The Extraction of Thallium-201 by the Myocardium

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SUMMARY The concentration of thallium-201 in the myocardium immediately following injection of tracer is the result of both blood flow delivering tracer to the heart and extraction by the myocardium. In these studies, the extraction of thallium-201 by the canine myocardium was determined as a function of heart rate, coronary blood flow, hypoxia, changes in pH, and following administration of propranolol, insulin, and strontphan. Under basal conditions, extraction fraction measured 88 ± 2.1%, following pacing to a rate of 195 beats/min extraction fraction remained unchanged at 88.5%. Similar results were found with changes in pH, propranolol, insulin, and strontphan. Hypoxia caused a significant decrease in extraction fraction to 77.9%. When coronary blood flow was increased in excess of demands by drugs, extraction fraction fell logarithmically.

THALLIUM-201 has been advocated for evaluation of regional myocardial perfusion and regional myocardial perfusion reserve in patients with suspected myocardial ischemia. However, it is frequently difficult to evaluate the small changes in regional myocardial tracer concentration by visual inspection when images are performed following injection of tracer at rest and following injection at maximum stress, due to changes in the concentration of thallium in the myocardium relative to that in the lungs. These problems have led to attempts at quantification of regional thallium concentration and complex efforts at determining the lung background to arrive at the net thallium concentration in the myocardium. An assumption implicit in all these studies is that the extraction of thallium by the myocardium remains constant. To determine if the extraction of thallium by the myocardium remains unchanged, these experiments were undertaken measuring the extraction fraction of the myocardium for thallium-201 during the initial transit of tracer through the heart using a dual tracer technique.

Materials and Methods

The double tracer method employs a mixture of two tracers: one a nonextractable reference or indicator such as I-125 — albumin and the other a test substance such as TI-201. A small quantity of this mixture is injected into the left atrium and a blood sample is taken from the venous effluent after a small pass of the bolus through the organ. The concentration of the indicator (I) and the test tracer (TI) is measured in the arterial bolus (a) and the venous sample (v). The extraction fraction is given by the formula:

\[
EF = \left[ \frac{I - \frac{TI}{a}}{\frac{TI}{v}} \right] \times 100\% \tag{1}
\]

Tracers

Thallium-201 in the form of ionic thallous chloride was obtained as a sterile, pyrogen-free radiopharmaceutical from E. R. Squibb & Sons, New Jersey. The iodinated albumin was tested by chromatography prior to use and at least 95% of the activity was protein-bound.

Various concentrations of the indicator and test tracer in the isotopic mixture were evaluated. It was found that a concentration ratio of 1:4 I\textsubscript{125}-albumin to TI\textsuperscript{201} enabled us to make at least five measurements in the same dog without having an excessively high background of I\textsubscript{125}-albumin in the blood or, on the other hand, excessive TI\textsuperscript{201} counts appearing in the I\textsubscript{125} window. The isotopic mixture containing 3\textsubscript{a}Ci I\textsubscript{125}-albumin and 12\textsubscript{a}Ci TI\textsuperscript{201} per ml was agitated by both mechanical and ultrasonic means in a vial to ensure adequate mixing. The initial volume injection was 0.4 ml and subsequently 0.4, 0.8, 1.2 and 2.0 ml were administered.

The samples were counted in a 5\textdegree diameter Na I scintillation counter as follows: Thallium-201 at a baseline of 130 keV and upper level of 180 keV; Iodine-125 at a baseline of 25 keV and an upper level of 35 keV. Standards of each tracer were counted in each window and appropriate ratio corrections were made for the activity from the higher energy TI\textsuperscript{201} appearing in the lower energy I-125 window. Less than 25% of the counts in the iodine window were due to thallium photons.

