The Effect of Total Body Perfusion on Digitalis Tolerance*

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INTRODUCTION

IT HAS BEEN OBSERVED THAT HUMANS and animals have an increased sensitivity to digitalis administered immediately after total body perfusion. The explanation for this change in digitalis tolerance is not known, nor is the duration of the period of heightened sensitivity accurately determined. Clinical and laboratory observations to date indicate that perfusion probably does not alter the tolerance or tissue concentrations of digitalis administered prior to perfusion (“tissue fixed” digitalis). The present investigation was undertaken to further evaluate the effect of perfusion on the tolerance of “tissue fixed” digitalis clinically in infants and children with congenital heart disease undergoing open heart surgery and experimentally in dogs subjected to total body perfusion. The animal study was also designed so as to obtain further information concerning tolerance to postperfusion administered digitalis and to more accurately determine the duration of the period of altered tolerance to digitalis administered following perfusion.

METHODS AND MATERIALS

1. Clinical Studies

Pre- and postperfusion electrocardiograms were analyzed in 84 infants and children who had undergone normothermic total body perfusion for correction of congenital heart defects at the Children’s Memorial Hospital, University of Oklahoma Medical Center during the past three and one-half years. These patients ranged in age from three months to 15 years. Fortytwo were boys and 39 were girls. Fifty of the 84 received no digitalis before or after total body perfusion. Thirty-four had been digitalized with digitalis lanata (Lanoxin), 1.0 to 1.50 mg./M², one week to three years prior to surgery and maintained on daily maintenance dosages of one-fourth to one-third of the digitalizing dose. In all except two patients, whose maintenance dose was omitted the day of surgery, the morning maintenance dose was administered orally or intramuscularly two to four hours prior to total body perfusion. No digitalis was administered for at least eight hours after perfusion in any patient. Electrocardiograms obtained immediately after total body perfusion and for periods of one to six hours thereafter, were compared to tracings taken immediately prior to thoracotomy. Prior to perfusion the tracings of the 34 digitalized patients showed evidence of early digitotoxicity in four (12 per cent) patients, of digitalis effect in 13 (38 per cent), and showed no evidence of digitalis effect in 17 (50 per cent) patients.

2. Animal Studies

Thirteen mongrel dogs were chronically digitalized with digitalis lanata (Lanoxin**). One animal expired during the period of chronic digitalization. The dogs ranged in weight from 18 to 30 pounds. All were male except two. They were digitalized over ten to 17-day periods to early digitalis intoxication (determined electrocardiographically). A digitalizing dose of 0.04 to 0.05 mg./lb. was given. Maintenance dosages ranging from 0.01 to 0.02 mg./lb./day were used in order to produce electrocardiographic signs of chronic cardiac digitotoxicity. Daily electrocardiograms were taken for six to hours after the administration of Lanoxin. After chronic digitalization was completed, anesthetized dogs were subjected to total body perfusion using a DeBakey type perfusion system at a perfusion rate of 75 ml./kg./min.

TABLE I—INCIDENCE OF TOTAL BODY PERFUSION between the DIGITALIZE

<table>
<thead>
<tr>
<th>1. Patients digitalized prior to perfusion</th>
<th>2. Patients not digitalized prior to perfusion</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>AS=aortic stenosis</td>
<td>VSD=ventricular septal defect</td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Ventricular septal defect</td>
<td></td>
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<tr>
<td>Pulmonary hypertension</td>
<td></td>
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</tbody>
</table>

