Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease

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Abstract

Objective.—To determine how severe tricuspid regurgitation influences exercise capacity and functional state in patients who have undergone successful mitral valve replacement for rheumatic mitral valve disease.

Design.—9 patients in whom clinically significant tricuspid regurgitation developed late after mitral valve replacement were compared with 9 patients with no clinical evidence of tricuspid regurgitation. The two groups were matched for preoperative clinical and haemodynamic variables. Patients were assessed by conventional echocardiography, Doppler echocardiography, and a maximal treadmill exercise test in which expired gas was monitored by mass spectrometry.

Setting.—University Hospital of Wales, Cardiff.

Subjects.—18 patients who had been reviewed regularly since mitral valve replacement.

Main outcome measure.—Objective indices of exercise performance including exercise duration, maximal oxygen consumption, anaerobic threshold, and ventilatory response to exercise.

Results.—Mitral valve prosthetic function was normal in all patients and estimated pulmonary artery systolic pressure and left ventricular function were similar in the two groups. Right ventricular diameter (median (range) 5.0 (4.3-5.6) vs 3.7 (3.0-5.4) cm, p < 0.01) and the incidence of paradoxical septal motion (9/9 vs 3/9, p < 0.01) were greater in the group with severe tricuspid regurgitation. Exercise performance—assessed by exercise duration (6.3 (5.0-10.7) vs 12.7 (7.2-16.0) min, p < 0.01), maximum oxygen consumption (11.2 (7.3-17.8) vs 17.7 (11.8-21.4) ml min⁻¹ kg⁻¹, p < 0.01), and anaerobic threshold (8.3 (4.6-11.4) vs 0.7 (7.3-15.5) ml min⁻¹ kg⁻¹, p < 0.05)—was significantly reduced in the group with severe tricuspid regurgitation. The ventilatory response to exercise was greater in patients with tricuspid regurgitation (minute ventilation at the same minute carbon dioxide production 41.0 (25.9-59.5) vs 33.6 (26.8-39.3) l/min, p < 0.01).

Conclusions.—Clinically significant tricuspid regurgitation may develop late after successful mitral valve replacement and in the absence of residual pulmonary hypertension, prosthetic dysfunction, or significant left ventricular impairment. Patients in whom severe tricuspid regurgitation developed had a considerable reduction in exercise capacity caused by an impaired cardiac output response to exercise and therefore experienced a poor functional outcome. The extent to which this was attributable to the tricuspid regurgitation itself or alternatively to the consequences of right ventricular dysfunction was not clear and requires further investigation.

Successful mitral valve replacement for rheumatic mitral valve disease is accompanied in most patients by a sustained symptomatic improvement. Continuation or return of limiting symptoms may indicate the presence of prosthetic valve failure, impairment of left ventricular function, persistent pulmonary hypertension, or the development of important aortic valve disease. All may lead to a rise in right heart pressures and the subsequent development of functional tricuspid regurgitation. We found that severe tricuspid regurgitation can develop in the absence of these factors and that it can also be responsible for a poor functional outcome. Attention has been paid in the past to the importance of right ventricular function as a determinant of exercise capacity in heart failure. In chronic left ventricular failure, exercise capacity seems to correlate with resting right ventricular ejection fraction and pulmonary vascular resistance. Although not previously studied, the presence of severe tricuspid regurgitation is likely to be associated with a reduced right ventricular output and would also be expected to compromise exercise capacity in the absence of left ventricular impairment.

Clinical assessment was a poor guide to true functional state after valve replacement and the criteria applied are by their nature subjective with poor interobserver reproducibility. Exercise testing, incorporating expired gas analysis, is now well established as a safe, reliable, and reproducible method of studying the pathophysiological response to exercise in...
patients with heart failure. It is also valuable as a method of assessing accurately the severity of cardiac disease and correlating this with the extent of functional limitation.

The aim of this study was to establish by exercise testing with expired gas analysis how the presence of severe tricuspid regurgitation influences exercise capacity and functional state in patients who had undergone successful mitral valve replacement for rheumatic mitral valve disease.