Animal Preparation

Adult mongrel dogs weighing 20 to 40 kg were anesthetized with 30–35 mg/kg intravenous sodium pentobarbital, intubated and placed on a Harvard pump-respirator. The heart was exposed through a left lateral thoracotomy in the fourth interspace and the pericardium was incised and retracted. A 2mm diameter polyethylene catheter was introduced in the coronary sinus in such a way that no obstruction to coronary sinus flow occurred. The proximal left circumflex artery was dissected and an electromagnetic flow-meter probe (Biotronix) placed around the artery to record changes in coronary blood flow. A catheter was positioned in the left atrium for injection of the tracers and for measuring pressures. The heart was paced (Grass stimulator) by wires attached to the left atrial appendage. Pressures were recorded with a Statham DB 20 strain gauge and a Honeywell multichannel recorder. Catheters for recording pressures, drawing blood samples and administering of fluids or drugs were positioned in the superior vena cava, inferior vena cava, ascending aorta and abdominal aorta. Blood gas and pH determinations were made with an International Electronics Blood Gas Analyzer.
**Method**

**Determination of the Normal Extraction Fraction**

Twenty dogs were paced at heart rates of approximately 160 beats per minute while the ECG and aortic pressures were monitored. Prior to each measurement of extraction fraction, an arterial blood sample was taken to determine blood gases and background activity. Aortic pressure and coronary flow were measured at the time of tracer injection. The isotopic bolus (both tracers) was injected into the left atrium and at the same time withdrawal of blood from the coronary sinus was initiated, at a constant rate of approximately 1 ml per second. Each consecutive sample was taken for 5 seconds and the total withdrawal time for 5 samples was 25 seconds. The experiment was repeated after 20 minutes and care was taken to maintain the dogs in a stable condition over this period.

Blood samples were weighed and counted in a scintillation counter. From each 5 sec blood sample collected from the coronary sinus an instantaneous extraction fraction was calculated using equation 1. To obtain a mean extraction fraction for the bolus, the instantaneous extraction fractions were weighted according to the concentration of indicator over that time interval. The extraction fraction was calculated over the intervals from first appearance through the sample to where indicator concentration decreased to one-third of peak concentration.

**Effect of Heart Rate**

The sinoatrial node of eight dogs was crushed and the hearts paced at a mean rate of 106 beats per minute. The extraction fraction was measured as described. The hearts were then paced at a mean value of 195 beats per minute for 20 minutes and a second determination of extraction fraction was done.

**Effect of Acid-Base Balance**

The extraction fraction of thallium was measured in six dogs under control condition. Alkalosis was induced in three of these dogs by infusing 500 ml 2.1% NaHCO₃ over 1 hour while the dogs were being hyperventilated at a rate of 50 cycles per minute. During the ensuing alkalosis, two more measurements of extraction fraction were done at 20 minute intervals.

In the remaining three dogs, acidosis was induced by infusing 1000 ml 0.5% NH₄Cl over one hour and ventilation at 15 cycles per minute. Two measurements of thallium extraction fraction were done at 20 minute intervals during this acidic state.

**Effect of Changes in Coronary Blood Flow**

Thallium extraction fraction was evaluated in eight dogs in a control condition. In each of these eight dogs, coronary blood flow was then increased by one of the following methods: reactive hyperemia following occlusion for 15 seconds; adenosine 2 mg per kg i.v.; Minoxidil 1.3 mg per kg i.v.; Minoxidil 1.3 mg per kg plus angiotensin i.v.; Minoxidil 1.3 mg per kg plus angiotensin plus snare around the aorta. During the resulting period of increased coronary blood flow a second determination of extraction fraction was done at the time of peak increase in blood flow.

**Effect of Hypoxia**

Following a control measurement of thallium extraction fraction in five dogs, the animals were ventilated for 30 minutes on a gas mixture containing 5% O₂ and 95% N₂ and the extraction fraction measurements repeated. The dogs were allowed to recover while being ventilated for 1 hr on normal air and final measurements of extraction fraction made.

**Effect of Insulin**

Thallium extraction fraction was measured in five dogs under control conditions. At the same time, measurement of aortic pressure, coronary blood flow, blood gases, and serum electrolytes were done. Heart rate was kept constant for each dog by atrial pacing.

