Evaluation of Mitral Insufficiency in Dogs by Electronic Analog Simulation of Radioisotope Dilution Data

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Left atrial and left ventricular volumes, regurgitant flows and systolic efficiencies have been calculated for dogs with and without mitral valve insufficiency, using a technic of electric analog simulation of radioisotope dilution data. Amounts of blood between the valve of the pulmonary artery and the left atrium were calculated by use of mean transit time and flow, and compared to those of the analog. It is concluded that the analog technic is practical and will be more useful when data is available on flow patterns in the pulmonary bed.

The study to be described is concerned with electronic analog simulation of radioisotope dilution data obtained from the cardiopulmonary circulation in dogs; the objective being evaluation of mitral valve insufficiency and measurement of left ventricular systolic ejection efficiency.

Considerable attention has been focused on the development of hydraulic formulas for calculation of the dimensions of heart valve lesions from catheterization pressures. Gorlin and Gorlin\(^1\) and Gorlin and Dexter\(^2\) applied their theoretical considerations on constant flow to blood flow which is pulsatile. McDonald\(^3\) has investigated the relation of pulsatile pressure to flow in arteries, while Burger, van Brummelen and Dannenburg\(^4\) developed descriptive equations for pulsatile flow through constriction. Solution of these hydraulic formulas require, in addition to a knowledge of pressure differences across the orifice in question, that either the flow rates through the orifice or the area of the orifice be known. Experimental determination of these values in the intact animal or in man is difficult.

Korner and Shillingford\(^5\) have estimated valvular incompetence from indicator-dilution curves obtained both in hydraulic models and in man. They regarded the indicator-dilution curves as frequency distribution curves, and by means of empirical regression equations were able to express the variance in terms of flow and volume between injection and sampling sites. Model backflows calculated by their equations agreed within 11 per cent with the backflow values registered by a Pitot flowmeter. Ideally, however, in patients a set of equations should be derived for each set of curves obtained.

In the present analysis of concentration time data a tracer substance was injected into the right venous system and the time-passage of this material past two appropriate and accessible points in the cardiopulmonary circulation was observed. Volume and flow rates were obtained by postulating a simple circulatory model in which the lungs, left atrium and left ventricle are represented by mixing pools. It would appear reasonable to represent the left atrium and left ventricle as single mixing pools in which uniform mixing is achieved in less than 1 sec. However, it was recognized at the outset of this study that a single mixing pool probably would not adequately represent the characteristics of the lung. Justification for using such an analog in the calculation of left heart volumes and outputs rests on the premise that the concentration-time pulse entering the lung analog would be distorted, with respect to time delay.
and dispersion, approximately in the same way in which it is distorted in the lungs of the experimental animal.

**MATERIALS AND METHODS**

Mongrel dogs, 7 to 20 Kg., were anesthetized with sodium pentobarbital (approximately 30 mg./Kg.) and heparinized (approximately 5 mg./Kg.). Following left thoracotomy, polyethylene sampling catheters were inserted in the pulmonary artery via the right ventricle, and into the left atrium. Generally two successive injections of human serum albumin labeled with $^{131}I$ were performed on each animal. For the first injection approximately 2 $\mu$C of $^{131}I$ human serum albumin/Kg. were carefully measured into a 1 ml. syringe fitted with a 21-gage needle. The radioactivity of syringe and needle was counted before injection by means of a suitably shielded sodium iodide scintillation crystal connected to a scaler. The radioactivity remaining in the syringe and needle after injection was counted, and the difference between the two readings used as a measurement of $^{131}I$ (HSA) injected. Since the radioactivity of the blood was substantially raised after the first experiment, the amount of isotope injected for the second experiment was doubled in order to achieve a good "signal-to-background ratio." Injection of $^{131}I$ was always made in less than 1 sec.

After injection, samples of blood were withdrawn simultaneously at 1 sec. intervals by means of two automatic pipetting machines, adjusted to deliver 0.5 ml. into a sample vial each second. Usually some 60 consecutive samples were withdrawn through each sampling catheter, followed by equilibrium samples taken at 3, 5 and 10 min. intervals after injection. The automatic pipetting machines were calibrated so that the first sample collected in the first vial corresponded to a sample in the blood stream at the sampling catheter tip 1 sec. after injection. Since approximately 100 ml. of blood were withdrawn during sampling, original blood volume was restored between injections by transfusing either whole blood or a 6 per cent dextran solution in isotonic sodium chloride.