Patients and methods
Eighteen patients were studied; nine (eight women, one man) had developed clinically significant tricuspid regurgitation late after successful mitral valve replacement for rheumatic mitral valve disease. Their mean age was 59 years (range 48–67). All patients had experienced an initial symptomatic improvement after operation but they described the return of limiting symptoms when clinical signs of tricuspid regurgitation became apparent. Clinically significant tricuspid regurgitation was diagnosed in the presence of a raised jugular venous pressure with prominent cv wave, pulsatile hepatomegaly, and fluid retention requiring intensive diuretic treatment. Nine patients (eight women, one man) who had also undergone mitral valve replacement for rheumatic mitral valve disease were chosen as a closely matched control group. Their mean age was 62 years (range 56–67). When we selected these patients we attempted to match clinical, preoperative haemodynamic, operative, and current echocardiographic indices as closely as possible (tables 1 and 2). None had clinical signs of tricuspid regurgitation or a history of postoperative fluid retention. All patients in both groups were in atrial fibrillation.

Patients were questioned about current cardiac symptoms, and functional capacity was assessed according to the New York Heart Association (NYHA) classification. During clinical examination we noted the presence or absence of physical signs suggesting tricuspid regurgitation. The jugular venous pressure was measured with the patient sitting at 45°. The mean of the venous waveforms was estimated clinically and the height measured in centimetres above the sternal angle. This value was used to derive an indirect measurement of right atrial pressure. Results of preoperative cardiac catheterisation and the details of valve surgery were obtained from the patient records.

ECHOCARDIOGRAPHY
Standard transthoracic echocardiography was performed with a Hewlett Packard 77510A scanner in all patients. Cross sectional, M mode, and Doppler echocardiography with continuous wave, pulsed wave, and colour flow Doppler were performed in all standard views. The examination was performed with all subjects in the left lateral decubitus and supine positions. M mode echocardiograms were recorded at a paper speed of 100 mm/s. Variables derived from the M mode echocardiogram and Doppler recordings were measured for five consecutive beats and a mean value was calculated.

The left ventricular dimensions were recorded in the long axis view as the greatest dimensions of the left ventricle obtained at the level of the mitral valve prosthesis. The minor axis dimensions were measured between the endocardial surfaces of the posterior wall and interventricular septum. The end diastolic dimension (EDD) was taken at the peak of the R wave of the simultaneously recorded electrocardiogram. The end systolic dimension (ESD) was defined as the minimum distance separating the endocardial surfaces at the peak upward anterior motion of the posterior ventricular wall. Fractional shortening was calculated by the following formula:

$$FS(\%) = \frac{LVEDD - LVESD}{LVEDD} \times 100$$

The right ventricular end diastolic dimension was measured as the distance between the endocardial surfaces of the right ventricle at the R wave of the simultaneously recorded electrocardiogram. The direction of septal motion in early systole was recorded and judged to be either normal or paradoxical.

Prosthetic valve function was studied by visual inspection of the cross sectional echocardiogram and by Doppler assessment. Continuous wave Doppler signals of diastolic mitral flow velocity were recorded and an estimate of mitral valve area was derived from the pressure half time. Mitral regurgitation was sought by pulsed wave echocardiography and colour flow Doppler mapping in apical and left parasternal views.

Tricuspid regurgitation was detected in all 18 subjects and was apparent with both continuous wave and colour flow Doppler. Doppler recordings of maximal velocity were obtained from the apical and left parasternal views and continuous wave Doppler signals were considered optimal once the maximum clearly defined spectral envelope was achieved. The peak velocity (v) of the tricuspid regurgitation jet was used to calculate the systolic tricuspid valve gradient from a modified Bernoulli equation:

$$TV \text{ gradient (mm Hg)} = 4 v^2$$

The systolic pressure gradient across the tricuspid valve represents the difference between the right ventricular and right atrial systolic pressures. The right ventricular systolic pressure (and also pulmonary artery systolic pressure) can therefore be estimated if the pressure gradient and right atrial pressure are known. Right atrial pressure was estimated by adding 5 cm to the mean clinical jugular venous pressure assessment and converted to mm Hg by dividing the right atrial pressure in centimetres by 1.3 to take account of the relative densities of mercury and blood at physiological temperatures.

