The Development and Calibration of a Method for the Continuous Measurement of Stroke-Volume in the Experimental Animal

L. A. Geddes, Ph.D.*, H. E. Hoff, M.D.*, and A. Mello, D.D.S.**

In the study of the response of the heart to work loads there has always been the need for a method which indicates the time-rate at which ventricular volume changes occur during a single heart beat. From this information and simultaneous pressure-time data can be calculated one of the most important parameters of cardiac action, cardiac power. Any technique which permits continuous measurement of the dynamic temporal variation in ventricular volume could contribute valuable information to an understanding of cardiovascular dynamics. The appendix to this paper contains a review of the methods employed to date to measure stroke-volume. A new technique for the measurement of stroke-volume has been developed by the authors. Initial studies indicate that calibration is possible.

Principle of the Method

The method treats the ventricles as conductivity chambers and the blood within them as a conducting medium. Changes in ventricular volume appear as changes in impedance*** measured between a pair of electrodes located at the apex and base of the heart. The tips of the electrodes are in contact with ventricular blood. Thus the blood in the ventricles acts as an electrical conductor. Changes in ventricular volume are indicated by a change in electrical resistance measured between the electrodes.

The resistance of a conductor depends on the resistivity of its component material, and varies with the length and inversely with the cross-sectional area. If the length is kept constant and the amount of conducting material between the electrodes is varied, the resistance will vary accordingly. Assuming that the apex-base length of the heart remains constant during systole, then the resistance measured between electrodes inserted into the base and apex of a ventricle varies inversely with cross-sectional area. In applying this reasoning to the resistance measured between electrodes inserted into the ventricular cavity of the dog, it is important to note that

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* Department of Physiology, Baylor University College of Medicine, Houston, Texas.
** Department of Physiology, Facultade de Farmacia e Odontologia de Araçatuba, Estado de São Paulo, Brazil.

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*** Impedance is the opposition to the flow of alternating current. It is analogous to resistance and in this application almost identical.
the conductivity of blood\textsuperscript{6},\textsuperscript{16},\textsuperscript{18}) is more than 5 times that of cardiac muscle,\textsuperscript{35}–\textsuperscript{37}) thus the majority of the current will be confined to blood within the ventricle. In addition, it has been shown by Rushmer\textsuperscript{26},\textsuperscript{27},\textsuperscript{32}) and Hawthorn\textsuperscript{11}) that during the cardiac cycle, the apex-base dimension changes by a relatively small amount; the major dimension change is in the diameter of the ventricles, as indeed, Harvey himself had noted. Thus a decrease in diameter during systole decreases the cross-sectional area of the conducting material (blood) and would be expected to increase the resistance measured between electrodes inserted into the cavity at the apex and base.

Because the blood in the ventricle constitutes a conductor of irregular and changing shape, it is necessary to establish the relationship between the changes in impedance and in volume during the cardiac cycle. Various methods of determining this relationship have been carried out and are described in this paper.

**Typical Records**

*Normal Record:*

When electrodes consisting of pointed rods 1 mm. in diameter (insulated everywhere except at the conical tip) are passed through the left ventricular wall as shown in Fig. 1 A, an increase in impedance occurs when blood is expelled and a decrease accompanies filling. Fig. 1 B illustrates the magnitude of the change in impedance. The ECG is included to indicate the temporal relationship of impedance change in the cardiac cycle.

*Atrial Fibrillation:*

The dynamic response of the impedance method to indicate changes in

![Diagram of heart with electrodes and impedance readings](image)

Fig. 1. A. Location of electrodes for measurement of stroke-volume by the impedance method.
B. Typical record of impedance change during emptying and filling of the left ventricle.
stroke-volume is dramatically illustrated by Fig. 2. In this illustration are shown left ventricular pressure, impedance and the ECG. In the first half of the record, the atria are fibrillating coarsely as verified by the absence of P waves in the ECG. At the middle of the record the fibrillation spontaneously ceased and on the right hand side of the record are shown the same 3 events with the pacemaker driving the ventricles.

Conspicuous in the first half of the record is the ventricular tachycardia characteristic of atrial fibrillation. Ventricular pressure and stroke-volume are very irregular. Some beats produce only a small systolic discharge from the heart. After cessation of atrial fibrillation, the stroke-volume is seen to increase immediately and on the top of the impedance record can be seen the contribution to ventricular volume by atrial systole. Comparing equal time periods of the latter portion of the record with the former, it is seen that the heart rate decreased by 40% and the cardiac output increased by 75%.

**Pressure-Volume Diagrams**:

A practical use for the impedance-volume signal is in the construction of pressure-volume diagrams, one of which is displayed in Fig. 3. In this illustration left ventricular pressure is displayed on the vertical axis and volume on the horizontal axis. This diagram is plotted to show increasing pressure as an upward deflection and decreasing volume is displayed to the left.