After samples were collected from the "normal" dogs and original blood volume restored, some of the chordae tendineae of the mitral valve were cut by means of a small buttonhook knife inserted through an incision in the left ventricular wall. A subsequent set of samples was then collected from the mitrally insufficient animal.

The collected samples were counted individually in a well-type scintillation counter and their activities plotted against time. Figure 1 shows a representative set of activity-time curves for both the pulmonary artery and left atrium of a "normal" dog. Generally, in animals made mitrally insufficient, the peak of activity for the left atrium curve was relatively lower, broader and displaced in time.

**DATA ANALYSIS**

The two models found to be appropriate and compatible with existing computer facilities are diagrammed in figure 2. In model 1, lungs, left atrium and left ventricle are represented by mixing pools $A$, $B$, and $C$; $f(t)$ represents the pulse of activity entering the lung mixing pool, and its size and shape described by the activity-time curve obtained from the pulmonary artery. Rate constants between mixing pools are represented by $k_1$, $k_2$, $k_3$, and $k_4$, expressed in reciprocal seconds. Rate constant $k_5$ represents the 0.5 ml./sec. drain-off from

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*Bremer Automatic Pipetting Machine, Model 120, Baltimore Biological Laboratory, Inc., Baltimore, Md.

†Polyethylene medical tubing, PE 205, I.D. 0.062 and O.D. 0.082.
the left atrium by the automatic pipetting machine.

Model 2 shows an additional parallel pulmonary circuit mixing pool. The incoming pulse of radioactivity is split as it enters these parallel pools. This division of \( f(t) \) is represented in the model by \( f_1(t) \) and \( f_2(t) \). The change in amounts of activity with time in each mixing pool can be represented by a differential equation. Thus, for model 1 the following equations can be written:

\[
\begin{align*}
\frac{dA}{dt} &= f(t) - k_A A \\
\frac{dB}{dt} &= k_A A + k_C C - k_B B \\
\frac{dC}{dt} &= k_B B - k_C C \\
\end{align*}
\]

And similarly for model 2, but including the effect of the \( D \) mixing pool:

\[
\begin{align*}
\frac{dA}{dt} &= f_1(t) - k_A A \\
\frac{dB}{dt} &= k_A A + k_D D + k_C C - k_B B - k_D D \\
\frac{dC}{dt} &= k_B B - k_C C \\
\frac{dD}{dt} &= f_2(t) - k_D D
\end{align*}
\]

If the mathematical form of pulmonary artery and left atrium curves could be determined, it would be possible by analytic means to completely characterize the system in terms of rate constants and chamber volumes. In lieu of a sufficiently accurate mathematical characterization of these data curves, it was necessary to solve the differential equations of models 1 and 2 with an electronic analog computer. Both models 1 and 2 were programmed on a Reeves Electronic Analog Computer, Model C-302, in which each mixing pool is represented by an integrating amplifier and each rate constant by a potentiometer setting. The input function, \( f(t) \), is fed into the computer by means of a curve follower which traces the actual pulmonary artery data curve (drawn on coordinate paper with silver conducting ink), and thus transforms curve amplitude into corresponding voltages. In this way, the input function, \( f(t) \), is generated.

The computer \( k \) valves are adjusted until the computer curve for the \( B \) mixing pool duplicates the experimental data curve obtained from the left atrium. A representative match of computer and data curves is shown in figure 3. Variations in \( k \) values of 5 per cent significantly affect the match of computer curve with experimental curve.

Rate constants are read directly from the computer potentiometer settings, or if a time factor has been introduced, they are multiplied by the appropriate constant. The cardiac output can be calculated from the pulmonary artery activity-time curve, using the Stewart principle and the well-known Hamilton equation:

\[
F = Q \int_0^t C dt,
\]

where \( F \) = flow rate, \( Q \) = amount of tracer injected, \( C \) = instantaneous concentration of tracer substance and \( t \) = time for all the injected tracer to pass the sampling point without recirculation.