The severity of tricuspid regurgitation was estimated echocardiographically and graded as mild, moderate, or severe. This semiquantitative assessment was made on the basis of the width of the regurgitant jet and the distance to...
which it extended into the right atrium, as detected by colour flow and pulsed wave Doppler. Tricuspid regurgitation was graded as mild if the regurgitant jet was narrow and extended into the right atrium no further than one third the length of the inter-atrial septum and severe if the jet was broad, reached the posterior atrial wall, and was detected in the hepatic vein. Intermediate findings were judged to reflect moderate tricuspid regurgitation.

**EXERCISE TESTING**
Symptom limited maximal exercise testing was performed according to the Weber treadmill protocol, which is a progressive exercise protocol designed for heart failure patients. Subjects continued their normal medication on the day of exercise testing. The heart rate and electrocardiogram were recorded continuously and a standard 12 lead electrocardiogram was performed every minute. Blood pressure was recorded by mercury sphygmomanometer every two minutes. Respiratory gas analysis was performed during exercise by means of the argon dilution technique. Minute oxygen consumption (V\text{O}_2, \text{ml min}^{-1} \text{kg}^{-1})

**RESULTS**

**CLINICAL**

Table 1 summarises clinical details of the two groups. They were well matched for age, sex, and duration of symptoms before operation and were studied at similar intervals post-operatively. All patients were in atrial fibrillation and none had significant coronary artery disease or aortic valve disease. The preoperative haemodynamic findings were similar in the two groups, as were the type and size of mitral valve prostheses implanted (table 1). None of the patients with clinically significant tricuspid regurgitation had an abnormal right atrial 'v' wave at preoperative cardiac catheterisation, while one patient in the control group had a right atrial 'v' wave up to 12 mm Hg. Mild tricuspid regurgitation was detected by palpation at operation in four of those who subsequently developed clinically significant tricuspid regurgitation but was absent in all patients in the control group.

**ECHOCARDIOGRAPHY**

Table 2 summarises the echocardiographic findings. All the indices of left ventricular function were similar in the two groups. None of the patients in either group had evidence of prosthetic valve dysfunction and none had developed significant aortic valve disease. The estimated pulmonary artery systolic pressure was not significantly higher in patients with severe tricuspid regurgitation, but the right ventricular diameter and the incidence of paradoxical septal motion were significantly greater (p < 0.01) in this group.

The tricuspid valve was found to be thickened in six patients with clinically significant tricuspid regurgitation and in eight patients in the control group. Tricuspid valve motion, however, remained free in all those studied and none had cross sectional echocardiographic features that suggested valve stenosis or valve prolapse. The degree of tricuspid regurgitation was judged to be severe in six patients and moderate in three of the patients with clinically significant tricuspid regurgitation. In contrast, regurgitation was found to be moderate in five patients and mild in four patients in the control group.
**Table 2** Echocardiographic results (median (range)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>TR (n=9)</th>
<th>Control (n=9)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (cm)</td>
<td>5.1 (2.3–7.9)</td>
<td>4.3 (3.7–5.5)</td>
<td>NS</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>3.8 (1.3–6.4)</td>
<td>3.2 (2.4–4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>FS (%)</td>
<td>23 (16–33)</td>
<td>24 (17–39)</td>
<td>NS</td>
</tr>
<tr>
<td>RV diameter (cm)</td>
<td>5.0 (4.3–5.6)</td>
<td>3.7 (3.0–5.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Paradoxical septal motion</td>
<td>9</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mm Hg)</td>
<td>33 (31–53)</td>
<td>27 (16–67)</td>
<td>NS</td>
</tr>
<tr>
<td>MV area (cm²)</td>
<td>2.7 (1.8–3.4)</td>
<td>1.9 (1.2–4.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

FS, fractional shortening; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; MV, mitral valve; RV, right ventricle; TR, tricuspid regurgitation.