**Donated by the Burroughs Wellcome Company.
Digitalis Tolerance

M. W. M. F. N. T. W. M. D.

had no digitalis before or at surgery. Thirty-four had been treated with digitalis lanata (Lanoxin), mg./M², one week to three days, and maintained on an average of one-fourth of the digitalizing dose. In all patients, whose maintenance doses were adjusted, the intant days of surgery, the intant dose was administered intravenously or intramuscularly, usually in one dose, to the total body perfusion. No one was administered for at least eight hours after the last dose. In every patient, electrolytes obtained immediately after the last dose of digitalis and for periods of one hour thereafter, were compared to the levels obtained immediately prior to thoracotomy. In all patients, the electrocardiogram showed normal heart rate and rhythm. In two of the patients, the tracings of the electrocardiogram obtained immediately after the last dose of digitalis and for periods of one hour thereafter, were compared to the levels obtained immediately prior to thoracotomy. In all patients, the electrocardiogram showed normal heart rate and rhythm. In two of the patients, the tracings of the electrocardiogram obtained immediately after the last dose of digitalis and for periods of one hour thereafter, were compared to the levels obtained immediately prior to thoracotomy. In all patients, the electrocardiogram showed normal heart rate and rhythm.

Results

1. Clinical Studies

Table 1 lists the total incidence, and the incidence for various types of heart defects, of significant electrocardiographic arrhythmias following open heart surgery in the 84 infants and children studied. The incidence of arrhythmias in 56 per cent of patients digitalized prior to perfusion appears to be significantly higher than the 32 per cent incidence in the nondigitalized patients; however, statistical analysis by the Chi square test showed that there was no difference between the incidence of arrhythmias in the digitalized and nondigitalized patients at the 5 per cent level. Additionally, when only the patients with postperfusion arrhythmias not proved to be due to the surgical procedure were considered, the incidence of only 12 per cent in the digitalized patients was lower than the 24 per cent incidence found in the

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>ASD</th>
<th>VSD</th>
<th>PS</th>
<th>AS</th>
<th>TOF</th>
<th>TAPVD</th>
<th>TRANS</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients digitalized prior to perfusion</td>
<td>34</td>
<td>2/4</td>
<td>5/12</td>
<td>1/2</td>
<td>2/3</td>
<td>2/2</td>
<td>7/11</td>
<td>19/34 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Patients not digitalized prior to perfusion</td>
<td>50</td>
<td>2/8</td>
<td>2/6</td>
<td>2/9</td>
<td>4/16</td>
<td>4/6</td>
<td>2/5</td>
<td>16/50 (32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>84</td>
<td>4/12</td>
<td>7/18</td>
<td>2/9</td>
<td>4/16</td>
<td>5/8</td>
<td>2/3</td>
<td>2/2</td>
<td>9/16</td>
<td>35/84 (42%)</td>
</tr>
</tbody>
</table>

Legend: AS = aortic stenosis; ASD = atrial septal defect; PS = pulmonary stenosis; TAPVD = total anomalous pulmonary venous drainage; TOF = tetralogy of Fallot; TRANS = transposition of the great vessels; VSD = ventricular septal defect.
non-digitalized patients. This difference was also subjected to the Chi square test and found to be not statistically significant. From the group of 34 patients digitalized prior to perfusion, the incidence of significant arrhythmias not due to the surgical procedure did not appear to be related to their preperfusion digitalis status (Table 2).

<table>
<thead>
<tr>
<th>Table 2—The Relationship of the Incidence of &quot;Unexplained&quot; Electrocardiographic Arrhythmias to the Preperfusion Digitalis Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preperfusion Digitalis Status</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Early Digitoxicity</td>
</tr>
<tr>
<td>Digitalis Effect</td>
</tr>
<tr>
<td>No ECG Evidence of Digitalis</td>
</tr>
<tr>
<td>TOTALS</td>
</tr>
</tbody>
</table>

*Detected electrocardiographically

2. Animal Studies

(a) General

The experimental procedure was completed satisfactorily in all except two of the animals. One expired from digitoxicity during chronic digitalization. The second was lost during the perfusion due to air embolization (Dog No. 5). Satisfactory completion of the experimental procedure was accomplished in the other 11 animals except that the minimal effective dose of acetyl strophanthidin was not satisfactorily determined in dogs No. 1 and 4. Only one animal (No. 8) survived the one hour period of total body perfusion for longer than eight hours.