For model 1, the cardiac output, expressed in ml./sec, is calculated by the equation,

\[
F = k_A A' + k_B B' = k_C C + k_B B'
\]

where \( A' \), \( B' \), and \( C \) represent the volumes in milliliters of each mixing pool. Knowing rate constants and cardiac output, mixing pool volumes can be calculated.

Similarly, for model 2, the cardiac output, expressed in ml./sec, may be equated to the net forward flow in all parts of the model.

\[
F = aF + dF = k_A A' + k_D D' = k_C C' + k_B B' + k_D D'
\]

where \( a \) and \( d \) are the proportions of the total flow, \( F \), entering mixing volumes \( A' \) and \( D' \) respectively. Since the values of \( a \) and \( d \) are known from computer potentiometer settings, it is also possible to calculate mixing pool volumes for model 2 and by the use of equation 3.

**RESULTS AND SIGNIFICANCE**

The data from 8 "normal" dogs, 6 with moderate and 2 with marked degrees of mitral

Table 1.—Left Heart Volumes and Regurgitant Flow in Dogs Calculated by Electric Analog Simulation of Radioisotope Dilution Data

<table>
<thead>
<tr>
<th>Dog type</th>
<th>Expt. no.</th>
<th>Cardiac output, (ml/sec.)</th>
<th>&quot;Pulmonary vol.&quot; (ml)</th>
<th>LA vol., (ml)</th>
<th>LV vol., (ml)</th>
<th>Regurgitant flow LV to LA (ml/sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Normal&quot;</td>
<td>7</td>
<td>31</td>
<td>49</td>
<td>33</td>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>20</td>
<td>25</td>
<td>33</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>11A</td>
<td>37</td>
<td>29</td>
<td>38</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>11B</td>
<td>20</td>
<td>25</td>
<td>17</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>15A</td>
<td>27</td>
<td>54</td>
<td>26</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>17A</td>
<td>35</td>
<td>29</td>
<td>30</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>19A</td>
<td>42</td>
<td>79</td>
<td>45</td>
<td>55</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>21A</td>
<td>41</td>
<td>71</td>
<td>40</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>Moderate degree mitral insufficiency</td>
<td>8</td>
<td>28</td>
<td>50</td>
<td>24</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>14A</td>
<td>26</td>
<td>66</td>
<td>23</td>
<td>46</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>14B</td>
<td>26</td>
<td>47</td>
<td>24†</td>
<td>40†</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>15B</td>
<td>21</td>
<td>54</td>
<td>22</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>24A</td>
<td>18</td>
<td>62</td>
<td>22</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>24B</td>
<td>18</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>15</td>
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<tr>
<td>Marked degree mitral insufficiency</td>
<td>22</td>
<td>34</td>
<td>165</td>
<td>37</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>34</td>
<td>314</td>
<td>42</td>
<td>54</td>
<td>42</td>
</tr>
</tbody>
</table>

Volumes of LA and LV measured at autopsy by hydraulic filling at atmospheric pressure were 34 ml. and 57 ml., respectively in * and 20 ml. and 48 ml., respectively in †.

Table 2.—Pulmonary Blood Volumes Calculated from Cardiac Output and Mean Transit Time Through Lungs