**Table 3** Ventilatory changes and indices of performance during exercise (median (range)).

<table>
<thead>
<tr>
<th>Variable</th>
<th>TR (n=9)</th>
<th>Control (n=9)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration (min)</td>
<td>6.3 (5.0–10.7)</td>
<td>12.7 (7.2–16.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RER</td>
<td>0.86 (0.72–0.88)</td>
<td>0.81 (0.74–0.88)</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.03 (0.93–1.06)</td>
<td>1.06 (0.95–1.22)</td>
<td>NS</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>27.9 (28.2–57.5)</td>
<td>30.8 (22.9–33.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Minute ventilation at CO₂ production of 1 l/min (l/min)</td>
<td>41.0 (29.9–59.9)</td>
<td>33.6 (26.8–39.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Maximum increase in SBP (mm Hg)</td>
<td>8.0 (16–30)</td>
<td>22.0 (2–50)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Maximum increase in HR (min⁻¹)</td>
<td>40 (11–78)</td>
<td>74 (20–77)</td>
<td>0.05</td>
</tr>
<tr>
<td>VO₂ max (ml min⁻¹ kg⁻¹)</td>
<td>11.2 (7.3–17.8)</td>
<td>17.7 (11.8–21.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anaerobic threshold (ml min⁻¹ kg⁻¹)</td>
<td>8.3 (4.6–11.4)</td>
<td>10.7 (7.3–15.9)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

HR, heart rate; RER, respiratory exchange ratio (CO₂ produced / O₂ consumed); SBP, systolic blood pressure; VE/VCO₂ slope is derived by linear regression and expresses the relation between ventilation (VE) and carbon dioxide production (VCO₂) during exercise; VO₂ max, maximum oxygen consumption.

**EXERCISE TESTING**

Resting respiratory exchange ratio was normal in all patients and increased during exercise (table 3). The mean respiratory exchange ratio at peak exercise in both groups exceeded 1.0, indicating maximal exercise and the onset of anaerobic metabolism, with production of lactate and therefore a rise in carbon dioxide production relative to the amount of oxygen consumed. An exaggerated hyperventilatory response to exercise was seen in patients with clinically significant tricuspid regurgitation but not in the control group. The linear relation between minute ventilation and carbon dioxide production (total ventilatory response) was significantly steeper (figure), so that minute ventilation was increased relative to the same carbon dioxide production (table 3). Patients with tricuspid regurgitation had a blunted haemodynamic response to exercise with significantly smaller rises in both heart rate and systolic blood pressure (table 3). Exercise duration, maximum oxygen consumption, and anaerobic threshold were significantly lower in patients with tricuspid regurgitation than in the controls (table 3).

**Discussion**

Our results show that the presence of clinically significant tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease was associated with a considerable impairment of exercise capacity and a poor functional outcome. We were careful to compare the exercise performance of patients with severe tricuspid regurgitation with that of a well matched control group to eliminate other variables that were likely to influence exercise capacity. In particular, we specifically chose patients in both groups with well preserved resting left ventricular function on echocardiography, in order to concentrate on the influence exerted by the right heart on exercise performance. Although this method of left ventricular assessment is relatively crude, our principal object was to minimise differences between the two groups rather than to establish whether or not left ventricular function was normal in all patients. Pulmonary artery systolic pressure was also similar in the two groups and none of the patients had prosthetic dysfunction or important aortic valve disease. We conclude that the substantial differences in exercise capacity seen between the groups could only be explained by the presence or absence of tricuspid regurgitation. An exaggerated hyperventilatory response to exercise and...
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It is not clear why significant tricuspid regurgitation developed in these patients. Echocardiography showed thickening of the tricuspid valve in two thirds of the patients with clinically significant tricuspid regurgitation; but this was also a common finding among those in the control group and was never accompanied by abnormal cusp motion. Thickening of the tricuspid valve is a non-specific finding at echocardiography and the echo sectional echocardiogram is generally able to identify when it is accompanied by valve stenosis and is a feature of organic rheumatic tricuspid valve disease. In the absence, therefore, of organic tricuspid valve disease, we assume that tricuspid regurgitation is functional in these patients. Neither significant pulmonary arterial nor venous hypertension were present and it is likely, therefore, that severe functional tricuspid regurgitation develops either as a result of progressive right ventricular dysfunction or as a result of persistent dilatation of the tricuspid valve annulus. Because we studied these patients when the consequences of severe tricuspid regurgitation were likely to be advanced, it is difficult to determine which is most likely. Right ventricular dysfunction could develop as a result of tricuspid regurgitation but the reverse is also true. This difficult question has important therapeutic implications. Surgical correction of tricuspid regurgitation may be of some benefit if persistent anular dilatation is the dominant underlying abnormality, while it may be no help or even detrimental if anular dilatation is secondary to right ventricular dysfunction.