Chronic digitalization produced significant gastrointestinal symptoms in all animals. They all showed a significant decrease in appetite and had three to five pound weight losses during the digitalization period. Intake was so poor in three animals that parenteral fluids were required. All except one of the dogs showed electrocar-

diographic evidence of first degree atrio-
ventricular block as evidence of chronic digitalis toxicity (Table 3). The minimal effective dose of acetyl strophanthidin was 0.0025 mg./lb. in six of 11 animals. This usually increased the atrioventricular block from first degree to second degree (Table 3).

<table>
<thead>
<tr>
<th>Table 3—Pre- and Postperfusion Acetyl Strophanthidin Tolerance Tests in Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Dogs</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1. 1°→2°</td>
</tr>
<tr>
<td>2. 1°→3°</td>
</tr>
<tr>
<td>3. 1°→2°</td>
</tr>
<tr>
<td>4. 1°→Bigeminy</td>
</tr>
<tr>
<td>5. 1°→2°</td>
</tr>
<tr>
<td>6. 1°→2°</td>
</tr>
<tr>
<td>7. 1°→2°</td>
</tr>
<tr>
<td>8. 1°→0°</td>
</tr>
<tr>
<td>9. 1°→2° + VPB's</td>
</tr>
</tbody>
</table>

*No change in the ECG evidence of digitalis toxicity from preperfusion or postthoracotomy ACS test; >> = Decreased ECG evidence of digitalis toxicity; << = Moderately increased ECG evidence of digitalis toxicity; << = Markedly increased ECG evidence of digitalis toxicity.

(b) Control Animals

Two of the control animals developed nodal bradycardia following thoracotomy, possibly indicating an increased sensitivity to “tissue fixed” digitalis. The third control animal showed a decrease in electrocardiographic evidence of digitoxicity following thoracotomy (Table 4). None of the control animals showed electrocardiographic evidence of increased sensitivity to postthoracotomy administered acetyl strophanthidin (Table 3).

(c) Perfusion Animals
evidence of first degree atrio-
block as evidence of chronic
toxicity (Table 3). The minimal
use of acetyl strophanthinidin was
0.8/lb, in six of 11 animals. This
eased the atroventricular block
degree to second degree (Table

| Table 4—Effect of Perfusion and
Thoracotomy on the Electrocardiographic
Evidence of Digitalis Toxicity in Dogs |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-perfusion or Post-thoracotomy</td>
</tr>
<tr>
<td>ECG Evidence of Digitalis Toxicity*</td>
</tr>
<tr>
<td>Postperfusion or Post-thoracotomy</td>
</tr>
<tr>
<td>ECG Evidence of Digitalis Toxicity*</td>
</tr>
<tr>
<td>Number &lt;= &gt; &lt;</td>
</tr>
<tr>
<td>1. Experimental (Digitalization + Perfusion)</td>
</tr>
<tr>
<td>8 2 5 1</td>
</tr>
<tr>
<td>2. Control (Digitalization + Thoracotomy)</td>
</tr>
<tr>
<td>3 0 1 2</td>
</tr>
</tbody>
</table>

*: =ECG unchanged from preoperative tracing; <= =Increased ECG evidence of digitalis toxicity postoperatively; >= =Decreased ECG evidence of digitalis toxicity postoperatively.

The effect of perfusion on electrocardiographic evidence of digitoxicity in the chronically digitalized dogs is summarized in Table 4. One of eight animals developed nodal bradycardia following perfusion possibly indicating increased sensitivity to “tissue fixed” digitalis. Two of the animals showed no change in electrocardiographic evidence of digitalis toxicity following perfusion. Five showed decreased electrocardiographic evidence of digitalis effect or toxicity following perfusion.

The results of pre- and postperfusion acetyl strophanthinidin tolerance tests are summarized in Table 3 and illustrated in Fig. 1. All seven animals tested showed decreased acetyl strophanthinidin tolerance one hour postperfusion. Four of five (80 per cent) showed decreased acetyl strophanthinidin tolerance four hours after perfusion and two of five (40 per cent) showed decreased tolerance seven hours after perfusion.

(d) Cardiac Output and Blood Chemical Changes

Of the parameters studied, no consistent change which would adequately explain the altered tolerance to digitalis was observed. Figure 2 is a summary of the cardiac output, temperature, and blood chemical changes and illustrates both the changes seen in the perfused animals and in the controls.