The cardiac cycle starts in the lower right hand corner of the diagram. The small projection at this point is the contribution of the left atrium to ventricular filling. After atrial systole, ventricular systole begins. Ventricular pressure rises with almost no decrease in ventricular volume. Then the aortic valve opens and ejection begins. Pressure at first rises and despite the
Fig. 3. Pressure-volume diagram of the left ventricle recorded by the impedance method. Increasing pressure is shown upward, decreasing volume is displayed to the left. The cardiac cycle starts in the lower right hand corner of the diagram. The small projection at this point is the contribution of the left atrium to ventricular filling. After atrial systole, ventricular systole begins. Ventricular pressure rises with almost no decrease in ventricular volume. Then the aortic valve opens and ejection begins. Pressure at first rises and despite the diminution in ventricular volume, continues to rise and then falls until the small loop in the upper left hand corner of the diagram is reached. This loop is a transient produced by closure of the aortic valve. After closure, the pressure drops and at the lower left hand corner of the diagram the mitral valve opens and the ventricular volume increases as shown.

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**Calibration Techniques**

Calibration of the impedance change in terms of volume of blood ejected per beat can be performed in many ways. The techniques which are used to measure cardiac output (Fick and indicator-dilution) can be employed to calculate minute volume which when divided by heart rate gives stroke-volume. A calibrated flowmeter placed in the aorta will also indicate stroke-volume (less coronary flow). Both of these techniques will be employed in the future. To date several other methods for calibration have been studied. Static impedance-volume studies using saline have been investigated on calcium-arrested hearts. Static impedance-volume calibrations on excised hearts and dynamic in-vivo calibrations have been made using blood. A description of each of these 3 methods is presented in the following sections.

*Static Impedance-Volume Calibrations on Calcium-Arrested Hearts:*

It has been shown that in the normal canine heart, the ejection of blood is produced largely by a decrease in ventricular diameter; the apex-base
length remains relatively constant. To further investigate this phenomenon, a series of studies was carried out in which the volume-impedance relationships were determined on the ventricles of dogs of similar size and weight. By intravenous infusion of differing amounts of calcium chloride solution, the ventricles were arrested in varying degrees of systole. In some animals ventricular fibrillation was employed to stop the hearts. As soon as cardiac arrest occurred, the ventricles were filled with plaster of Paris. After hardening, the casts were removed and measured (Fig. 4A). After obtaining the apex-base and diameter measurements, latex molds were made from the casts. The molds were then cured and stripped off. Electrodes were inserted in the same location employed for cardiac impedance measurements. The molds were filled with saline and the volumes and impedances were measured (Fig. 4B).

![Figure 4 A. Left ventricular casts.](image)

**Fig. 4 A.** Left ventricular casts.

**Fig. 4 B.** Impedance-volume characteristics of saline-filled molds of left ventricles.

Measurement of the apex-base lengths and the diameters of the casts revealed that the major decrease in dimension was across the diameter, which amounted to some 45%. The apex-base length decreased by only 20%. If under dynamic conditions the apex-base dimension decreases, the impedance increase will be diminished almost in direct proportion to the percentage decrease of this dimension.

The impedance-volume data of the saline-filled molds is shown in Fig. 4B. The mean slope of the points indicates a coefficient of 5.1 ohms change per ml. of saline. If the solution had been blood, one might expect a calibration factor of 11.2 ohms change in impedance per ml. of blood ejected.
based on the ratio of the resistivities of blood and saline corrected to body temperature.

Static Impedance-Volume Calibrations on Excised Hearts:

To investigate the relationship between impedance and volume of blood in the left ventricle by another method, the hearts of many of the experimental animals were excised. A loose ligature was placed around the A-V groove and a catheter was inserted into the left ventricle via the aorta. A tight ligature around the aorta prevented leakage of blood during the volume-impedance measurements. The catheter was connected to a 50 ml. syringe. Blood was forced into the ventricle until it was completely filled. When this occurred the A-V ligature was tightened. The impedance was then measured as blood was withdrawn in increments employing the standard base-apex electrodes.

All of the data from animals of differing size were plotted on the same graph after conversion to impedance ratios; the impedance of each full ventricle being taken as 1.0. The data obtained on small and large dogs are shown in Fig. 5 ABC. It is to be noted that the increase in impedance is relatively linear as blood is passively withdrawn from the ventricle. When the ventricle becomes nearly empty the impedance increases considerably. The curves for large dogs (B, C) and small dogs (A) are essentially similar in contour; the difference is due to the volume necessary to empty the ventricle. The coefficients calculated from the linear portion of these curves vary between 0.6 and 2.6 ohms change in impedance per ml. of blood withdrawn. As will be obvious later, this method does not produce calibration factors in agreement with other methods of calibration.
This particular method of measuring the change in impedance with various volumes of blood in the ventricles did, however, permit an analysis of the importance of the frequency of alternating current. Fig. 5 curve B illustrates that the increase in impedance when blood was withdrawn was essentially the same at 20, 50, 100 and 200 kilocycles, indicating that in this range the choice of frequency is relatively unimportant. The circuit between the electrodes in this frequency range was essentially resistive; the phase angle between the voltage and current varied between 4 and 16 degrees.