King et al retrospectively analysed their results of surgery for tricuspid regurgitation that developed late after mitral valve replacement. Of 32 patients, 14 had no evidence of prosthetic valve dysfunction or significant aortic valve disease; however, they did not comment on indices of left ventricular function or pulmonary artery systolic pressure in these patients. Tricuspid valve replacement was performed in 11 patients while three underwent tricuspid valve annuloplasty. Only four patients, however, improved by at least one NYHA class, while three patients died in the early postoperative period because of a low cardiac output and six died during the follow-up period. One patient remained in NYHA class IV. They concluded that tricuspid regurgitation developing late after mitral valve replacement in their patients was a manifestation of right ventricular failure and that restoring tricuspid valve competence was of little benefit. Though their results are certainly disappointing, we cannot conclude that tricuspid valve surgery has no part in the management of this heterogeneous group. It may be, for example, that patients with a relatively low pulmonary artery systolic pressure and well preserved left ventricular function would experience better results from tricuspid valve repair or replacement. Certainly, before dismissing the role of surgery, it would be necessary prospectively to study the benefits of correcting tricuspid regurgitation, both on functional state and on outcome, in patients with severe tricuspid regurgitation but without pulmonary hypertension, left ventricular dysfunction, or prosthesis thickening.

Of perhaps more importance, given the apparent high mortality of reoperation on the tricuspid valve and the considerable functional limitation that we showed in these patients, is that much is to be gained in attempting to reduce the likelihood of severe tricuspid regurgitation developing after mitral valve replacement. This may best be achieved by the accurate detection and correction of important tricuspid regurgitation at initial surgery. Tricuspid regurgitation is a common finding in patients with advanced mitral stenosis or regurgitation and may be present in more than 50% of those requiring mitral valve replacement. Traditional methods of assessment both preoperatively and at the time of surgery are imprecise. Haemodynamic measurements are of limited value in assessing the severity of tricuspid regurgitation and digital examination of the amount of tricuspid regurgitation present at operation is influenced by many variables which make it unreliable. These methods of pre and per operative assessment were used in our group of patients and it is possible that the degree of tricuspid regurgitation was underestimated. Czer et al suggest that intraoperative colour flow mapping is a more reliable and reproducible method of assessing the severity of tricuspid regurgitation and of selecting patients who need surgical repair of the tricuspid valve. They report a favourable comparison between this technique and right ventricular angiography, which has previously been regarded as the “gold standard” but which is rarely performed. Intraoperative colour flow mapping can certainly be performed easily and may be of benefit both in assessing the severity of tricuspid regurgitation and in judging the adequacy of tricuspid valve repair.