**DISCUSSION**

The electrocardiographic data from the digitalized and non-digitalized perfused infants and children studied indicate that sensitivity to “tissue fixed” digitalis is not altered by total body perfusion. The animal data also support this observation in that the incidence of possible electrocardiographic evidence of increased sensitivity to digitalis was greater in the control than in the perfused animals. Beneficial effects of preperfusion administered digitalis in experimental animals and humans have previously been reported. Braunwald et al.*

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**Figure 1**: Acetyl strophanthinidin tolerance test in the pre- and postperfusion periods. The preperfusion ECG shows first degree atroventricular block (A). After the preperfusion acetyl strophanthinidin test (0.0025 mg./lb.) there is increased block and then a slow nodal rhythm. One hour postperfusion, the same dose of acetyl strophanthinidin was followed by the development of a nodal rhythm in five minutes and cardiac arrest and death in ten minutes (B).
stated that, "the demonstration..." of the substantial augmentation of contractile force provided by digitalis has led to the establishment of a policy at the National Heart Institute to digitalize all patients prior to intracardiac surgery." Our observations in humans and animals who were digitalized prior to perfusion indicate that such a policy would not be associated with an increased incidence of postperfusion digitoxicity. Further studies are under way in our laboratory to evaluate the effect of postperfusion administered digitalis on myocardial contractility. It is possible that the dose of digitalis necessary to effectively increase contractility during the immediate postperfusion period will always result in severe or lethal rhythmic changes.

Our animal observations of decreased tolerance to postperfusion digitalis in 100 per cent of animals at one hour following perfusion was in agreement with the previous observation of Browning et al. Only 80 per cent of our animals continued to show decreased tolerance at four hours, and only 40 per cent at seven hours. Browning et al. found that tolerance had returned to normal in all of their animals by 24 hours. Our data suggest that heightened sensitivity is likely to persist beyond 12 hours in only a small per cent of animals. The data of Maginn et al. showed that tolerance to postperfusion administered digitalis was not changed after perfusion in non-digitalized dogs, and was possibly increased in chronically digitalized animals. The difference between their observations and those of Browning et al. and ours may be due to the fact that they tested their animals only 30 minutes following perfusion. They also used different digitalis preparations (digitoxin and ouabain) and different electrocardiographic criteria of toxicity, and did not do thoracotomy as a part of their control procedure. Differences in experimental results may also relate to the sex of the animal used since it has been shown that male and castrate female mongrel dogs have a greater susceptibility to the arrhythmic action of digitalis. Neither Browning et al. nor Maginn et al. included information as to the sex of the animals which were used in their studies.

The explanation for alteration in postperfusion digitalis tolerance is still unknown. The cot the experiments of deez et al., and that an increase in the glycoside, rate of excretion, muscle sensitivity, decreased to cardiopulmonary studies thus far change; however, possible that the tolerance is due to that myocardial other more elabone to demons.

Based on the this paper and reported by other in clinical policies contain in patients surgery have been (1) in addition evidence of conget patients undergoing defects with a si developing conges the postperfusion Lanoxin prior to or intramuscular the morning of the morning of the maxim hours) would then date postperfusion anence digitalis is na 24 hours after the acetyl strophanthin performed if it is administer digitali hours following pe

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1. The effect of digitalis tolerance in infants and childrens heart surgery and mongrel dogs subjected to fusion.

2. The clinical st parison of immedia
known. The combined information from the experiments of Doherty et al., Hernande
z et al., and Kouchoukos et al. indicate that an increased rate of tissue binding of
the glycoside, rather than changes in the rate of excretion, in distribution, or in
muscle sensitivity, is the primary cause of the decreased tolerance of the drug after
cardiopulmonary bypass. Blood chemical studies thus far have shown significant
change; however, in spite of this it is still possible that the alteration in digitalis tol-
erance is due to electrolyte alterations, but that myocardial tissue electrolyte studies or
other more elaborate technics will be required to demonstrate the changes.