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>Cardiac output, (ml/sec.)</th>
<th>Time, PA to LA, (sec.)</th>
<th>Pulmonary vol., (ml)</th>
<th>Per cent of total blood volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>31</td>
<td>5.5</td>
<td>170</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>9.2</td>
<td>239</td>
<td>16</td>
</tr>
<tr>
<td>11A</td>
<td>37</td>
<td>2.1</td>
<td>115</td>
<td>10</td>
</tr>
<tr>
<td>11B</td>
<td>20</td>
<td>7.0</td>
<td>140</td>
<td>13</td>
</tr>
<tr>
<td>15A</td>
<td>27</td>
<td>9.4</td>
<td>254</td>
<td>25</td>
</tr>
<tr>
<td>17A</td>
<td>35</td>
<td>6.0</td>
<td>210</td>
<td>12</td>
</tr>
<tr>
<td>19A</td>
<td>42</td>
<td>4.7</td>
<td>197</td>
<td>13</td>
</tr>
<tr>
<td>21A</td>
<td>41</td>
<td>6.5</td>
<td>267</td>
<td>14</td>
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<tr>
<td>8</td>
<td>28</td>
<td>7.0</td>
<td>196</td>
<td>19</td>
</tr>
<tr>
<td>14A</td>
<td>26</td>
<td>9.2</td>
<td>239</td>
<td>18</td>
</tr>
<tr>
<td>14B</td>
<td>26</td>
<td>8.5</td>
<td>226</td>
<td>17</td>
</tr>
<tr>
<td>15B</td>
<td>21</td>
<td>9.0</td>
<td>180</td>
<td>15</td>
</tr>
<tr>
<td>24A</td>
<td>18</td>
<td>7.0</td>
<td>126</td>
<td>12</td>
</tr>
<tr>
<td>24B</td>
<td>18</td>
<td>6.4</td>
<td>115</td>
<td>10</td>
</tr>
<tr>
<td>22</td>
<td>34</td>
<td>5.0</td>
<td>170</td>
<td>14</td>
</tr>
<tr>
<td>23</td>
<td>34</td>
<td>9.0</td>
<td>306</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 3.—Left Ventricle Systolic Ejection Efficiencies in Dogs with Mitral Valve Insufficiency

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>LV diastolic vol., (ml)</th>
<th>Stroke vol. LV, (ml/sec.)</th>
<th>Per Cent efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>50</td>
<td>32</td>
<td>65</td>
</tr>
<tr>
<td>22</td>
<td>45</td>
<td>37</td>
<td>84</td>
</tr>
<tr>
<td>23</td>
<td>54</td>
<td>38</td>
<td>70</td>
</tr>
<tr>
<td>24A</td>
<td>18</td>
<td>13</td>
<td>72</td>
</tr>
<tr>
<td>24B</td>
<td>18</td>
<td>13</td>
<td>72</td>
</tr>
</tbody>
</table>

valve insufficiency, have been analyzed in this way. The data and analytic results of 16 experiments appear in table 1.

With increasing degree of mitral insufficiency, as determined by the number and position of chordae tendineae severed, there was an increase in the calculated reverse flow from left ventricle to left atrium. However "normal" dogs also showed a small and fairly constant measure of reverse flow. The left atrium data curve of dogs indicating reverse flow rates from 42 to 54 ml/sec. could not be "matched" with model 1. It was necessary to use model 2 in order to effect a good match.
Left atrium curves from dogs with intermediate degrees of mitral valve insufficiency (i.e., 11 to 37 ml./sec. reverse flow) could be matched by using model 1.

Using the method of Hamilton, Moore, Kinsman and Spurring, the peak times for both pulmonary artery and left atrium activity-time curves were corrected by determining the center of gravity for the areas under each of the extrapolated curves. The difference between these corrected time coordinates was taken as the blood transit time through the lungs of dogs in which mitral valve insufficiency had not been induced. Pulmonary blood volume was calculated by multiplying transit time by cardiac output, and these values for 16 dogs are listed in abridged form in table 2. These values are slightly high since distal sampling was from the left atrium rather than from a pulmonary vein.

By obtaining heart rates from simultaneous electrocardiogram tracings, left ventricle stroke volume could be calculated from previous data. Left ventricle systolic ejection efficiency was calculated by dividing the stroke volume by the computer-calculated diastolic volume of the left ventricle. These calculations are presented in table 3 for 5 experiments.

DISCUSSION

It may be seen from table 2 that pulmonary blood volumes calculated from the computer analog by means of equation 2 are very much smaller than those calculated independently from the mean pulmonary transit time and the cardiac output. This observation in itself is sufficient to confirm the belief that the lung is not adequately represented by a simple mixing pool analog. From anatomic considerations the lung might be expected to behave more like a pipe in its effect on the pulse of activity passing through it, inasmuch as laminar (nonturbulent) flow would obtain in the capillaries of the pulmonary bed. Indeed, flow calculations for the pulmonary artery as it leaves the right ventricle show a Reynolds number under 2000—the transition region between laminar and turbulent flow.