*In-Vivo Calibration:*

An in-vivo method of calibration was carried out by catheterizing the left ventricle via the left carotid artery and adding or withdrawing blood when the heart was stopped by vagal stimulation. When blood was added by a syringe connected to the catheter, the aorta was clamped tightly around the catheter. When blood was withdrawn, the mitral valve was forced closed by thrusting the left atrium into the orifice. Impedance changes were measured for 1, 2, 5, and 10 ml. of blood volume changes. This technique permitted measuring the impedance-volume relationships determined around the existing diastolic size of the heart.

The data obtained in this manner in five 15 Kg. dogs are shown in Table I. From this table, in which the results of 134 trials are shown, an average calibration factor of 6.62 ohms per ml. of blood was attained. While the range of variation is appreciable, the dogs were only of the same weight, not of the same size.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Trials</th>
<th>Ohms/ml.</th>
<th>Heart Rate</th>
<th>Stroke Volume (ml.)</th>
<th>Cardiac Output L./min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>10.0</td>
<td>187</td>
<td>10.3</td>
<td>1.99</td>
</tr>
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<td>2</td>
<td>8</td>
<td>5.40</td>
<td>240</td>
<td>12.4</td>
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<td>3</td>
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<td>160</td>
<td>23.0</td>
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<tr>
<td>5</td>
<td>96</td>
<td>4.24</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>134</td>
<td>Av. 6.62</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table I. shows the stroke-volumes derived from the change in impedance as blood was added or withdrawn. Cardiac output, as calculated from the product of stroke-volume and heart rate, is shown on the right. The values are similar to those found in anesthetized dogs of this size by other methods.38)
DISCUSSION OF CALIBRATION METHODS

Three methods for calibrating the ventricular volume-impedance relationship yielded calibration factors of 11.2, 0.6–2.6 and 6.62 ohms change per ml. of blood ejected from the left ventricle. Of the 3 methods, the calibration factor obtained by the in-vivo technique of injecting and withdrawing blood from the left ventricle when it was arrested at its diastolic size is believed to be the most accurate. The cardiac outputs calculated by the product of stroke-volume and heart rate are in good agreement with those values expected for the size and state of the animals studied. The calibration factors obtained on excised hearts are quite different from the values derived from the in-vivo method. The difference is probably due to the fact that in the excised heart, the shape of the ventricle with different volumes is not that which obtains during systole and diastole.

Accurate calibration of the impedance method requires measurement of cardiac outputs obtained under stable conditions using the standard Fick and dye-indicator methods. In addition dynamic calibration requires the use of an aortic blood flowmeter. The use of these techniques will be reported in the future.

APPENDIX

The instantaneous response of the heart to imposed work loads can only be obtained from the simultaneous pressure and volume-time changes which occur during individual heart beats. High fidelity ventricular pressure-time records are easily obtained. It is however much more difficult to obtain ventricular volume changes which are the measure of cardiac output designated as stroke-volume. Over the last century, many ingenious methods have been developed for the measurement of stroke-volume. With only a few has it been possible to obtain true temporal changes in this parameter. The earliest method employed the pericardium as a cardiometer.39) Shortly thereafter cardiometers made of rubber or glass were employed.12),43) The pressure changes within them, reflecting volume changes in the ventricles, were recorded on a smoked surface. Changes in ventricular diameter, the square of which reflects stroke-volume, have been recorded by tambours,5) by inductance gauges30),31) ultra-sound,33) and by the x-ray visualization of metal markers applied to the ventricular walls.29) Volume changes as reflected by changes in cardiac circumference have been recorded by mercury-in-rubber strain gauges.21),32) Changes in circumference and length have been simultaneously recorded by use of an electronic caliper and a circum-
ferential strain gauge to compute stroke-volume. Changes in the size of the x-ray shadow of the heart, as well as variations in the intensity of an x-ray beam traversing the heart have also been employed to record stroke-volume. The dilution method has been adopted to compute stroke-volume by injection of an indicator into the left or right ventricle and recording the beat-by-beat concentration in the aorta or pulmonary artery, making use of saline, cold saline, dyes and radioisotopes. More recently, attempts have been made to quantitate the trans-thoracic cardiac impedance changes in terms of stroke-volume.

The technique of indicating ventricular volume changes electrically was first described by Cremer who, in 1907 placed a frog heart between the plates of a condenser and recorded the changes in charging and discharging current with a source of direct current applied to the plates. Rappoport and Ray recorded the volume changes of a tortoise ventricle by measuring impedance changes at 200–300 cps, the blood in the heart constituting one electrode while the heart and the other electrode were submerged in a beaker of saline. In the mammal, Rushmer et al. affixed electrodes to the interior walls of the left and right ventricles of dogs and recorded the impedance changes during cardiac activity. Although the recordings resembled those obtained with cardiometers, their studies indicated that the method involved variables which were difficult to quantify. The studies with this method, which were the subject of this paper, indicate that with the newly designed electrodes, the method is practical and is capable of calibration and possesses characteristics which permit the continuous measurement of stroke-volume of the right and left ventricles in the anesthetized and unanesthetized experimental animal.

References