Based on the observations reported in this paper and the studies previously re-
ported by other investigators, the following clinical policies concerning the use of digi-
tals in patients undergoing open heart surgery have been adopted at our hospital:
1) in addition to patients with clinical evidence of congestive heart failure, all pa-
tients undergoing open heart surgery for defects with a significant propensity for
developing congestive heart failure during the postperfusion period are digitalized with
Lanoxin prior to perfusion; (2) no oral or intramuscular digitalis is administered
the morning of the surgical procedure since the maximal effective time (six
hours) would then be very near the immediate postperfusion period; (3) mainte-
nance digitalis is not renewed until 12 to 24 hours after the perfusion; and (4)
acetyl strophanthidin tolerance tests are performed if it is considered advisable to
administer digitalis during the first 18 hours following perfusion.

**SUMMARY**

1. The effect of total body perfusion on digitalis tolerance was studied clinically in
84 infants and children undergoing open heart surgery and experimentally in eight
mongrel dogs subjected to total body perfusion.

2. The clinical studies consisted of comparison of immediate postperfusion electro-
cardiograms to preperfusion electrocardiograms. There was no statistically significant
difference between the incidence of post-
perfusion electrocardiographic arrhythmias in patients who had been digitalized prior
to perfusion and in patients who had not
received digitalis. Additionally there was no correlation between the incidence of
postperfusion arrhythmias and the degree of the preperfusion electrocardiographic
evidence of digitalis effect.

3. Studies of the effect of perfusion on digitalis tolerance in the dog were per-
formed both for digitalis administered prior to perfusion ("tissue fixed") and for
digitalis administered following perfusion. Per-
fusion was associated with no significant change in sensitivity to "tissue fixed" digi-
talis; however, all of the animals tested
showed a decreased tolerance to digitalis administered one hour following perfusion.
Decreased tolerance to digitalis persisted at
four hours in 80 per cent of animals and
at seven hours in 40 per cent of animals.

4. The application of this information to the administration of digitalis to patients
undergoing open heart surgery is discussed.

**Resumen**

1. El efecto de la perfusión total del cuerpo sobre la tolerancia de la digital se estudio clíni-
camente en 84 infantes y niños a quienes se sometió a cirugía a corazón abierto y experimentalmente
en ocho perros comunes a los que se sujetó a perfusión total del cuerpo.

2. Los estudios clínicos consistieron en la comparación inmediata de los electrocardiogramas
post-perfusión. No hubo diferencia de significancia estadística entre la frecuencia de arritmia,
el grado de la perfusión y el efecto de digitales en el ECG.

3. Los estudios del efecto de la perfusión en la tolerancia de la digital en el perro se observaron
para la digital administrada antes de la perfusión ("fijada en tejidos") como para la
digital administrada después de la perfusión. La
perfusión no se asoció con cambios significativos en la sensibilidad a la digital "fijada en tejidos;" sin
embargo, todos los animales en la experiencia mostraron una tolerancia disminuida a la digital
administrada una hora después de la perfusión.
La tolerancia a la digital disminuida persistió por 4 horas en el 80 por ciento de los animales y
siete horas en 40 por ciento de los animales.
4. La aplicación de esta información a la administración de digital en los enfermos que se someten a operaciones a corazón abierto es motivo de disertación.

**RESUMÉ**

1. L’effet d’une perfusion corporelle totale sur la tolérance à la digitaline a été étudié cliniquement chez 84 nourrissons et enfants subissant une intervention à cœur ouvert, et expérimentalement chez 8 chiens mongrel sujets à une perfusion corporelle totale.

2. Les études cliniques comprenaient la comparaison des électrocardiogrammes immédiatement après la perfusion à ceux précédant la perfusion. Il n’y a pas eu de différence statistiquement significative entre la proportion d’arythmies après perfusion chez les malades qui avaient eu de la digitaline avant leur perfusion, et chez les malades qui n’avaient pas reçu de digitaline. De plus, il n’y avait pas de corrélation entre la survenue d’arythmie après perfusion et le degré des signes électrocardiographiques d’effet digitalique existant avant perfusion.