Plain insulin was now infused at a constant rate of between 15 and 20 I.U./hr/100 lb body weight. During this infusion, the blood sugar was kept above 150 mg% by the infusion of 50% dextrose solution when necessary. After 45 minutes of insulin infusion, all the measurements were repeated.

**Effect of Propranolol**

Following control measurement of thallium extraction fraction in seven dogs, an intravenous injection of between 0.22 and 1.02 mg propranolol per kg dog weight was given and 15 minutes later the thallium extraction fraction was determined.

**Effect of Ast. Strophantidine**

In six dogs, extraction fraction was measured under control conditions. Ast. Strophantidine was administered intravenously at a dose of 20 µg per kg and extraction fraction done after 4 minutes and again after 19 minutes. At the same time, the measurements of heart rate, mean blood pressure, serum K and coronary blood flow were recorded.

**Results**

**Extraction Fraction**

In 20 dogs, the mean extraction fraction of thallium-201 by the heart under basal anesthetized conditions were found to be 88.1% with a standard deviation of 2.1%. The mean heart rate of these dogs were 161 beats per minute; blood pressures and blood gases were normal.

**The Effect of Changes in Heart Rate**

The mean extraction fraction in eight dogs with crushed coronary sinuses paced at a heart rate of 106 beats per minute was 86.8% (sd = 4.48). When these dogs were paced at a heart rate of 195 beats per minute, the extraction fraction was 88.5% (sp = 3.58). The results are summarized in table 1. During this accelerated heart beat the mean coronary flow increased by 84% and the mean rate-pressure products by 86% over the control values. The increase in extraction fraction was not statistically significant.
TABLE 1. The Effect of Heart Rate on the Extraction Fraction of Thallium-201 by the Myocardium

<table>
<thead>
<tr>
<th>Dog</th>
<th>Slow Heart Rate bpm</th>
<th>EF</th>
<th>Fast Heart Rate bpm</th>
<th>% change in coronary flow</th>
<th>% change in rate x pressure</th>
<th>EF</th>
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<tr>
<td>1</td>
<td>117</td>
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<td>198</td>
<td>29</td>
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<td>110</td>
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<td>80</td>
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<td>83.4</td>
<td>200</td>
<td>101</td>
<td>18</td>
<td>85.5</td>
</tr>
</tbody>
</table>
| Mean| 106                 | 86.8| 195                 | 88%                      | 84%                         | 88.5| ± 3.56

Abbreviations: bpm = beats/min; EF = ejection fraction.

The Effect of Acid-Base Balance

The mean extraction fraction in six dogs under control conditions, pH of 7.41 ± 0.07 was 87.5% ± 4.5%. After acidosis had been induced, the extraction fraction came down to a mean value of 78.8% (two determinations for both animals) (pH = 7.02). (P < 0.01, different from control paired t test), while after alkalosis, the extraction fraction remained at 87.6% (pH = 7.80) (NS).

Effect of Coronary Flow

Sixteen measurements of extraction fraction were performed in eight dogs where the coronary flow was increased in excess of the myocardial needs (fig. 1). The mean rate-pressure product was increased by only 8%. In all dogs, the extraction fraction decreased with an increase in coronary flow. This relationship is given by the formula:

EF = 87.04 - 39.10 log coronary flow

where the coronary flow under control basal conditions are taken as one (r = 0.91).

The Effect of Hypoxia

The mean control extraction fraction was 88.6% in these five dogs. After ventilation on a 5% O₂ mixture for 30 min, the mean pO₂ was reduced from 120 to 30, the extraction fraction was reduced to 77.9% (P < 0.005 Student's t-test) and mean coronary flow increased by 70%. After 60 min recovery, arterial pO₂ and mean coronary flow were back to normal but extraction fraction was still reduced at 80.3%.

