kDa FK506-binding protein (FKBP12.6) modulating calcium conductance through ryanodine channels in pace-maker cells and a decrease in conductance of potassium over the inward rectifying K^+ (IK1) and transient outward K^+ (IKTO) channels.[3,7] Furthermore, the profound myocardial thickening and reduced luminal cavity by the influence of tacrolimus were noted concurrent with the ECG changes resulting in tachycardia and increased contractility.

In conclusion, the hypothesis that ECG voltages would decrease as luminal volume decreases and the wall thickens was accepted. This study demonstrates that factors other than wall mass must be considered in electrocardiology.

CONFLICTS OF INTEREST: None.

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