3. Les études sur l’effet de la perfusion sur la tolérance de la digitaline chez le chien ont été faites à la fois en ce qui concerne la digitaline administrée avant la perfusion ("fixée par les tissus") et en ce qui concerne la digitaline administrée après la perfusion. La perfusion n’a pas amené de modification significative dans la sensibilité à la digitaline "fixée par les tissus"; cependant tous les animaux testés ont présenté une diminution de la tolérance à la digitaline administrée une heure après la perfusion. Cette diminution de la tolérance a persisté pendant 4 heures chez 80 pour cent des animaux, et pendant 7 heures chez 40 pour cent des animaux.

4. L’application de ces résultats en ce qui concerne l’administration de digitaline aux malades subissant une intervention à cœur ouvert est prise en considération.

**ZUSAMMENFASSUNG**

1. Die Wirkung der totalen Korperdurchströmung unter Digitalintoléranz wurde klinisch an 84 Säuglingen und Kindern während Operationen am offenen Herzen studiert und experimentell analysiert bei 8 Bastardhunden, die einer totalen Körperperfusion unterworfen wurden.


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ythem nach der Perfusion und elektrokatarrhalischer Anhalt-
line Digitalis-wirkung vor der Per-
hungen über die Wirkung der Per-
Digitalisverträglichkeit des Kindes
für Digitalis beobachtet, das vor
zugeführt worden war (im Gewebe
für Digitalis, das nach der Perfu-
: worden war. Die Perfusion war
mässigen Änderung in der Sensi-
veksifizierter Digitalis verknüpf.
nten Tiere eine herabge-
olerzartung bei Verabfolgung eine
der Perfusion. Geringe Digitalis-
4 Stunden lang bei 80% der
sten und lang bei 40% der Tiere.
tragung dieser Informationen auf
vorgen Digitalis bei Patienten
mit offenen Herzen wird diskutiert.

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EMPYEMA THORACIS

During the past 18 years, 82 patients with emp-
emas were treated at St. Louis Children's Hospital
with a mortality rate of 10.9 per cent. There has
been a definite increase in staphylococcal empyema
during the past five years. There is a predilection
of staphylococcal empyema for young infants ac-
companied by a higher mortality in that age group.
Pyopneumothorax is a frequent complication (46.6
per cent) of staphylococcal empyema. The associa-
ction of predominantly one phase type with staphy-
lococcal empyema is an unexpected finding, and its
significance is not yet understood. The staphylo-
cocci are usually resistant to penicillin, tetracycline
and sulphonamide and, in recent years, appear to be
developing resistance to erythromycin and chloram-
phenicol.

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VENTRICULAR SEPTAL DEFECT

Experience with the transatrial approach in 14
cases of ventricular septal defect and five cases of
Follot's anomaly is reported. There was no mor-
tality and no block in this series of patients. The
method is an advantage in cases of ventricular septal
defect, especially when combined with high pres-
sures. The transatrial approach can also be used in
certain cases of Follot's anomaly, but is, however,
technically more difficult and time consuming al-
though the postoperative course has been smooth.
The necessity for prolonged ventilation postope-
atively by a volume-regulated respiratory (Enstrom)
in order to diminish the demand on cardiac output in
patients in failure is stressed.

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INCISED COMMISSURE IN MITRAL STENOSIS

Commissurotomy incisions were studied in 27 pa-
ients who had had mitral stenosis. By comparing
the cases of those patients who survived two months
ten years after commissurotomy to those who
bilateral operation of mitral valve edges and then
extends into the commissurotomy incision and covers
the cut margin which is composed of flattened
fibrous connective tissue.

Recurrent mitral stenosis could be explained by
deposits of calcium and scarring of the valves them-
selves, recurrent rheumatic valvulitis, or originally
inadequate commissurotomy. In cases in which the
valve ring is incised to the extent that the edges
are widely gaping, complete healing does not take
place and therefore does not contribute to re-
stenosis.

Study of the Incised Comissure in Mitral Stenosis," J.