Though the lung analog is inadequate, the time delay and dispersion suffered by the incoming signal as it "passes through the lung mixing pool" are probably close to the distortion actually imposed by the lungs, for the following reasons:

Data analysis yields left heart volumes which are reasonable for dogs, and which checked closely in two instances with volumes measured at atmospheric pressure at autopsy by hydraulic filling (table 1).

The computer analysis is sufficiently sensitive to require a constant regurgitant flow from left ventricle to left atrium of approximately 2 ml./sec., or approximately 1 ml./systole, in "normal" dogs. When the mechanical functioning of the mitral valve is considered it would appear logical to expect a small amount of reflux during the phase of increasing left ventricle pressure and mitral valve closing.

Computer-calculated regurgitant flow rates in animals made mitrally insufficient are grossly of the order of magnitude one would expect from the amount of damage done to the mitral valve leaflets.

For these reasons it is believed that the analog computer analysis used in this study has given values for left heart volumes and regurgitant flows which probably are valid. More complete analysis must await data on concentration of tracer in various parts of the lungs and availability of additional computer facilities so that a more exact lung analog can be employed. Agreement of computer-calculated lung volumes with the lung volumes calculated independently from cardiac output and mean blood transit time through the lungs will eventually be used as one of the criteria for correctness of the lung analog.

SUMMARY

Values for left heart volumes and regurgitant flow through the mitral valve have been calculated for 8 dogs with induced mitral valve insufficiency and for 8 dogs without mitral valve insufficiency, using a technic of
electric analog simulation of radioisotope dilution data. Dogs without mitral valve insufficiency and with cardiac outputs ranging from 20 to 42 ml./sec. showed calculated regurgitant flows from left ventricle to left atrium varying from 2 to 4 ml./sec. Dogs with a moderate degree of mitral valve insufficiency and with cardiac outputs ranging from 18 to 28 ml./sec. had calculated regurgitant flows from 11 to 37 ml./sec. Two dogs with a marked degree of mitral valve insufficiency and with cardiac outputs of 34 ml./sec. showed regurgitant flows of 42 and 54 ml./sec. Full evaluation of the validity of the analysis must await development of a more exact lung analog.

In 5 instances left ventricle systolic ejection efficiencies have been calculated: these varied from 65 to 84 per cent. Pulmonary blood volumes in dogs with and without mitral valve insufficiency have been calculated from the mean transit time through the lungs and the cardiac output. Average pulmonary blood volume was approximately 14 per cent of total blood volume.

**Summario in Interlingua**

Valores de volumines sinistro-cardiac e de fluxos regurgitante per le valvula mitral esseva calculate pro canes con inducite insufficiencia de valvula mitral e in octo canes sin insufficiencia de valvula mitral, con le uso de un technica de simulation per computator analoge electronic de datos de dilution radioisotropic. Canes sin insufficiencia de valvula mitral e con rendimentos cardiac de inter 20 e 42 ml per secunda monstrava calculate fluxos regurgitante ab le ventriculo sinistre al atrio sinistre de inter 2 e 4 ml per secunda. Canes con moderate grados de insufficiencia del valvula mitral e con rendimentos cardiac de inter 18 e 28 ml per secunda habeva calculate fluxos regurgitante de inter 11 e 37 ml per secunda. Duo canes con marcate grados de insufficiencia de valvula mitral e con rendimentos cardiac de 34 ml per secunda monstrava fluxos regurgitante de 42 e 54 ml per secunda. Le complete evaluation del validitate del analyse debe attender le disveloppaniento de un plus exacte analogo del pulmon.

In 5 casos le efficacia systolo-ejectori del ventriculo sinistre esseva calculate. Le resultatos variava ab 65 usque a 84 pro cento. Volu- mines de sanguine pulmone in canes con e sin insufficiencia del valvula mitral esseva calculate super le base del valor medie del tempo- re de transito pulmone e del rendimento cardiac. Le volumine medie del sanguine pulmone esseva approximativamente 14 pro cento del volumine de sanguine total.

**REFERENCES**

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