The Effect of Insulin

In five dogs, the mean extraction fraction was measured as 89.0%. After 45 minutes on a slow insulin infusion, the extraction fraction was 85.5% (NS). Coronary flow increased by 30% while the rate-pressure product decreased by 10%. The serum potassium came down from 4.0 to 2.8 mEq/L during the infusion.

The Effect of Propranolol

In seven dogs the control mean extraction fraction was 86.8% ± 3. After propranolol, the extraction fraction was 86.3% ± 4.4 (NS); while the coronary flow increased by 27% and the rate-pressure product decreased by 16%.

The Effect of Acetyl Strophanthin

Control mean extraction fraction in six dogs was 89.1% ± 2.2. Acetyl Strophanthin was given and 19 min later the extraction fraction was 85.8% ± 2.6. The coronary flow came down by 7% and the rate-pressure product increased by 6%.

Discussion

The content of thallium-201 in an organ represents the net result of both input and output factors. The major factors controlling input are the amount of thallium delivered to the organ (blood flow) and the ability of the organ to extract that tracer from the blood (Na-K ATPase pump). The major factors controlling the loss of thallium from the organ are the relative tracer concentration in the organ compared to that in blood, solubility of the material in the intracellular fluid, and membrane permeability. In these studies, we investigated only the ability to extract the tracer from the blood in the first passage through the coronary circulation. The double tracer method of measuring extraction fraction was selected because it obviated the requirement of collecting the total venous effluent of the heart. The method assumes that the entire myocardium has a uniform extraction of thallium and that sampling at the coronary sinus, which drains about 80% of the myocardium, would provide results reflecting the average condition throughout the heart.
For this reason, all interventions evaluated affected the entire heart.

The results of these studies suggest that the myocardial ability to extract thallium from blood is not significantly altered by heart rate, insulin, propranolol, alkalosis, or acetyl strophanthin. Increases in coronary flow in excess of myocardial demands however, result in a progressive decrease in thallium extraction. This alteration in extraction fraction with flow in excess of demands may represent a true shunting of blood from "nutritional" to nonnutritional pathways. An alternative explanation, which would fit with the data, and is more likely, is that the cell membrane extracts only that amount of material required for maintenance of the intact cell; when the cell is working harder, the concentration of nutrients must be replaced at a more rapid rate: flow increases, extraction remains fixed but amount entering the cell per unit time increases. Whereas, as a fixed workload, the cellular requirements can be met by a certain amount of tracer entering the cell per unit time, when the quantity presented to the cell increases far above cellular demand, the extraction falls.

Another possible but less likely explanation is that a finite time is required for extraction of tracer from the blood, and at extremely high flows the time of tracer contact with cell membrane surface is too short to permit extraction. The experimental data found in this study suggests that this explanation is not valid, since when coronary flow was doubled by atrial pacing, the extraction of thallium remained unchanged from control values; however, when coronary flow was doubled (fig. 1) while rate-pressure product decreased slightly, the extraction fell significantly.

The explanation of hypoxia causing a decrease in extraction fraction is likely related to the effect of hypoxia on the Na-K ATPase pump system. Hypoxia causes a marked decrease in the pump activity, and hence, would be expected to result in a decrease of thallium extraction. Similarly, acidosis is known to cause an increase in the transmembrane transport of hydrogen in place of potassium (TI), which could explain the decrease in extraction seen with acidosis.

An explanation of the lack of effects seen with acetyl strophanthin and insulin on extraction fraction is not obvious. When insulin was infused, there was a marked fall in serum potassium, and when acetyl strophanthin was used, a digitalis effect was seen on the electrocardiogram, indicating that both drugs were having a pharmacologic effect.

However, even in those instances when extraction fraction was affected by the intervention, it did not change markedly. These data suggest that the extraction of thallium by the myocardium is not affected to an extent that would be clinically significant in the circumstances tested. If an image were obtained immediately after thallium administration, the regional concentration of tracer in the myocardium would be representative of blood flow.

References
The extraction of thallium-201 by the myocardium.
H F Weich, H W Strauss and B Pitt

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