Although accurate assessment of tricuspid regurgitation is now possible, its subsequent surgical management remains controversial. Braunwald et al originally suggested that nonorganic tricuspid regurgitation would regress after adequate correction of left sided lesions, but it is now recognised that this is often not the case. Failure to correct significant tricus-
Tricuspid regurgitation at the time of surgery may be an important factor that leads to subsequent progressive right heart failure and worsening tricuspid regurgitation. There is much debate, however, about the best method of preventing this. Tricuspid valve replacement is usually reserved for those with either very severe tricuspid regurgitation or organic tricuspid valve disease with accompanying stenosis. In those without organic tricuspid valve disease or with less severe tricuspid regurgitation, annuloplasty may be performed. Deloche et al established that in functional tricuspid regurgitation five sixth of the annular dilatation occurs at the base of the anterior and posterior leaflets, with only one sixth occurring at the insertion of the septal leaflet. Kay et al described a method of annuloplasty of the tricuspid valve involving plication of the postero leaflet, producing a bicuspid valve but eliminating only 50% of the annular dilatation. This was accompanied by high and unpredictable failure rates. The method of De Vega, however, leads to a uniform plication of the anterior and posterior leaflets because circumferential sutures are placed around the annulus; this results in a semicircular deformation of the tricuspid orifice. Alternatively, insertion of a prosthetic valve ring was described by Carpenter et al, with the shape of the ring conforming to that of the tricuspid valve and producing a predictable correction with a normal valve orifice and usually excellent valve function. Rivera et al compared the use of De Vega annuloplasty and the Carpentier ring and found better results with the Carpentier ring. The Carpentier ring procedure produced a better anatomical repair and by the use of interrupted sutures distributed the holding force over the entire ring, producing a more effective and durable reduction in tricuspid regurgitation. Whichever approach is adopted it seems that the long term prognosis is often poor. McGrath et al report that 50% of patients undergoing a tricuspid valve procedure during surgery for valvar heart disease, 14-7% died in hospital, while 40% of those who survived the original procedure died during late follow up. The presence of significant tricuspid regurgitation usually indicates advanced valve disease and it is possible that earlier surgery would reduce the necessity for intervention at the tricuspid valve and improve the overall long term results of surgery.

In conclusion, we showed that patients who develop significant tricuspid regurgitation late after successful mitral valve replacement for rheumatic mitral valve disease have a considerable reduction in exercise capacity resulting in a poor functional outcome. Exercise testing with expired gas analysis indicates that this is attributable to an impaired cardiac output response to exercise resulting from failure of the right ventricle or from the influence that tricuspid regurgitation itself has in limiting a rise in right ventricular cardiac output. Residual pulmonary hypertension was not present and left ventricular function was well preserved in these patients. Given the relatively high risk of re-operation involving the tricuspid valve and the degree of functional limitation shown in these patients, efforts should be made to reduce the likelihood of severe tricuspid regurgitation developing after mitral valve replacement. This may best be achieved by the accurate intraoperative detection and correction of important tricuspid regurgitation at the time of initial surgery. If surgery were considered during an earlier stage of valve disease functional tricuspid regurgitation might become less of a problem.

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PLANTS IN CARDIOLOGY


Quinine and quinidine

The bark of the South American tree Cinchona (Rubiaceae) contains quinine, and also quinidine—isolated by Pasteur in 1853. Its use in treating fevers was learnt in Peru by Spanish missionaries who in 1630 brought the bark to Europe where its value in malaria was discovered. In 1749 Jean-Baptiste de Senac wrote “Long and rebellious palpitations have ceded to this febrifuge". In the nineteenth century quinine was used to augment digitalis therapy, and quinidine was described as “das opium des herzens". But the definitive use of quinidine in arrhythmias came about only because of an astute observation in 1912 by a patient of Professor Karel F Wenckebach who then related the story in the Journal of the American Medical Association (1923;81:472-4). The patient was a man with attacks of atrial fibrillation who said that “being a Dutch merchant used to good order in his affairs he would like to have good order in his heart business also and asked why there were heart specialists if they could not abolish this very disagreeable phenomenon . . . he knew himself how to get rid of his attacks and as I did not believe him he promised to come back next morning with a regular pulse, and he did”.

The man had found by chance that when he took one gram of quinine during an attack it reliably halted it in 25 minutes: otherwise it would last for 2–14 days. Quinine was used then not only in malaria but also as a non-specific remedy for minor ailments as aspirin is today. Wenckebach often tried quinine again but he succeeded in only one other patient. However, it led W Frey in Berlin to study all four cinchona alkaloids in atrial fibrillation and in 1918 he showed that quinidine was the most effective. In 1920 Thomas Lewis put forward his famous hypothesis of circus movement and proposed that quinidine restored normal rhythm by closing the gap between the crest and wake of the circus wave.

The family Rubiaceae is huge with over 10 000 species worldwide. Emetine comes from ipecacuanha and caffeine from coffee but there are no other medicinal species. One genus has the splendid name of Captaincookia. Quinidine and quinidine are still obtained naturally, from the species Cinchona ledgeriana grown commercially in the tropics.

A HOLLMAN
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